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Particles Formation Using Supercritical Fluids

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1. Introduction

The particle precipitation into micro and nanoparticles has been an active research field for decades (Chattopadhyay & Gupta, 2001; Kalogiannis et al., 2005; Rehman et al., 2001; Reverchon, 1999; Velaga et al., 2002; Yeo&Lee, 2004). The greatest requirement in the application of nanomaterials is its size and morphology control which determine the potential application of the nanoparticles, as their properties vary significantly with size. Micro and nanoparticles can be obtained by different techniques. Conventional techniques (spray drying, solute recrystallization, coacervation, freeze-drying, interfacial polymerization) present drawbacks such as excessive use of solvent, thermal and chemical solute degradation, structural changes, high residual solvent concentration, and mainly, difficulty of controlling the particle size (PS) and particle size distribution (PSD) during processing (He et al., 2004), so these techniques for particle formation may not be advisable.

However, the application of supercritical fluids (SCFs) is an attractive alternative for this particle formation because remove these drawbacks. These supercritical fluids have larger diffusivities than those of typical liquids, resulting in higher mass-transfer rates. Moreover its solvent power and selectivity can be tuned altering the experimental conditions.

There are two main ways of precipitating micro and nanoparticles using supercritical fluid as solvent, the RESS technique (Rapid Expansion of Supercritical Solutions); or using it as antisolvent, the SAS technique (Supercritical AntiSolvent); the choice between one or another depends on the active substance high or low solubility in the supercritical fluid.

The RESS process consists of solubilising the active ingredient of interest in the supercritical fluid and then rapidly depressurising this solution through a nozzle, thus causing the precipitation, extremely fast, of this compound. In other words, the process is based on the transition of active compound from soluble to insoluble state when the carbon dioxide passes from the supercritical to the gaseous phase. This technique has been applied on the particle precipitation and co-precipitation of many active ingredients/polymers (Kongsombut et al., 2009; Sane & Limtrakul, 2009; Turk et al., 2006; Vemavarapu et al., 2009; Wen et al., 2010).

The SAS technique, in all its variants, generally consists of spraying a solution of the solute to be precipitated into the supercritical fluid. The mass transfer behavior of the droplets is thought to be a key factor affecting particle morphology (Werling & Debenedetti, 1999). The volumetric expansion of the solvent reduces the solvation capacity of the solvent, causing the supersaturation of the liquid phase and the consequent generation of the particles. The SAS process has been carried out for many particles precipitation and polymeric encapsulation of particles of active ingredients (Ai-Zheng et al., 2009; Chong et al., 2009a;

Franceschi et al., 2008; Heyang et al., 2009; Kalogiannis et al., 2006; Kang et al., 2008; Thote & Gupta, 2005; Reverchon et al., 2008a; Ron et al., 2010; Tozuka et al., 2010).
The application of SAS processing has until now been explored in a wide range of fields including: explosives (Teipel et al., 2001), polymers (Garay et al., 2010), pharmaceutical compounds (Chen et al., 2010; Park et al., 2010), colouring matter (Reverchon et al., 2005), superconductors (Reverchon et al., 2002), catalysts and inorganic compounds (Lam et al., 2008). SAS exhibits the capacity of producing free-flowing particles in a single step at moderate pressure and temperature. In the pharmaceutical field, products with a high level of purity, suitable dimensional characteristics such as PS in the micrometer and sub-micrometer ranges, narrow PSD and spherical morphologies, have been obtained for use in developing delivery systems for drug targeting and controlled release.
In the facilities of University of Cádiz, amoxicillin (AMC) and ampicillin (AMP) micronization and polymer-drug co-precipitation have been carried out by SAS process. Several designs of experiments to evaluate the operating conditions influences on the PS and PSD have been made. In SAS, supercritical CO_2, is used as an antisolvent. The solution, containing solute, is shape as tiny droplets, produced by a nozzle through which the solution is sprayed into a high pressure vessel. When the droplets contact the supercritical CO_2 a very rapid diffusion takes place, including phase separation and precipitation of the solute (Chong et al., 2009b).
In the particle precipitation, mass transfer occurs between a droplet of organic solvent and a compressed antisolvent. In miscible conditions, above mixture critical point, there is no obvious way to define the interface between the two fluids. Dukhin et al. has evidenced the transient existence of droplets at conditions slightly above the mixture critical point, due to the existence of a dynamic interfacial tension, so a description of mass transfer from a droplet even in miscible conditions seems reasonable (Dukhin et al., 2003).
Two ways diffusion process, between a solvent droplet and its antisolvent environment at supercritical conditions, take place. There are evidences that antisolvent–solvent mass transfer is more important than jet break-up and droplet formation in determining particle size and morphology (Heater & Tomasko, 1998; Randolph et al., 1993).
However, the complexity of SAS process, which involves the interaction of thermodynamics, mass transfer, jet hydrodynamics and nucleation kinetics, makes it difficult to isolate one phenomenon as being responsible for a given trend in particle characteristics (Werling & Debenedetti, 2000).

2. Supercritical fluids

A supercritical fluid can be defined as a substance above its critical temperature and pressure. At this condition the fluid has unique properties, where it does not condense or evaporate to form a liquid or gas. A typical pressure-temperature phase diagram is shown in Figure 1. These supercritical fluids have diffusivities that are two orders of magnitude larger than those of typical liquids, resulting in higher mass-transfer rates. Properties of SCFs (solvent power and selectivity) can also be adjusted continuously by altering the experimental conditions (temperature and pressure). Supercritical fluids show many exceptional characteristics, such as singularities in compressibility and viscosity, diminishing difference in vapor and liquid phases and so on. Although a number of substances are useful as supercritical fluids, like water, carbon dioxide has been the most widely used. Supercritical CO_2 avoids water discharge; it is low in cost, non-toxic and non-flammable. It has low critical parameters (304 K, 73.8 bar) and the carbon dioxide can also be recycled (Özcan et al., 1998).

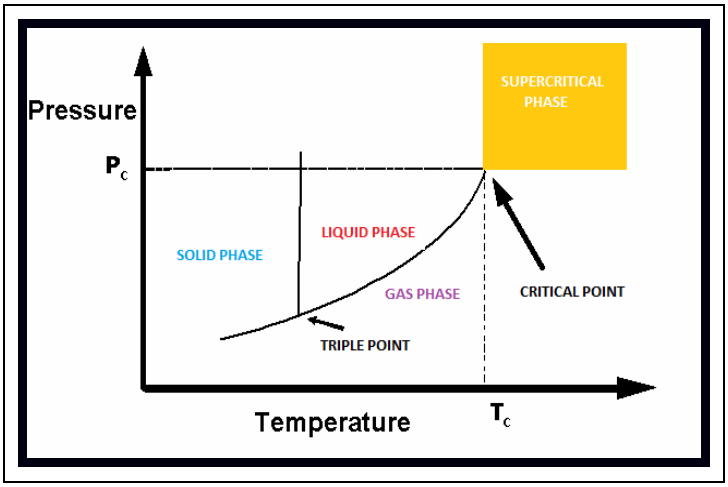

Fig. 1. Pressure-temperature phase diagram

3. Precipitation using supercritical fluids

In order to design a supercritical precipitation process several aspects must be taken into account. First, the solubility of the solute to micronize in supercritical fluids must be known in order to choose RESS or SAS process. Then, a solvent able to turn the solute soluble must be chosen, and elucidate the ternary phase equilibrium diagram solvent-solute-CO_2 or the binary phase equilibrium solvent-CO_2 when the solubility of the solute into CO_2 is neglected. Volumetric expansion curves and volumetric equilibrium data are required. Not only the thermodynamic data but also the hydrodynamic of the process should be investigated.

3.1 Solubility

Over the last few decades, the solubilities of solids and liquids in supercritical fluids (SCF) have been measured extensively. For instance, in the facilities of University of Cádiz, the solubility of solid dyes like 1,4-dimethylaminoanthraquinone (Disperse Blue 14) in supercritical carbon dioxide has been determined in the pressure range of 100-350 bar and in the temperature range of 313-353 K and correlated with empirical and semi empirical equations based model and models based on thermodynamic aspects and the use of equations of state (Gordillo et al., 2003). The solubility of palmitic acid in supercritical carbon dioxide was determined experimentally in the pressure range, 100 to 350 bar, and the temperature range, 308 to 323 K. A cubic equation of state and an empirical equation were used to correlate the solubility of this fatty acid in supercritical carbon dioxide (Gordillo et al., 2004). Such information takes an important part of establishing the technical and economic feasibility of any supercritical fluid process. Most of the investigations on solubility have been concerned about binary systems consisting of a single solute in contact with a single SCF. The solubility of solutes in supercritical fluids is related to its physical and chemical properties such as polarity, molecular structure, and nature of the material particles, and it is also related to the operating conditions such as temperature, pressure, density of solvent and co-solvents, and solvent flow rate in the supercritical region. From the 90s to now, many

articles about solubility of drugs in supercritical fluids were published. At the University of Cádiz, the solubility of the antibiotic Penicillin G in supercritical carbon dioxide was measured at pressures from 100 to 350 bar and temperatures from 313.15 to 333.15 K using a dynamic flow apparatus. Moreover a new empiric equation was proposed to improve the correlation with experimental data relating neperian logarithm with pressure and temperature (Gordillo et al., 1999). The model has been applied on several systems and the obtained results allow affirm that the thermodynamic model applied to fluid–solid equilibrium calculations is useful to predict the behaviour of this system.

Kikic et al developed an estimation method based on the Peng–Robinson´s equation of state in order to calculate the solubility of drugs such as acetaminophen, acyclovir, atenolol, Carbamazepine, ibuprofen, naproxen, nimesulide, and sotalol hydrochloride in mixtures of CO_2 and common organic solvents at a constant temperature but at variable pressure (Kikic et al., 2010). Wubbolts et al studied the systems p-acetamido phenol + ethanol + CO_2 (Wubbolts et al., 2004). In this way, Muntó et al measured the solubility of the two non-steroidal anti-inflammatory drugs ibuprofen and naproxen in CO_2-expanded ethanol and CO_2-expanded acetone. The obtained data reflected that naproxen solubility behavior was strongly dependent on the protic or aprotic nature of the organic solvent whereas for ibuprofen this solvent characteristic seemed to be less important (Munto et al., 2008). Tomasko et al. carried out a detailed review of solubilities of CO_2 into polymers as well as of other thermodynamic and transport properties of CO_2-polymer systems (Tomasko et al., 2003). Ugaonkar et al examined the rate of dissolution of carbamazepine, a hydrophobic drug for treating epilepsy, in supercritical CO_2 and its partitioning into polyvinylpyrrolidone and concluded that partitioning occurs by surface adsorption and impregnation within the polymer matrix (Ugaonkar et al., 2011).

The choice of RESS or SAS process depends on the active substance high or low solubility in the supercritical fluid. The very low solubility of solids in carbon dioxide makes the RESS process unattractive, since a very small amount of material is processed. A solvent mixture composed of carbon dioxide and a co- solvent (Bush et al., 2007; Hosseini et al., 2010) could be an alternative, since more material could be processed at high supersaturation rates in the RESS process. It is also possible to overcome the limitation of low solubility in CO_2 by employing alternative organic supercritical solvents such as trifluoromethane or clorodifluoromethane.

However, the very low solubility of solids in carbon dioxide makes the SAS process very attractive because in this process the solute must not be soluble in this fluid. So, understanding the phase behavior of solvent-supercritical fluid system can therefore provide important information regarding the role of this supercritical fluid as a solvent or reaction medium in diverse applications.

The miscibility of a dense gas with a liquid solvent is a fundamental requirement of a lot of precipitation techniques which use a gaseous or supercritical antisolvent. Vapour–liquid equilibria and volumetric expansion data for the CO_2-solvent binary system are a good starting point in order to design every supercritical process. While the vapour–liquid equilibrium data of solvents and CO_2 are usually available, the solubility of solids in a mixture of a common solvent and CO_2 are not. Gordillo et al developed and applied a thermodynamic model to several systems and the results obtained let affirm that the thermodynamic model applied to fluid–solid equilibrium calculations was useful to predict the behaviour of this system (Gordillo et al., 2005a). These authors proved that depending on the group contribution methods chosen to estimate the parameter critical the agreement

between measured and calculated solubility data varied (Gordillo et al., 2005b). Moreover, the results obtained in another work about the dye solubility correlation showed that the choice of group contribution method was more important than the choice of the equation of state used, Redlich-Kwong, Soave-Redlich-Kwong and Peng-Robinson (Gordillo et al., 2005c)

However in SAS process, according to usual practice in the ternary systems, it has been considered that the presence of non soluble drugs does not affect the solvent–CO_2 equilibrium, therefore to represent the ternary equilibrium of drug–solvent–CO_2, the solvent–CO_2 pseudo-binary diagram is used. Volumetric expansion curves provide a mean to determine an allowed range of pressure for solubility measurements at a given temperature and for a given solvent. Thus it is possible to know prior to the analysis whether the operating conditions are above, near or below the mixture critical point (MCP). The mass transfer between CO_2 and solution depends on the situation in this diagram. In Figure 2 it is shown a phase equilibrium diagram of the binary system NMP–CO_2, at two temperatures, estimated using the equation of state of Peng–Robinson, for the system NMP-CO_2. The data corresponding to this equilibrium diagram were obtained from the development of a computer program in Matllab 7.0 (Tenorio et al., 2008).

On the other hand, the presence of the solute can induce changes in the phase diagrams of the binary solvent–SC-CO_2 systems. These changes have been rarely measured and they are difficult to evaluate. However, when the solute has small interactions and a very low solubility in SC-CO_2, its influence on the phase diagrams should be small (Kikic et al., 2006). In systems with strong interactions between CO_2 and solute a drastic alteration of the phase diagrams is possible.

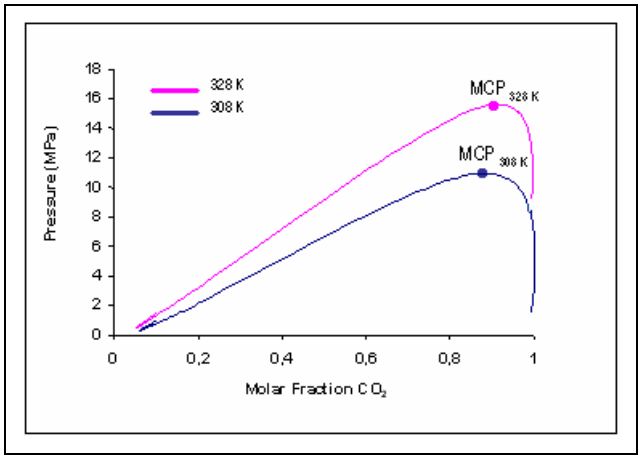

Fig. 2. P–x–y diagram of the CO_2–NMP system (Tenorio et al., 2008)

3.2 Precipitation

As it has been argued, the supercritical fluid technology has emerged as an important alternative to traditional processes of generation of micro and nanoparticles, offering opportunities and advantages such as higher product quality in terms of purity, more uniform dimensional characteristics, a variety of compounds to process and a substantial improvement on environmental considerations, among others.

Previously, it was discussed that the different particle formation processes using SCF are classified depending on how this SCF behaves, i.e., the supercritical CO_2 can play the role as antisolvent (AntiSolvent Supercritical process, SAS) or solvent (RESS process).
The SAS process (Figure 3) uses both the high power of supercritical fluids to dissolve the organic solvents and the low solubility of the compounds in supercritical fluids (Shekunov and York, 2000) to cause the precipitation of such compounds once they are dissolved in the organic phase. The dissolution of the supercritical fluid into the organic solvent goes along with a large volume expansion and, consequently, a reduction of the liquid density, and therefore, of its solvent power, causing a sharp rise in the supersaturation within the liquid mixture. Because of the high and uniform degree of supersaturation, small particles with a narrow particle size distribution are expected (Dukhin et al., 2005).

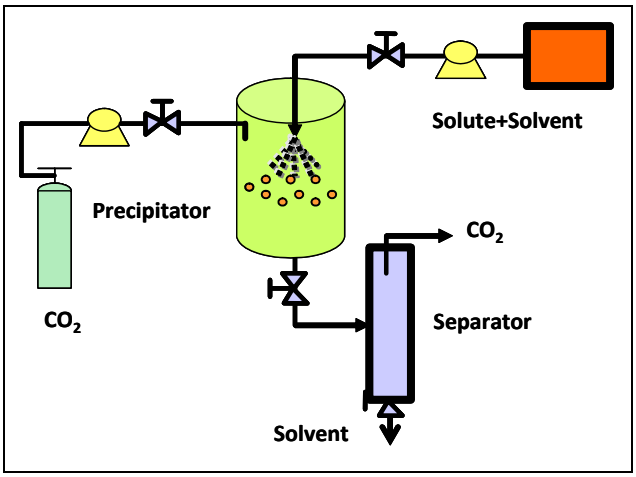

Fig. 3. SAS process diagram

In the RESS method, the sudden expansion of supercritical solution (solute dissolved in supercritical carbon dioxide) via nozzle and the rapid phase change at the exit of the nozzle cause a high super-saturation, thus causing very rapid nucleation of the substrate in the form of very small particles that are collected from the gas stream (Figure 4). Hence, the conditions inside the expansion chamber are one key factor to control particle size and the particles grow inside the expansion chamber to their final size. This result clarifies the influence of two important process parameters on particle size. Both, a shorter residence time and, hence, less time available for particle growth as well as a higher dilution of the particles in the expansion chamber result in smaller particles.
Harrison et al. performed RESS studies on benzoic acid, cholesterol and aspirin, in which the influence of several expansion parameters on the particle size were studied: the variation of the pre-expansion pressure and temperature, distance from the nozzle, and on the amount and type of co-solvent added. To characterize the supercritical CO_2 expansion, a modelling to calculate pressure, temperature, density and velocity, along the nozzle was developed. The average particle diameter decreased with increasing pre-expansion pressure, and increased with increasing pre-expansion temperature. This is probably due to a lower mass flow rate, which is associated to a lower pre-expansion pressure or higher pre-expansion temperature (Harrison et al., 2007).

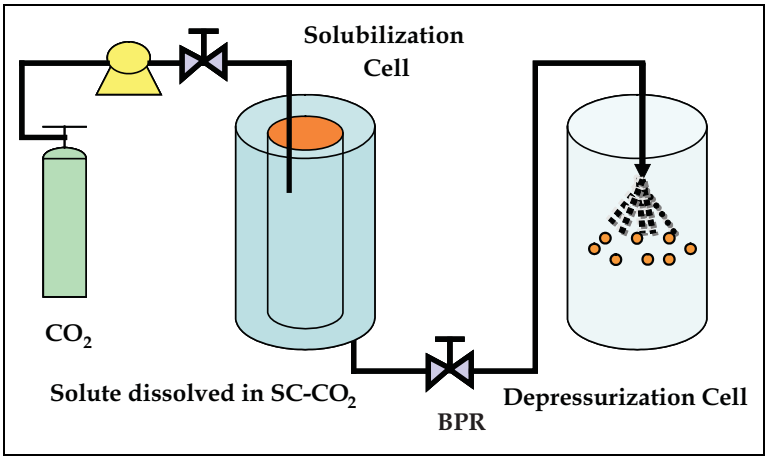

Fig. 4. RESS process diagram

In this way, Corazza et al. carried out an analysis of supersaturation of the system during expansion of the supercritical solution. For that the phase equilibrium problem was solved at system temperature and pressure for each specific position. Supersaturation values were very high in the free-jet expansion region, but depending on the preexpansion conditions, the supersaturation profile in the free jet region was quite different. These observations suggest that pre and post expansion conditions can have a remarkable effect on the characteristics of precipitated particles (Corazza et al., 2006). The results presented in this work indicate that the fluid residence time in the capillary region was very low, and thus the mechanism for microparticle formation could also be affected by mass transfer phenomena in addition to thermodynamic equilibrium. One more time, mass transfer must be studied from thermodynamic and hydrodynamic point of view.

4. SAS process

4.1 Mass transfer

In SAS process, mass transfer occurs between a droplet of organic solvent and a compressed antisolvent. In miscible conditions, above mixture critical point, there is no obvious way to define the interface between the two fluids. Dukhin et al. has evidenced the transient existence of droplets at conditions slightly above the mixture critical point, due to the existence of a dynamic interfacial tension, so a description of mass transfer from a droplet even in miscible conditions seems reasonable (Dukhin et al., 2003).

On the other hand, in the SAS process the solution is generally dilute and the equilibrium compositions of the binary and ternary mixtures are not significantly different. Accordingly to this, the solid present in the solution is not likely to affect the rates of mass transfer of CO_2 and solvent to and from the droplet respectively.

Mass transfer depend on the densities differences between solvent and antisolvent, viscosity, diffusivity, droplet or particle diameter and solvent flow rate. Chong et al. developed a mathematical model form mass transfer between a droplet of organic solvent and a compressed antisolvent in complete miscibility in SAS process. Calculations using Peng-Robinson equation of state showed that droplets swell upon interdiffusion when the

solvent is denser than the antisolvent and shrink when the antisolvent is denser (Chong et al., 2009b).

Some authors have modelled the behavior of an organic solvent droplet, considering different local mass transfer both at subcritical (Werling & Debenedetti, 1999) and supercritical (Werling & Debenedetti, 2000) conditions. In this case, the droplet is considered to be stagnant. Therefore, the only convective motion considered is that induced by the diffusion. At subcritical conditions, calculations showed that there is an initial period of droplet swelling, due to the diffusion of CO_2 into the organic solvent. Droplet lifetime decreases as the pressure increases, and increases sharply at near-critical conditions, because diffusivities tend to zero near the critical point. At miscible conditions, mass transfer is much faster than at subcritical conditions. Droplet diameter increases if the density of the organic solvent is higher than that of the CO_2, and vice versa. However, this ideal and local approach is often not enough to interpret the results. Elvassore et al. developed a model based on the mass transfer simulations of Werling and Debenedetti. This model included the solute in mass transfer calculations (Elvassore et al., 2004).

Pérez de Diego et al. and Martin et al. developed both models for the evaporation of dichloromethane (Pérez de Diego et al., 2006) and ethanol (Martín et al., 2007) droplets respectively which accounted for the higher mass transfer coefficients due to the convective motion of CO_2, explaining the change in particle morphology.

Shekunov et al proposed a simplified approach based on the calculation of different characteristic times (diffusion, jet break up...). They studied the phenomena of turbulent dispersion and micromixing in supercritical carbon dioxide using paracetamol as a model drug compound. They tried to describe the effect of mass-transfer on the particle size and morphology and suggested that particle growth is the time-limiting step (Shekunov et al., 1999).

Then, in order to describe the mass transfer, the drop size distribution, nucleation and particle growth during the drying of the drops as well as the fluid dynamics of the dispersed liquid must be known. Other works also carried out a complete modelling. In these cases, the overall process is modelled, taking into account thermodynamic, hydrodynamic, crystallization and mass transfer aspects (Cardoso et al., 2008; Martin & Cocero, 2004; Lora et al., 2000; Reverchon et al., 2010).

At the University of Cádiz, Tenorio et al, by determining the thermodynamic properties of the phases involved in the process, and applying empirical equations (operations with dimensionless numbers), have estimated the different disintegration regimes of the jet when an N-methyl-pyrrolidone (NMP)-ampicillin solution was injected into the CO_2-pressurized chamber. The application of the empirical hydrodynamics model proved the existence of significant mechanisms that stabilize the liquid jet, and it showed that there were limiting hydrodynamic conditions that had to be overcome to drive the process toward the formation of uniform spherical nanoparticles and the achievement of higher yields (Tenorio et al., 2009)

Reverchon et al., in some recent papers (Reverchon et al., 2007, 2008b, 2008c, 2011) studied the link between SAS morphologies and the relative position of the SAS operating point with respect the mixture critical point of the solvent-CO_2 mixtures. It was proposed several mechanisms and their interactions to elucidate the different morphologies and dimensions of precipitates. From a practical point of view, the knowledge of the competing mechanisms allows to select the dimensions of the precipitated particles. If nanoparticles are the objective of the process, low concentrations of the liquid solution are preferable and SAS operation

should be performed at completely developed supercritical conditions (when surface tension vanishes before jet break up occurs). If spherical microparticles are the target, the process conditions in which jet break-up produces micrometric droplets are the right ones; the increase in concentration of the starting solution will increase the average diameter of the particles, but, also their polydispersity.

4.2 Polymer and biopolymers

Among organic and inorganic compounds that have been processed with SAS process, polymers have remarkable interest and significance. Yeo and Kiran (Yeo & Kiran, 2005) and Tomasko et al. (Tomasko et al., 2003) presented extensive reviews of the supercritical processing of polymers. Because most of polymers are not soluble in supercritical fluids, this antisolvent process is especially suitable for their recrystallization or precipitation in form of microparticles. The polymer is firstly dissolved in a liquid organic solvent and a supercritical fluid is employed as an antisolvent for the polymer. Polymers in form of small particles are useful for several applications like stationary phases in chromatography, adsorbents and catalyst supports, as well as drug delivery systems (Dixon et al., 1993). The polymers must fulfil several requisites: its biocompatibility, non toxicity, providing a suitable medium for preserving the properties and activity of the active substance and easy to process with the selected precipitation technique.

It is particularly important for polymer processing with supercritical processes is the glass transition and the melting point temperature depressions induced by the supercritical fluid. In particular, the dissolution of SC-CO_2 into the polymer can reduce the glass transition temperature of amorphous polymers (Tomasko et al., 2003), an effect that is caused by intermolecular interactions between the dissolved CO_2 and the polymer. The melting point depression caused by the dissolution of CO_2 is less noticeable in magnitude.

A number of RESS processes for the encapsulation of particles with polymer (polylactic acid (PLA), polyethylene glycol (PEG), Eudragit) or composite particle formation for the controlled release of drugs have been reported as it was referenced before.

However, the potential application of RESS for particle coating or encapsulation is limited because the solubility of polymers in SC-CO_2 is generally very poor (O'Neill et al., 1998)

Compared to RESS, the SAS process offers much more flexibility in terms of choosing suitable solvents. Furthermore, SAS has advantages over RESS because SAS is usually operated under mild conditions compared with those of RESS, which is associated to relatively high temperature and high pressure. Therefore RESS is also less attractive from the perspectives of safety and cost. The SAS process has been carried out for many particles precipitation and polymeric encapsulation of particles of active ingredients.

In order to obtain polymer-drug composites several researches have been carried out at our laboratory. Ethyl cellulose (EC) is a biocompatible and non biodegradable polymer. Ethyl cellulose is commonly used as drug carrier in controlled delivery systems. For instance, ethyl cellulose microcapsules has been used as a drug-delivery device for protecting folic acid from release and degradation in the undesirable environmental conditions of the stomach, whilst allowing its release in the intestinal tract to make it available for absorption. In the same way, ethyl cellulose and antibiotic microcapsules have been developed to use as drug delivery protecting antibiotic of conditions of the stomach.

At University of Cádiz, ethyl cellulose microparticles were successfully precipitated from dichloromethane (DCM) by SAS process (Gordillo et al., 2008) and particles were reduced from 50-100 to 3-5 μm (Figure 5). The concentration was the factor that had the greatest

influence on the PS and PSD. An increase in the initial concentration of the solution led to larger particles sizes with a wider distribution.

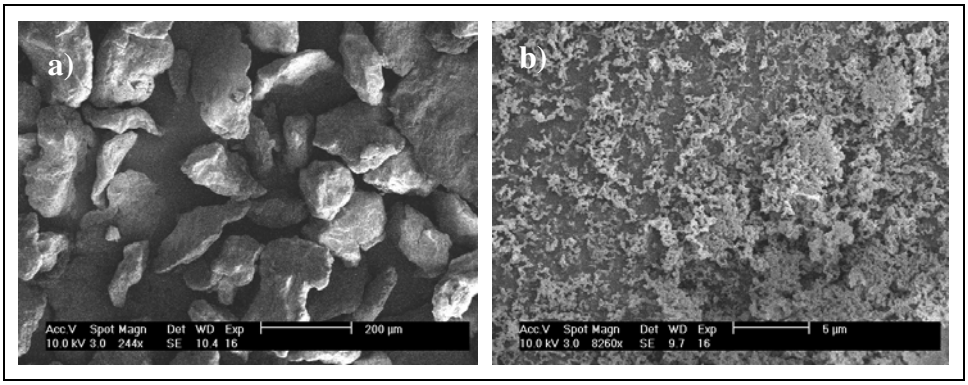

Fig. 5. SEM images of a) raw ethyl cellulose and b) precipitated ethyl cellulose

A pilot plant, developed by Thar Technologies® (model SAS 200) was used to carry out all the experiments. A schematic diagram of this plant is shown in Figure 6. The SAS 200 system comprises the following components: two high-pressure pumps, one for the CO_2 (P1) and the other for the solution (P2), which incorporate a low-dead-volume head and check valves to provide efficient pumping of CO_2 and many solvents; a stainless steel precipitator vessel (V1) with a 2-L volume consisting of two parts, the main body and the frit, all surrounded by an electrical heating jacket (V1-HJ1); an automated back-pressure regulator (ABPR1) of high precision, attached to a motor controller with a position indicator; and a jacketed (CS1-HJ1) stainless steel cyclone separator (CS1) with 0.5-L volume, to separate the solvent and CO_2 once the pressure was released by the manual back-pressure regulator (MBPR1).The following auxiliary elements were also necessary: a low pressure heat exchanger (HE1), cooling lines, and a cooling bath (CWB1) to keep the CO_2 inlet pump cold and to chill the pump heads; an electric high-pressure heat exchanger (HE2) to preheat the CO_2 in the precipitator vessel to the required temperature quickly; safety devices (rupture discs and safety valve MV2); pressure gauges for measuring the pump outlet pressure (P1, PG1), the precipitator vessel pressure (V1, PG1), and the cyclone separator pressure (CS1, PG1); thermocouples placed inside (V1-TS2) and outside (V1-TS1) the precipitator vessel, inside the cyclone separator (CS1-TS1), and on the electric high pressure heat exchanger to obtain continuous temperature measurements; and a FlexCOR coriolis mass flowmeter (FM1) to measure the CO_2 mass flow rate and another parameters such as total mass, density, temperature, volumetric flow rate, and total volume.

4.3 Pharmaceuticals

Pharmaceutical preparations are the final product of a technological process that gives the drugs the characteristics appropriate for easy administration, proper dosage and enhancement of the therapeutic efficacy. Among several kinds of development of modified release preparation, the design of pharmaceutical preparations in nanoparticulate form has emerged as a new strategy for drug delivery (Pasquali et al., 2006). Particle size and particle size distribution are critical parameters that determine the rate of dissolution of the drug in

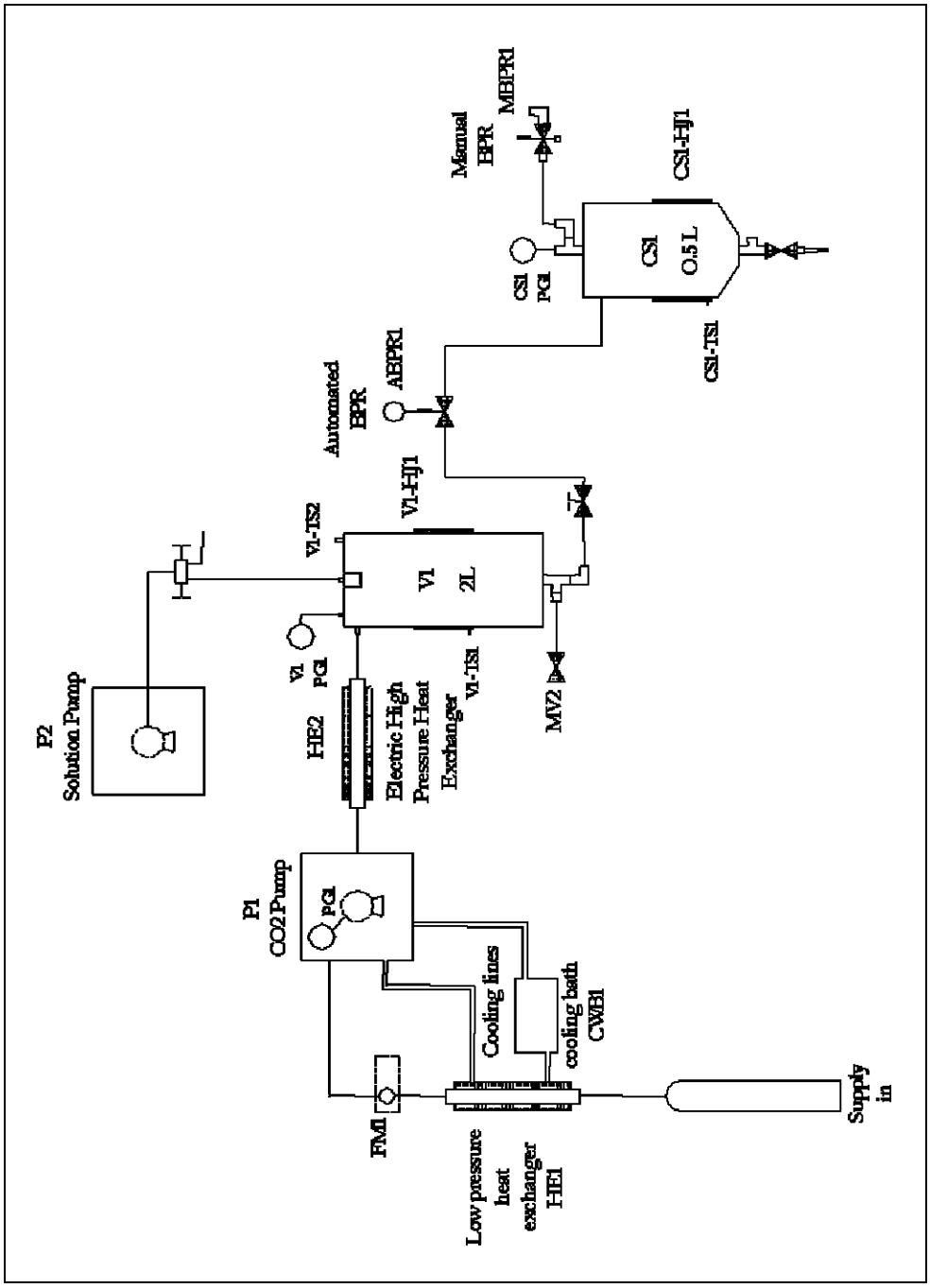

Fig. 6. Schematic diagram of the pilot plant

the biological fluids and, hence, have a significant effect on the bioavailability of those drugs (Perrut et al., 2005; Van Nijlen et al., 2003).

Methods used in the past for the manufacture of drug nanoparticles usually do not allow very accurate control of the particle size, and so broad particle size distributions are obtained. Supercritical antisolvent (SAS) processes have been widely used for the last ten years to precipitate Active Pharmaceutical Ingredients (APIs) (Chattopadhyay& Gupta, 2001; Rehman et al., 2001; Velaga et al., 2002; Yeo & Lee, 2004).

Supercritical antisolvent techniques overcome the main drawbacks of conventional techniques, such as the degradation of the active ingredients because of the high profiles of temperatures and tensile stresses reached and the large amount of organic solvent used, resulting in the need to remove the solvent from the final product.

Amoxicillin and ampicillin micronization have been carried out by SAS process in our laboratory (Montes et al., 2010, 2011; Tenorio et al., 2007a, 2007b, 2008). Several experiments designs to evaluate the operating conditions influences on the PS and PSD have been made. Pressures till 275 bar and temperatures till 338K have been used and antibiotic particle sizes have been reduced from 5-60 μm (raw material) to 200-500 nm (precipitated particles) (Figure 7).

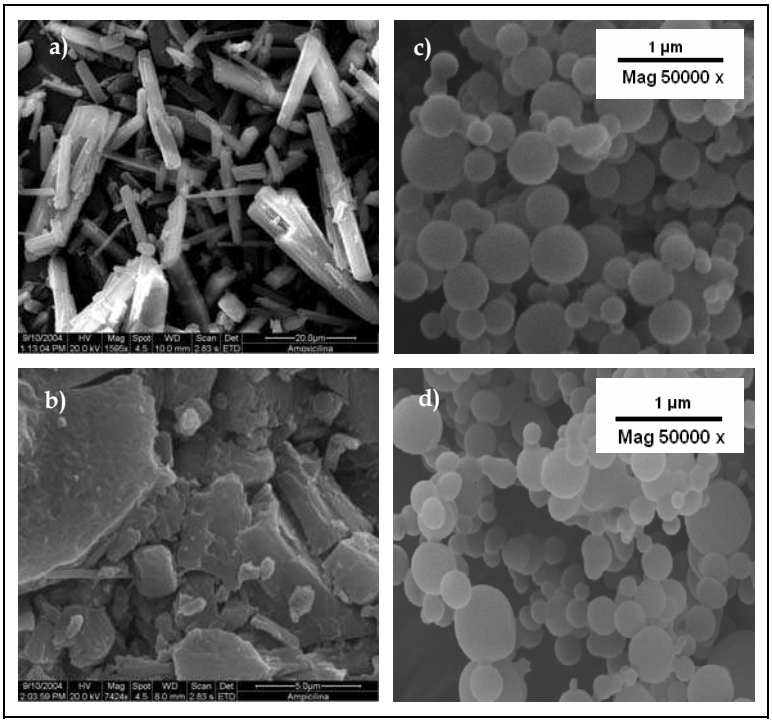

Fig. 7. SEM images of commercial a) amoxicillin and b) ampicillin, c)precipitated amoxicillin and d) ampicillin

The initial concentration of the drug solution pumped into the vessel, is the factor that has the greatest influence on both PS and PSD. Therefore, both PS and the PSD required for the

final formulation of drug could be adjusted well by a change in the initial concentration of the solution. An increase in initial concentration of the solution has two opposite effects: On one hand, with a higher concentration, it is possible to achieve higher supersaturations, which tends to diminish the particle size. On the other hand, condensation is directly proportional to the concentration of solute, and the increase of the condensation rate at higher concentrations tends to increase the particle size (Martin & Cocero, 2004). In our case, an increase in the initial concentration of the solution led to larger particles sizes with a wider distribution.

Thus, the second effect (condensation rate) prevailed under the operating conditions used in this work; that is, the higher the initial concentration of the solution, the higher the condensation rate, and thus, the greater the particle sizes produced. This result is consistent with those obtained by Reverchon et al., which were also explained in terms of competition between nucleation and growth processes (Reverchon et al., 2000).

4.4 Composites and encapsulates

The ability to tune polymer and drug simultaneously can be used to control the nature and extent of drug loading. In order to obtain polymer-drug composites several researches have been carried out. Composites are frequently produced by the simultaneous precipitation of the core and coating materials, leading to a dispersion of particles of the core material into a matrix of coating material while encapsulates are produced when the coating material is precipitated as a thin shell over a previously existing core material particle. These systems let achieve a controlled delivery of the active ingredients into its targeted media. In addition to oral administration, these particulate carriers can also be injected intramuscularly or intravenously as long as their particle size is within physiologically acceptable range to achieve a controlled dissolution of the active substance (Cocero et al., 2009).

In the pharmaceutical compounds encapsulation, the coating material must be biocompatible and non toxic, providing a suitable medium for preserving the properties and the activity of the active substance and easy to process with the precipitation technique.

In our research group, ethyl cellulose amoxicillin and ampicillin co-precipitation has been carried out. For that, commercials EC and AMC and AMP have been dissolved in a mixture of DCM and dimethylsulfoxide DMSO and this solution has been pumped by the high pressure pump of the SAS equipment. A temperature increase from 308 to 328 K, independently of pressure, is traduced to particle size increase but an agglomeration of particles formed by irregular block is observed when the temperature is increased to 333 K. However, at three temperatures, an increase of pressure leads to a smaller particle size. This fact can also be explained on the basis of the numerical modelling of mass transfer proposed by Werling and Debenedetti (Werling& Debenedetti, 2000). An increase of pressure brings the system to miscible conditions. These conditions result in faster mass transfer, causing a higher degree of supersaturation that results in higher nucleation rates, thus producing smaller particle size.

To study the ability of ethyl cellulose to encapsulate amoxicillin, a suspension of AMC microparticles in a solution of EC in DCM has been used. This suspension is sprayed by a nozzle using a KD410 Syringe Pump instead of the solvent pump of the SAS equipment to avoid blocking the pump. The supercritical CO_2 acts as an antisolvent for the DCM. A rapid mutual diffusion between the supercritical CO_2 and the organic solvent causes supersaturation of the polymer solution, leading to nucleation and precipitation of the

polymer to encapsulate the AMC particles. In the precipitation over a suspension of particles, the particles behave as nuclei for the precipitation of the polymer, and a polymer matrix of encapsulated particles is produced by agglomeration (Cocero et al., 2009).
SEM images of these microparticles are shown in Figure 8. SEM images are not accurate enough to observe the distribution of both compounds because all the active substance could be situated on the surface of these microspheres and/or into the core. Thus, X-ray photoelectron spectroscopy (XPS) is one of the main techniques used to determine the success of the encapsulation process by the chemical analysis of the particles on the precipitated surface (Morales et al, 2006). In this case, the elements that differentiate amoxicillin from ethyl cellulose are sulphur (S) and nitrogen (N) atoms. Therefore, these elements can indicate the location of the drug in the precipitated powders. In the co-precipitated the sulphur peak can be identified but there is an absence of this peak in the encapsulate. Moreover, an elemental analysis of the encapsulate is needed to confirm that the drug was situated into the core.

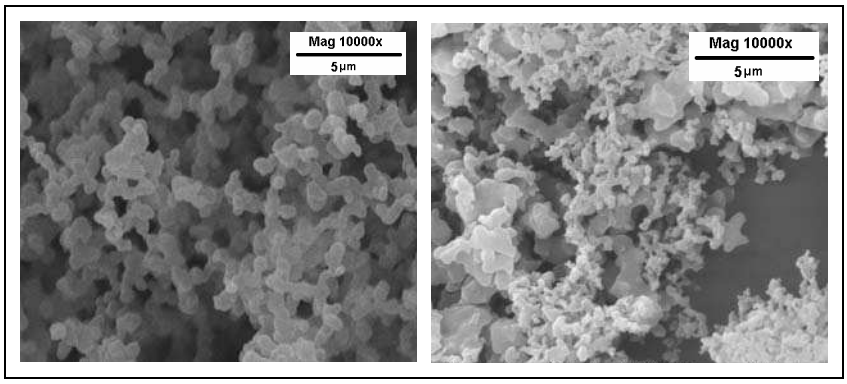

Fig. 8. SEM images of amoxicillin ethyl cellulose a) encapsulates and b) co-precipitated

5. Conclusions

Supercritical Fluid process can be an excellent alternative to conventional precipitation and encapsulation processes. RESS and SAS processes have been applied on the particle precipitation and co-precipitation of many active ingredient/polymer. Furthermore, SAS has advantages over RESS because SAS is usually operated under mild conditions compared with those of RESS, which is associated to relatively high temperature and high pressure. Anyway, the technical viability of the SAS process requires knowledge of the phase equilibrium of the system; its hydrodynamics (the disintegration regimes of the jet); the mass transfer between the jet generated and the continuous phase; and the mechanisms and kinetics of nucleation and crystal growth. Above MCP the surface tension vanishes before jet break up occurs and the jet evolves as gaseous plume producing nanoparticle. However near MCP the jets atomize into droplets producing spherical microparticles.
At the University of Cádiz, amoxicillin, ampicillin and ethyl cellulose have been sucessfully precipitated by SAS process. The concentration was the factor that had the greatest influence on the PS and PSD. An increase in the initial concentration of the solution led to larger particles sizes with a wider distribution. Moreover, ethyl cellulose- amoxicillin and ethyl

cellulose-ampicillin systems have been obtained successfully in our laboratory. A temperature increase of the experiments is traduced to particle size increase. An agglomeration of particles formed by irregular block is observed when the temperature is increased to 333 K. However, an increase of pressure leads to a smaller particle size.

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7. References

Ai-Zheng C. , Yi, L. , Foo-Tim, C. , Tsui-Yan, L. , Jun-Yan, H., Zheng, Z. ,Daniel Kam-wah, M. (2009). Microencapsulation of puerarin nanoparticles by poly(L-lactide) in a supercritical CO_2 process. *Acta Biomaterialia* , 5, pp. 2913-2919.

Bush, J. R., Akgerman, A., Hall, K. R. (2007). Synthesis of controlled release device with supercritical CO_2 and co-solvent. *J. Supercrit. Fluids*, 41, pp. 311–316.

Cardoso, M. A. T.; Monteiro, G. A.; Cardoso, J. P.; Prazeres, T. J. V.; Figueiredo, J.M. F.; Martinho, J. M. G.; Cabral, J. M. S.; Palavra, A. M. F. (2008). Supercritical antisolvent micronization of minocycline hydrochloride. *J. Supercrit. Fluids*, 44, pp. 238–244.

Chattopadhyay, P., Gupta, R. B. (2001). Production of antibiotic nanoparticles using supercritical CO_2 as antisolvent with enhanced mass transfer, *Ind. Eng. Chem. Res.*, 40, pp. 3530-3539.

Chen, Y.-M., Tang, M., Chen. Y.-P. (2010). Recrystallization and micronization of sulfathiazole by applying the supercritical antisolvent technology. *Chem. Eng. J.*, 165, pp. 358–364.

Chong, G.H., Spotar, S.Y., Yunus, R. (2009). Numerical Modeling of Mass Transfer for Solvent-Carbon Dioxide System at Supercritical (Miscible) Conditions. *J. Appl. Sci.*, 9(17), pp. 3055-3061.

Chong, G.H., Yunus, R., Abdullah, N., Choong, T.S.Y., Spotar, S. (2009). Coating and Encapsulation of Nanoparticles using Supercritical Antisolvent. *Am. J. Appl. Sci.*, 6 (7), pp. 1352-1358.

Cocero, M. J., Martin, A., Mattea, F., Varona, S. (2009). Encapsulation and co-precipitation processes with supercritical fluids: Fundamentals and applications. *J. Supercrit. Fluids*, 47, pp. 546-555.

Corazza, M. L., Filho, C. L., Dariva, C. (2006). Modeling and simulation of rapid expansion of supercritical solutions. *Brazilian J. of Chem. Eng.*, 23(3), pp. 417-425.

Dixon, D.J., Johnston, K.P., Bodmeier, R.A. (1993).Polymeric materials formed by precipitation with a compressed fluid antisolvent, *AIChE J.*, 39 (1), pp. 127–139.

Dukhin, S.S., Zhu, C., Pfeffer, R., Luo, J.J., Chavez, F., Shen, Y. (2003). Dynamic interfacial tension near critical point of a solvent–antisolvent mixture and laminar jet stabilization, *Physicochem. Eng. Aspects*, 229, pp. 181-199.

Dukhin, S. S., Shen, Y., Dave, R., Pfeffer, R. (2005). Droplet mass transfer, intradroplet nucleation and submicron particle production in two-phase flow of solvent-supercritical antisolvent emulsion. *Colloids Surf. A*, 261, pp. 163-176.

Elvassore, N., Cozzi, F., Bertucco, A. (2004). Mass transport modeling in a gas antisolvent process, *Ind. Eng. Chem. Res.*, 43, pp. 4935–4943.

Franceschi, E., De Cesaro, A. M., Feiten, M., Ferreira, S. R.S., Darivac, C., Kunita, M.H., Rubira, A. F., Muniz, E. C., Corazza, M. L., Oliveira, J. V. (2008). Precipitation of β-carotene and PHBV and co-precipitation from SEDS technique using supercritical CO_2. *J. Supercrit.Fluids*, 47, pp. 259-269.

Garay, I., Pocheville, A., Madariaga, L. (2010). Polymeric microparticles prepared by supercritical antisolvent precipitation. *Powder Technology*, 197, pp. 211–217.

Gordillo, M.D., Blanco, M.A., Molero, A., Martinez De La Ossa, E. (1999). Solubility of the antibiotic Penicillin G in supercritical carbon dioxide, *J.Supercrit. Fluids*, 15 (3), pp. 183-190.

Gordillo, M.D., Pereyra, C., Martinez de la Ossa, E.J. (2003). Measurement and correlation of solubility of Disperse Blue 14 in supercritical carbon dioxide, *J. Supercrit. Fluids*, 27 (1), pp. 31-37.

Gordillo, D., Pereyra, C., De La Ossa, E.J.M. (2004). Supercritical fluid-solid phase equilibria calculations by cubic equations of state and empirical equations: Application to the palmitic acid + carbon dioxide system. J. *Chem. Eng. Data*, 49 (3), pp. 435-438.

Gordillo, M.D., Blanco, M.A., Pereyra, C., Martínez De La Ossa, E.J. (2005) .Thermodynamic modelling of supercritical fluid-solid phase equilibrium data, *Computers and Chemical Engineering*, 29 (9), pp. 1885-1890.

Gordillo, M.D., Sánchez-Oneto, J., Pereyra, C., De La Ossa, E.J.M. (2005). Review of the main methods of critical parameter estimation: Application to the correlation of palmitic acid / supercritical carbon dioxide phase equilibrium data. *Reviews in Chemical Engineering*, 21 (2), pp. 71-94.

Gordillo, M.D., Pereyra, C., Martínez de la Ossa, E.J. (2005) Solubility estimations for Disperse Blue 14 in supercritical carbon dioxide. *Dyes and Pigments*, 67 (3), pp. 167-173.

Gordillo, M.D., Di Giacomo, G., Schindhelm, S., Pereyra, C.M., Martínez de la Ossa, E.J. (2008). 11th Mediterranean Congress of Chemical Engeenering, Barcelona.

Harrison, J. J., Lee, C., Lenzer, T., Oum, K. (2007). On-line in-situ characterization of CO_2 RESS processes for benzoic acid, cholesterol and aspirin. *Green Chem.*, 9, pp. 351–356.

He, W.Z., Suo, Q.L., Jiang, Z.H., Shan, A., Hong, H.L. (2004). Precipitation of ephedrine by SEDS process using a specially designed prefilming atomizer, *J. Supercrit. Fluids*, 31, pp. 101-110.

Heater, K.J., Tomasko, D.L. (1998). Processing of epoxy resins using carbon dioxide as an antisolvent, *J. Supercrit. Fluids*, 14, pp. 55-65.

Heyang , J., Fei, X., Cuilan , J., Yaping, Z., Lin, H. (2009). Nanoencapsulation of Lutein with Hydroxypropylmethyl Cellulose Phthalate by Supercritical Antisolvent. *Chin. J. Chem. Eng.*, 17(4), pp. 672-677.

Hosseini, M. H., Alizadeh, N., A.R. Khanchi. (2010). Effect of menthol as solid cosolvent on the solubility enhancement of clozapine and lamorigine in supercritical CO_2. *J. Supercrit. Fluids*, 55, pp. 14–22.

Kalogiannis, C. G., Pavlidou, E., Panayiotou, C. G. (2005). Production of Amoxicillin Microparticles by Supercritical Antisolvent Precipitation. *Ind. Eng. Chem. Res.*, 44, pp. 9339-9346.

Kalogiannis, C. G., Michailof, C. M., Panayiotou. C. G. (2006). Microencapsulation of Amoxicillin in Poly(L-lactic acid) by Supercritical Antisolvent Precipitation. *Ind. Eng. Chem. Res.*, 45, pp. 8738-8743.

Kang, Y., Wu, J., Yin, G., Huang, Z., Liao, X., Yao, Y., Ouyang, P., Wang, H., Yang, Q. (2008). Characterization and Biological Evaluation of Paclitaxel-Loaded Poly(L-lactic acid) Microparticles Prepared by Supercritical CO_2, *Langmuir*, 24, pp. 7432-7441.

Kikic, I., Alessi, P., Eva, F., Moneghini, M., Perissutti, B. (2006). Supercritical antisolvent precipitation of atenolol: the influence of the organic solvent and of the processing approach, *J. Supercrit. Fluids*, 38 (3), pp. 434–441.

Kikic, I., De Zordi, N., Moneghini M., Solinas, D. (2010). Solubility estimation of drugs in ternary systems of interest for the antisolvent precipitation processes *J. Supercrit. Fluids*, 55, pp. 616–622.

Kongsombut, B., Tsutsumi, A., Suankaew, N., Charinpanitkul, T. (2009). Encapsulation of SiO2 and TiO2 Fine Powders with Poly(DL-lactic-co-glycolic acid) by Rapid Expansion of Supercritical CO_2 Incorporated with Ethanol Cosolvent. *Ind. Eng. Chem. Res.*, 48, pp. 11230-11235.

Lam, U. T., Mammucari, R., Suzuki, K., Foster, N. R. (2008). Processing of Iron Oxide Nanoparticles by Supercritical Fluids. *Ind. Eng. Chem. Res.*, 47, pp.599-614

Lora, M., Bertucco, A., Kikic, I. (2000). Simulation of the Semicontinuous Supercritical Antisolvent Recrystallization Process. *Ind. Eng. Chem. Res.*, 39, pp. 1487-1496.

Martín, A., Cocero, M.J. (2004). Numerical modeling of jet hydrodynamics, mass transfer, and crystallization kinetics in the supercritical antisolvent (SAS) process *J. Supercrit. Fluids*, 32, pp. 203–219.

Martín, A., Bouchard, A., Hofland, G.W., Witkamp, G.-J., Cocero, M.J. (2007) .Mathematical modeling of the mass transfer from aqueous solutions in a supercritical fluid during particle formation, *J. Supercrit. Fluids*, 41 (1), pp. 126–137.

Montes, A., Tenorio, A., Gordillo, M.D., Pereyra, C., Martínez de la Ossa, E. (2010). Screening design of experiment applied to supercritical antisolvent precipitation of amoxicillin: exploring new miscible conditions. *J. Supercrit. Fluids*, 51, pp. 399-403

Montes, A., Tenorio, A., Gordillo, M.D., Pereyra, C., Martínez de la Ossa, E. (2011). Supercritical Antisolvent Precipitation of Ampicillin in Complete Miscibility Conditions. *Ind. Eng. Chem. Res.*, 50, pp. 2343–2347.

Morales, M. E., Ruiz, M. A., Oliva, I., Oliva, M., Gallardo, V. (2007). Chemical characterization with XPS of the surface of polymer microparticles loaded with morphine. *Int. J. Pharm*., 333, pp. 162-166.

Muntó, M., Ventosa, N., Sala, S., Veciana, J. (2008). Solubility behaviors of ibuprofen and naproxen drugs in liquid "CO_2–organic solvent" mixtures. *J. Supercrit. Fluids*, 47, pp. 147–153.

O'Neill, M.L, Cao, Q., Fang, M., Johnston, K.P., Wilkinson, S.P., Smith, C., Kerschner, J.L., Jureller, S.H. (1998). Solubility of homopolymers and copolymers in carbon dioxide. *Ind. Eng. Chem. Res.*, 37, pp. 3067-3079.

Park, J., Park, H.J., Cho, W., Cha, K.-H., Kang, Y.-S., Hwang, S.-J. (2010). Preparation and pharmaceutical characterization of amorphous cefdinir using spray-drying and SAS-process. *Int.l J. Pharm*., 396, pp. 239–245.

Pasquali, I., Bettini, R., Giordano, F. (2006). Solid-state chemistry and particle engineeringwith supercritical fluids in pharmaceutics, *Eur. J. Pharm. Sci.,* 27, pp. 299-310.

Pérez de Diego, Y., Wubbolts, F.E., Jansens, P.J. (2006). Modelling mass transfer in the PCA process using the Maxwell–Stefan approach, *J. Supercrit. Fluids*, 37, pp. 53–62.

Perrut, M., Jung, J., Leboeuf, F. (2005). Enhancement of dissolution rate of poorly-soluble active ingredients by supercritical fluid processes. Part I. Micronization of neat particles, *Int. J. Pharm*., 288, pp. 3-10.

Randolph, T.W., Randolph, A.D., Mebes, M., Yeung, S. (1993). Sub-micrometer sized biodegradable particles of poly(L-lactic acid) via the gas antisolvent spray precipitation process, *Biotechnol. Prog*., 9,pp. 429-435.

Rehman, M., Shekunov, B. Y., York, P., Colthorpe, P. (2001). Solubility and precipitation of nicotinic acid in supercritical carbon dioxide, *J. Pharm. Sci*., 90, pp. 1570-1582.

Reverchon, E. (1999). Supercritical antisolvent precipitation of micro- and nanoparticles. *J. Supercrit. Fluids*, 15, pp. 1-21.

Reverchon, E.; Della Porta, G.; Falivene, M. G. (2000). Process parameters and morphology in amoxicillin micro and submicro particle generation by supercritical antisolvent precipitation. *J. Supercrit. Fluids*, 17, pp. 239- 248.

Reverchon , E. De Marco, I., Della Porta, G. (2002). Tailoring of nano- and micro-particles of some superconductor precursors by supercritical antisolvent precipitation. *J. Supercrit. Fluids*, 23, pp. 81–87.

Reverchon, E., Adami, R., De Marco, I., Laudani, C.G., Spada, A. (2005). Pigment Red 60 micronization using supercritical fluids based techniques. *J. Supercrit. Fluids*, 35, pp. 76–82.

Reverchon, E., DeMarco, I., Torino, E. (2007). Nanoparticles production by supercritical antisolvent precipitation: a general interpretation. *J. Supercrit. Fluids*, 43(1), pp.126–138.

Reverchon, E., Adami, R., Caputo, G., De Marco, I. (2008). Spherical microparticles production by supercritical antisolvent precipitation: interpretation of results. *J. Supercrit. Fluids*, 47(1), pp. 70–84.

Reverchon, E., Adami, R., Caputo, G., De Marco, I. (2008).Expanded microparticles by supercritical antisolvent precipitation: interpretation of results. *J. Supercrit.Fluids*, 44(1), pp. 98–108.

Reverchon, E., Lamberti, G., Antonacci, A. (2008). Supercritical fluid assisted production of HPMC composite microparticles. J. *Supercrit. Fluids*, 46, pp. 185-196.

Reverchon, E.; Torino, E.; Dowy, S.; Braeuer, A.; Leipertz, A. (2010). Interactions of phase equilibria, jet dynamics and mass transfer during supercritical antisolvent micronization. *Chem. Eng. J.*, 156, pp. 446-458.

Reverchon, E., DeMarco, I. (2011). Mechanisms controlling supercritical antisolvent precipitate morphology. *Chem. Eng. J.* In press.

Ron Tau Yee Lima, Wai Kiong Nga, Reginald B.H. Tan. (2010). Amorphization of pharmaceutical compound by co-precipitation using supercritical anti-solvent (SAS) process (Part I). *J. Supercrit. Fluids*, 53, pp. 179-183.

Sane, A., Limtrakul, J. (2009). Formation of retinyl palmitate-loaded poly(l-lactide) nanoparticles using rapid expansion of supercritical solutions into liquid solvents (RESOLV). *J. Supercrit. Fluids*, 51, pp. 230-237.

Shekunov, B.Yu., Hanna, M., York, P. (1999). Crystallization process in turbulent supercritical flows .*J. Cryst. Growth* ,198/199, pp. 1345-1351.

Shekunov, B. Y., York, P. (2000). Crystallization processes in pharmaceutical technology and drug delivery design, *J. Cryst. Growth.*, 211,pp.122-136.

Thote, A. J., Gupta, R. B. (2005). Formation of nanoparticles of a hydrophilic drug using supercritical carbon dioxide and microencapsulation for sustained release. *Nanomedicine: Nanotechnology, Biology, and Medicine*, 1, pp. 85-90.

Teipel, U., Kröber, H., Krause, H. (2001). Formation of Energetic Materials Using Supercritical Fluids. *Propellants, Explosives, Pyrothecnics*, 26, pp. 168-173.

Tenorio, A., Gordillo, M. D., Pereyra, C.M., Martínez de la Ossa, E.J. (2007a). Controlled submicro particle formation of ampicillin by supercritical antisolvent precipitation, *J. Supercrit. Fluids*, 40, pp. 308-316.

Tenorio, A.; Gordillo, M. D.; Pereyra, C. M.; Martínez de la Ossa, E. M. (2007b). Relative importance of the operating conditions involved in the formation of nanoparticles of ampicillin by supercritical antisolvent precipitation. *Ind. Eng. Chem. Res.*, 46, pp. 114-123.

Tenorio, A., Gordillo, M. D., Pereyra, C.M., Martínez de la Ossa, E.J. (2008). Screening design of experiment applied to supercritical antisolvent precipitation of amoxicillin, *J. Supercrit. Fluids*, 44, pp. 230-237.

Tenorio, A., Jaeger, P., Gordillo, M.D., Pereyra, C.M., Martínez de la Ossa, E.J. (2009). On the selection of limiting hydrodynamic conditions for the SAS process, *Ind. Eng. Chem. Res.*,48 (20), pp. 9224–9232.

Tomasko, D.L., Li, H., Lui, D., Han, X., Wingert, M.J. Lee, L.J., Koelling, K.W. (2003).A Review of CO_2 applications in the processing of polymers, *Ind. Eng. Chem. Res.*, 42, pp. 6431–6456.

Tozuka, Y., Miyazaki, Y., Takeuchi, H. (2010) .A combinational supercritical CO_2 system for nanoparticle preparation of indomethacin. *Int. J. Pharm.*, 386, pp. 243-248.

Turk , M., Upper , G., Hils, P. (2006). Formation of composite drug–polymer particles by co-precipitation during the rapid expansion of supercritical fluids. *J. Supercrit. Fluids*, 39, pp. 253-263.

Ugaonkara, S., Needhama, T. E., Bothun, G. D. (2011). Solubility and partitioning of carbamazepine in a two-phase supercritical carbon dioxide/poly vinylpyrrolidone system. *Int. J. Pharm.*, 403, pp. 96–100.

Van Nijlen, T., Van Den Mooter, G., Kinget, R., Augustijns, P., Blaton, N., Brennan, K. (2003). Improvement of the dissolution rate of artemisinin by means of supercritical fluid technology and solid dispersions, *Int. J. Pharm.*, 254, 173-181.

Velaga, S. P., Ghaderi, R., Carlfors, J. (2002). Preparation and characterisation of hydrocortisone particles using a supercritical fluids extraction process, *Int. J. Pharm.*, 231, pp. 155-166.

Vemavarapu, C., Mollan , M. J., Needham, T.E. (2009). Coprecipitation of pharmaceutical actives and their structurally related additives by the RESS process. *Powder Technology*, 189, pp. 444-453.

Wen, Z., Liu, B., Zheng, Z., You, X., Pua, Y., Li, Q. (2010). Preparation of liposomes entrapping essential oil from Atractylodes macrocephala Koidz by modified RESS technique. *Chem. Eng. Res. Des.*, 88, pp. 1102-1107.

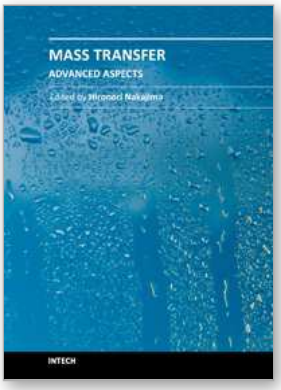
Werling, J. O., Debenedetti, P. G. (2000). Numerical modeling of mass transfer in the supercritical antisolvent process: miscible conditions. *J. Supercrit. Fluids*, 18, pp. 11-24.

Werling, J. O., Debenedetti, P. G. (1999). Numerical modeling of mass transfer in the supercritical antisolvent process. *J. Supercrit. Fluids*, 16, pp. 167–181

Wubbolts, F.E., Bruinsma, O.S.L., Van Rosmalen, G.M. (2004). Measurement and modelling of the solubility of solids in mixtures of common solvents and compressed gases. *J. Supercrit. Fluids*, 32, pp. 79–87.

Yeo, S. D., Lee, J. C. (2004). Crystallization of sulfamethizole using the supercritical and liquid antisolvent processes, *J. Supercrit. Fluids*, 30, pp. 315-323.

Yeo, S.-D., Kiran, E. (2005). Formation of polymer particles with supercritical fluids: A review, J. *Supercrit. Fluids*, 34, pp. 287–308.



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Our knowledge of mass transfer processes has been extended and applied to various fields of science and engineering including industrial and manufacturing processes in recent years. Since mass transfer is a primordial phenomenon, it plays a key role in the scientific researches and fields of mechanical, energy, environmental, materials, bio, and chemical engineering. In this book, energetic authors provide present advances in scientific findings and technologies, and develop new theoretical models concerning mass transfer. This book brings valuable references for researchers and engineers working in the variety of mass transfer sciences and related fields. Since the constitutive topics cover the advances in broad research areas, the topics will be mutually stimulus and informative to the researchers and engineers in different areas.

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