SUPERCRITICAL ANTI-SOLVENT PRECIPITATION OF SODIUM IBUPROFEN

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Abstract. In recent years, significant effort has been devoted to the development of drug formulation with the purpose of targeting and controlled release. The micro/nanosizing of drugs has been identified as a potentially effective and broadly applicable approach. In the pharmaceutical industry several conventional techniques have been utilized for particle size reduction. The disadvantages of these techniques are thermal and chemical product degradation, high energy requirements, use of large amounts of solvent and broad particle size distributions. Therefore, the search for more effective techniques applicable to drugs formulation continues. Accordingly, the objective of this work was to apply the Supercritical Anti-Solvent (SAS) process to nanosize sodium ibuprofen, a nonsteroidal anti-inflammatory drug, evaluating the effect of operational parameters in particle size and morphology. Initially the solute (sodium ibuprofen) was dissolved in acetone and then the operational parameters for SAS process were regulated. The anti-solvent, supercritical CO_2 (SC-CO_2) which presents high diffusivity, was introduced into the precipitation chamber, in a concentric tube together with the acetone/ibuprofen liquid solution. The complete miscibility between acetone and SC-CO_2 causes the ibuprofen precipitation. The following ranges evaluated the SAS process: pressure (80-140bar), temperature (35-55°C), solute concentration (0.5-1.5mg/mL) and solution flow rate (1-3mL/min). The process used 99.9% pure CO_2, applied at constant flow rate of 1kg/h. The particles obtained from all conditions were evaluated by their size and morphology, using a scanning electronic microscopy, and their thermal profiles by differential scanning calorimetry. All conditions applied reduced the particle size from 144±87μm to 87-380nm.

Keywords: SAS process, supercritical technology, particle formation, morphology.

1. Introduction

In pharmaceutical industries a large number of drugs are insoluble or poorly soluble in water. The drug bioavailability (the percentage of the drug absorbed in the organism compared to its initial dosage) is limited by its insolubility in water. The dissolution rate is function of the surface area of the drug particles and its solubility. The surface area can be determined through the control of the particle size. Therefore, the bioavailability of water insoluble drugs can be improved by reducing their particle size [1].

The nanosizing of drug particles has been identified as a potentially effective and broadly applicable approach, with implications beyond the mitigation for water insolubility. For example, smaller-diameter particles correspond to a faster dissolution rate, thus potentially higher activity and easier absorption. Other distinct advantages include tissue or cell specific targeting of drugs, longer blood circulation capacity, higher stability against enzymatic degradation, and reduction of unwanted side effects [2-5]. A significant disadvantage with nanoscale drug particles is related to the production difficulties. The physical instability of nanoscale particles is also a problem in the drug storage and administration [3, 5]. Several traditional particle size reduction techniques such as mechanical milling and precipitation–condensation presented some success in nanosizing drug material, although problems such as broad particle size distribution and excessive use of organic solvent were also related to these methods [6].

In the past decade, supercritical fluid techniques have gained significant attention in many fields, such as extraction, chromatography, chemical reaction engineering, organic and inorganic synthesis, waste management, material processing, porous materials, and pharmaceutical applications materials [7-12]. Supercritical fluids present: low viscosity, permitting matrix penetration as gas-like; relatively high density, which promotes liquid-like solute solubilization; high diffusion; and near-zero surface tension. At the critical point, the density of the gas phase becomes equal to that of the liquid phase, and the interface between gas and liquid disappears. Supercritical CO_2 (scCO$_2$) is the most widely used supercritical fluid because of its relatively low critical conditions (T_c = 31.1 ^{o}C, P_c = 7.38 MPa), nontoxicity, no flammability, and low price [13]. Particle processing is one of the major developments of supercritical fluid applications in industrial fields such as the chemistry, pharmaceutical, cosmetic, and agriculture and food industries, especially in pharmaceutical research, and it also integrates the principles of green chemistry [12]. Various modified supercritical techniques based on different nucleation and growth mechanisms of precipitating particles have been developed [14]. The well-known techniques for particle formation using scCO$_2$ include the rapid expansion of supercritical solutions (RESS) [15] and a variety of antisolvent processes such as Gas AntiSolvent (GAS) [16], Aerosol Solvent Extraction Systems (ASES) [17], Particles from Gas-Saturated Solutions (PGSS) [18], Supercritical AntiSolvent (SAS) processes [19-21], and Solution-Enhanced Dispersion by Supercritical fluids (SEDS) [22].

The SEDS process is a specific SAS process where the scCO$_2$ and the liquid solution are simultaneously introduced into the high-pressure vessel using a specially designed coaxial nozzle. When the solution droplets contact the scCO$_2$, a rapid mutual diffusion takes place instantaneously at the interface , inducing phase separation and supersaturation of the polymer solute, leading to nucleation and precipitation of the polymer particles [14]. The supercritical fluid is used as anti-solvent due to its chemical properties and also as 'spray enhancer' by mechanical effects. The accurate control of SEDS operational conditions (temperature, pressure, liquid solution and supercritical fluid flow rates) provides uniform conditions for particle formation, allowing the control of the particle size and morphology of the product [13, 23].

Ibuprofen is a chiral nonsteroidal anti-inflammatory drug (NSAID), which exhibits poor solubility in water, and its bioavailability can be enhanced by reducing the particle size of the drug. Charoenchaitrakool et al. [24] studied the effect of pre-expansion pressure, spraying distance and the nozzle length on size and morphology of the RESS processed ibuprofen particles. Charoenchaitrakool et al. [24] also studied and compared the dissolution kinetics of original ibuprofen and ibuprofen particles produced by the RESS process. Young et al. [25] presented an alternative method to the RESS, which is called Rapid Expansion from Supercritical to Aqueous Solution (RESAS), and applied it to cyclosporine (a water insoluble drug). In the RESAS process, the supercritical solution was expanded into an aqueous Tween-80 (Polysorbate-80) solution instead of expanding into air. Considering the cited literature information, this work aimed to apply the SAS process to nanosize sodium ibuprofen, evaluating the effect of operational parameters in particle size and morpgology, in order to improve its solubility in water and its bioavailability by reducing its particle size.

2.   Material and Methods

2.1 Materials

Sodium ibuprofen (Sigma Aldrich, Brazil) was used as the solute for the precipitation processes. In order to form the precipitation solution, different concentrations of sodium ibuprofen were solubilized by the primary solvent acetone (P.A., Nuclear, CAQ Ind. e Com. LTDA., Brazil) using constant agitation and heat application (40 ^{o}C, 10 minutes) until reach complete solubilization. The SAS process used 99.9% pure carbon dioxide (White Martins, Brazil), delivered at 60 bar.

2.2 Conformation of SFE equipment to SAS process

A Supercritical Fluid Extraction unit detailed by Zetzl et al. [26], was adapted to the SAS process and is showed in Figure 1. Both Supercritical Fluid Extraction and Supercritical Precipitation/Encapsulation process require the use of a pump (M111, Maximator, Germany) for obtain the desired high pressures. A heat exchanger (cooler – C10-K10, TermoHaake) (1: Figure 1) was used to warrantee the CO_2 liquid state before pumping. The throttle valve (VT: Figure 1) controls the piston oscillation frequency. The gear ratio of the booster piston is 1:130. The spring-loaded backpressure regulator (Tescom Cat. no 26-1761-24-161 - V1: Figure 1) controls the system pressure. The piston sensor opens when the required process pressure is

reached. Then the preheated fluid flows from the valve box (4: Figure 1) back to the sucking section inside the condenser (1: Figure 1). Consequently, the pump produces continuously a compressed CO_2 flow in a closed loop. The closed loop assembly allows a constant solvent supply with low-pressure fluctuation. Before and after the valves, the expansion-induced freezing of the CO_2 flow (Joule Thompson effect) may lead to a complete blocking of the tubes by dry ice particles. Therefore, all relevant valves were placed in a tempered heating bath (4: Figure 1). Changing the original configuration, the extraction/precipitation chamber is heated in a second tempered heating bath, regulated in the operational temperature desired.
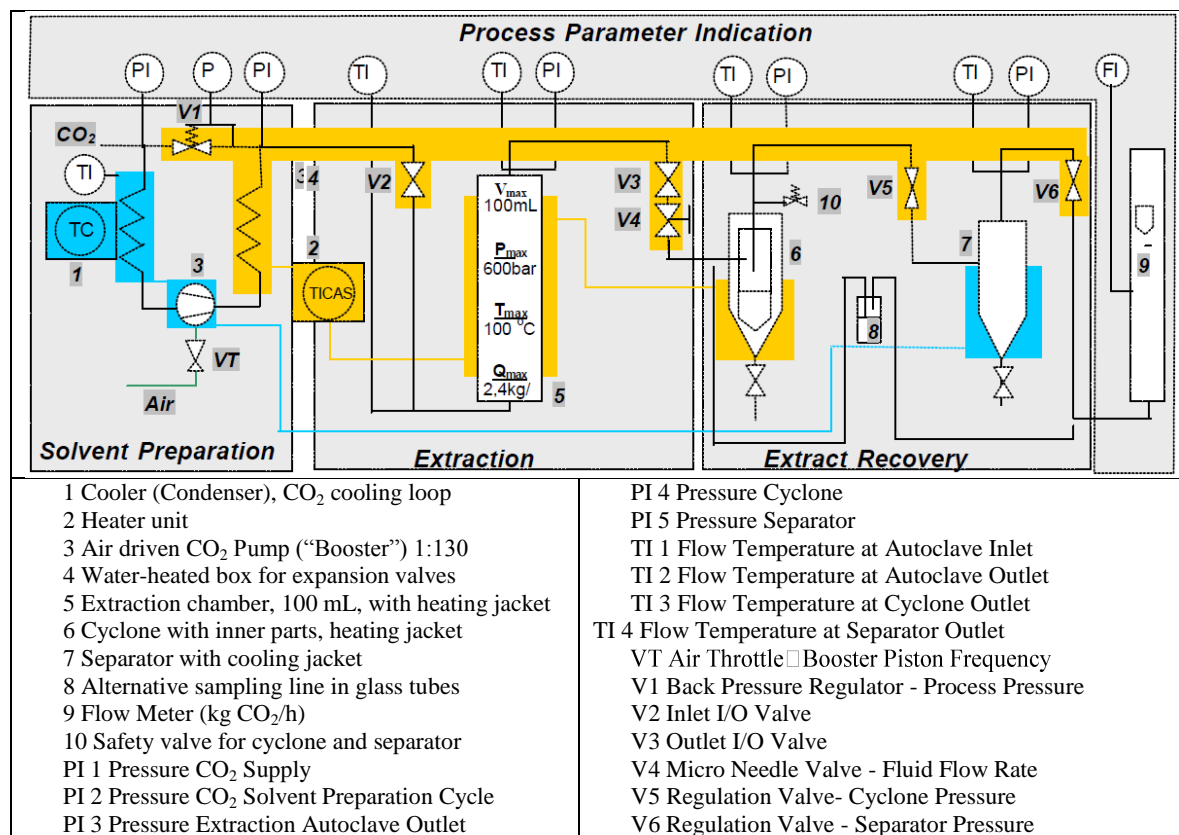

1 Cooler (Condenser), CO_2 cooling loop	PI 4 Pressure Cyclone
2 Heater unit	PI 5 Pressure Separator
3 Air driven CO_2 Pump ("Booster") 1:130	TI 1 Flow Temperature at Autoclave Inlet
4 Water-heated box for expansion valves	TI 2 Flow Temperature at Autoclave Outlet
5 Extraction chamber, 100 mL, with heating jacket	TI 3 Flow Temperature at Cyclone Outlet
6 Cyclone with inner parts, heating jacket	TI 4 Flow Temperature at Separator Outlet
7 Separator with cooling jacket	VT Air Throttle☐Booster Piston Frequency
8 Alternative sampling line in glass tubes	V1 Back Pressure Regulator - Process Pressure
9 Flow Meter (kg CO_2/h)	V2 Inlet I/O Valve
10 Safety valve for cyclone and separator	V3 Outlet I/O Valve
PI 1 Pressure CO_2 Supply	V4 Micro Needle Valve - Fluid Flow Rate
PI 2 Pressure CO_2 Solvent Preparation Cycle	V5 Regulation Valve- Cyclone Pressure
PI 3 Pressure Extraction Autoclave Outlet	V6 Regulation Valve - Separator Pressure

Figure 1. Flow sheet of the Supercritical Fluid Extraction (Zetzl et al., 2003)

Figure 2 presents the modifications of the extraction unit (Figure 1) with the purpose of realize the precipitation/encapsulation processes using $scCO_2$. The precipitator cell used to perform the SAS process is the same extraction chamber of SFE unit, assembled in AISI 316 stain- less steel with vessel dimensions: volume of 103,28 mL, height of 31,6 cm and inner diameter of 2,012 cm (6: Figure 2). The vessel is thermostatically controlled by a regulated water bath (4: Figure 2 - DC30-B30, Thermo Haake). One porous frit, screen size 1 µm is placed in the end of the precipitator and used to help the collection of precipitated particles. An air driven piston pump (3: Figure 2 - M111, Maximator) and an HPLC pump (4: Figure 2 - Constametric 3200 P/F, Thermo Separation Processs) are used to feed the $scCO_2$ and the organic solution into the vessel. The two streams (CO_2 and solution) were mixed by means of a concentric tube nozzle placed at the top of the precipitation vessel (5: Figure 1). The liquid organic solvent is solubilized by the CO_2 and, through system depressurization, the organic solvent is deposited in a glass flask (8: Figure 2) and the flow rate of gaseous CO_2 is measured by a rotameter (RM: Figure 2 – 10A61, ABB Automatic Products) and, after, it is discharged to the atmosphere. The conditions of temperature and pressure were measured with instruments directly connected to the precipitation vessel, with accuracies of ±0.5 °C and ±2 bar, respectively.
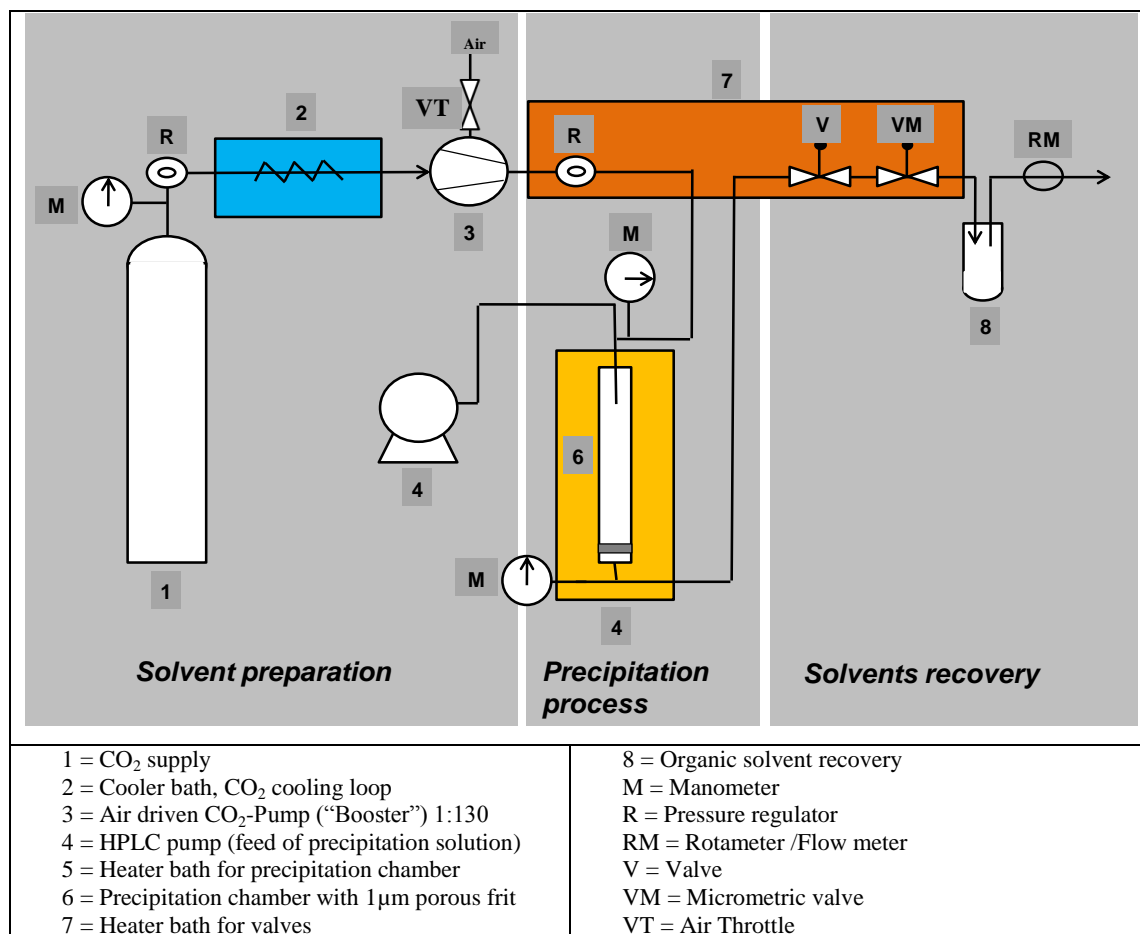
1 = CO$_2$ supply	8 = Organic solvent recovery
2 = Cooler bath, CO$_2$ cooling loop	M = Manometer
3 = Air driven CO$_2$-Pump ("Booster") 1:130	R = Pressure regulator
4 = HPLC pump (feed of precipitation solution)	RM = Rotameter /Flow meter
5 = Heater bath for precipitation chamber	V = Valve
6 = Precipitation chamber with 1μm porous frit	VM = Micrometric valve
7 = Heater bath for valves	VT = Air Throttle

Figure 2. Flow sheet of the Supercritical Anti-Solvent (SAS) unit adapted from the equipment from Zetzl et al. (2003)

2.3   Precipitation processes of sodium ibuprofen

The precipitation process of the sodium ibuprofen was performed in the SAS unit detailed in subsection 2.2. The effect of the precipitation conditions was evaluated: pressure (80, 110 and 140 bar), temperature (35, 45 and 55 ^{o}C), solution flow rate (1.0, 2.0 and 3.0 mL/min) and extract concentration on feed solution (0.5, 1.0 and 1.5 mg/mL), at constant 1 kg/h of CO$_2$. The primary solvent used in the feed solution was acetone P.A. due to its high solvency of the sodium ibuprofen in atmospheric conditions and high solubility in supercritical CO$_2$ at the operational conditions.

The experiments started by pumping pure CO$_2$ into the precipitator vessel. When the desired operating conditions (temperature, pressure and CO$_2$ flow rate) was achieved and remained stable, the solution was feed to the precipitator. After the injection of the pre-defined amount of solution (approximately 30 mL), the liquid pump stopped and then, only pure CO$_2$ was pumped inside the cell during 15 min in order to guarantee total drying of the particles. Subsequent to the decompression, a sample of the precipitated particles retained in the frit was collected for the particle analysis described in subsection 2.4. All samples were stored at temperatures below -10 ^{o}C and protected from light to avoid the decomposition of the product.

2.4   Particles analysis

Scanning eletronic microscopy (SEM). Samples of the powder collected from the SAS precipitator were analyzed by a scanning electronic microscope (SEM) model JEOL JSM-63990LV. A gold sputter was used to cover the samples with a thin layer of gold to allow the light reflection for particle evaluation. The mean particle size was measured by ZEISS image analysis software. The measurements were performed in quadruplicate for each sample.

Differential Scanning Calorimetry (DSC) analysis. Thermal analyses of precipitated samples were performed with a Mettler TA 4000 differential scanning calorimeter. Samples were analyzed under nitrogen atmosphere for temperatures between -10 and 120°C with a heating rate of 5 °C/min. DSC analyses were conducted in order to estimate modifications of the composition, crystallinity degree and melting temperature caused by the SAS process.

3.   Results and Discussion

The Supercritical Anti-Solvent process produced particles for all operational conditions tested. Figure 3 shows the micrographs of the particles obtained by different SAS operational conditions, compared with the original sodium ibuprofen (non-processed). According to Figure 3, the SAS process reduced the original size of sodium ibuprofen particles, from micrometic to nanometric order. Besides that, the micrographs presented in Figure 4 indicated the presence of filaments in the samples obtained in assays 4 and 10, processed at the higher temperature (55 °C) and higher solution flow rate (3 mL/min), respectively, which may disturbed the ideal operational conditions to the particle formation process in the feed tube nozzle of the precipitation chamber.

Table 1 presents the particles average diameter for each operational condition applied. Results show that SAS process reduced the original size of sodium ibuprofen particles from 144 ± 87 μm to 87-380 nm. According to the values from Table 1, the lowest particle size was obtained at intermediate pressure (110 bar), lower temperature (35 °C), lower solution flow rate (1 mL/min) and lower solute concentration (0.5 mg/mL).

Figure 4 shows the calorimetries obtained by the differential scanning calorimeter for some samples of ibuprofen processed by SAS (selected according to the variability of SEM results) and for original sodium ibuprofen (non-processed). According to the profiles presented in Figure 4, the original sodium ibuprofen shows two peaks, probably typical from the bases that composed the original product. Otherwise, the processed samples showed only one peak, displaced from the original one and located next to 110 °C. The literature [6] cite that the calorimetry results of pure ibuprofen shows a single peak between 90 and 120 °C, which can suggest that the SAS process reduced the particle size and also purified the original sodium ibuprofen.

Table 1. Operational conditions and average particle diameters of original sodium ibuprofen and ibuprofen processed by Supercritical Anti-Solvent (SAS) process.

Assay	Ibuprofen concentration (mg/mL)	Solution flow rate (mL/min)	CO_2 flow rate (kg/h)	Pressure (bar)	Temperature (°C)	Average particle diameter (nm)
1	1	1	1	80	35	240 ± 87
2(a) 2(b) 2(c)	1	1	1	110	35	173 ± 34
3	1	1	1	140	35	380 ± 84
4	1	1	1	110	55	153 ± 47
5	1	1	1	110	45	127 ± 9
6	0.5	1	1	110	35	87 ± 28
7	0.5	1	1	110	55	167 ± 9
8	1.5	1	1	110	35	209 ± 15
9	1	2	1	110	35	207 ± 47
10	1	3	1	110	35	156 ± 67
Original sodium ibuprofen (non-processed)						144 ± 87 (x 10^3)
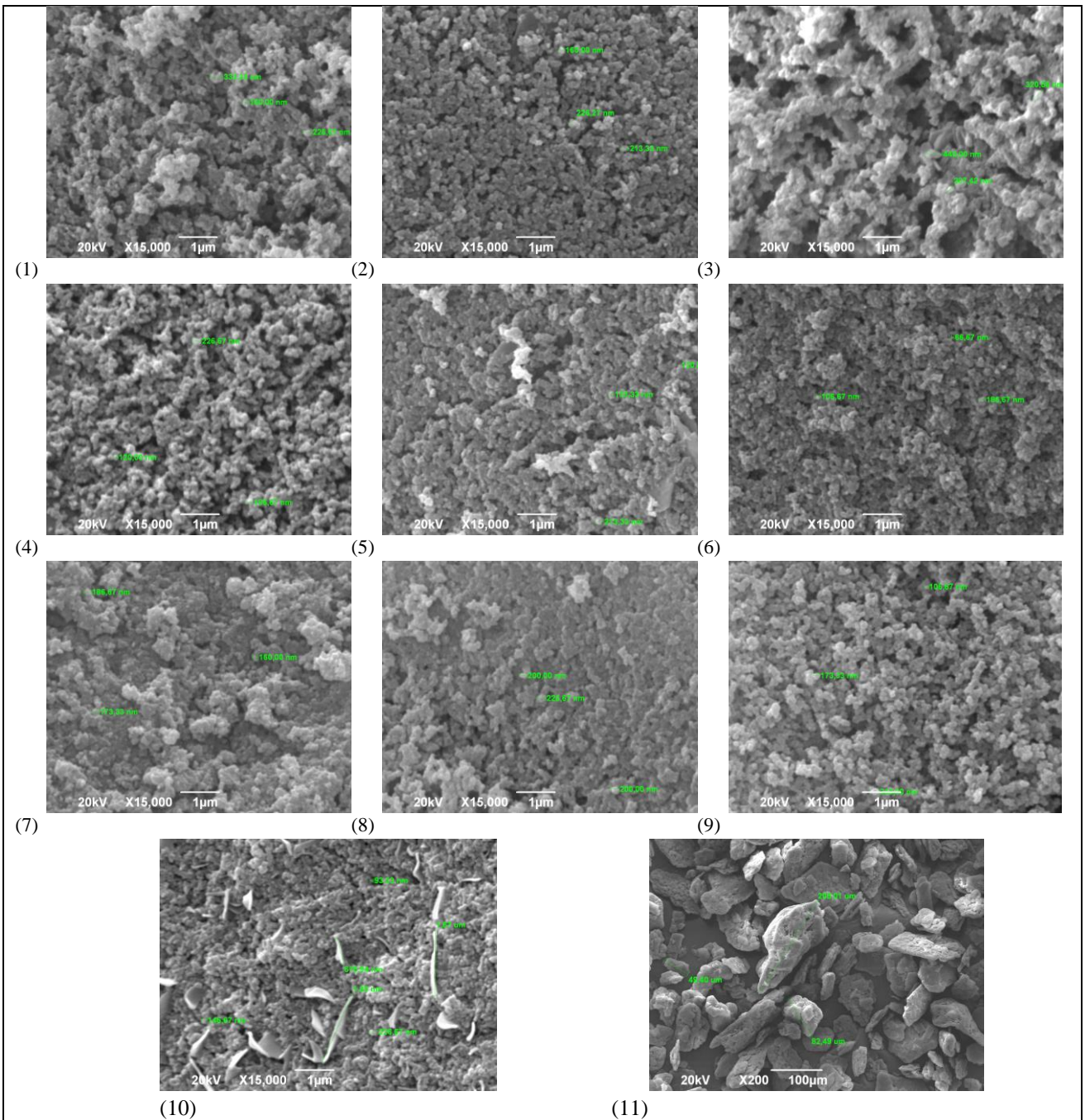
Assays: (1): 1mg$_{ibuprofen}$/mL, 1mL$_{solution}$/min, 1 kg$_{CO2}$/h, 80 bar and 35 ^{o}C; (2):1mg$_{ibuprofen}$/mL, 1mL$_{solution}$/min, 1 kg$_{CO2}$/h, 110 bar and 35 ^{o}C; (3): 1mg$_{ibuprofen}$/mL, 1mL$_{solution}$/min, 1 kg$_{CO2}$/h, 140 bar and 35 ^{o}C; (4): 1mg$_{ibuprofen}$/mL, 1mL$_{solution}$/min, 1 kg$_{CO2}$/h, 110 bar and 45 ^{o}C; (5): 1mg$_{ibuprofen}$/mL, 1mL$_{solution}$/min, 1 kg$_{CO2}$/h, 110 bar and 55 ^{o}C; (6): 0.5mg$_{ibuprofen}$/mL, 1mL$_{solution}$/min, 1 kg$_{CO2}$/h, 110 bar and 35 ^{o}C; (7): 0.5mg$_{ibuprofen}$/mL, 1mL$_{solution}$/min, 1 kg$_{CO2}$/h, 110 bar and 55 ^{o}C; (8): 1.5mg$_{ibuprofen}$/mL, 1mL$_{solution}$/min, 1 kg$_{CO2}$/h, 110 bar and 35 ^{o}C; (9): 1mg$_{ibuprofen}$/mL, 2mL$_{solution}$/min, 1 kg$_{CO2}$/h, 110 bar and 35 ^{o}C; (10): 1mg$_{ibuprofen}$/mL, 3mL$_{solution}$/min, 1 kg$_{CO2}$/h, 110 bar and 35 ^{o}C; (11) Commercial sodium ibuprofen (original without processing).

Figure 3. Eletronic micrographs of ibuprofen processed by Supercritical Anti-Solvent (SAS) process and of original sodium ibuprofen (non-processed).
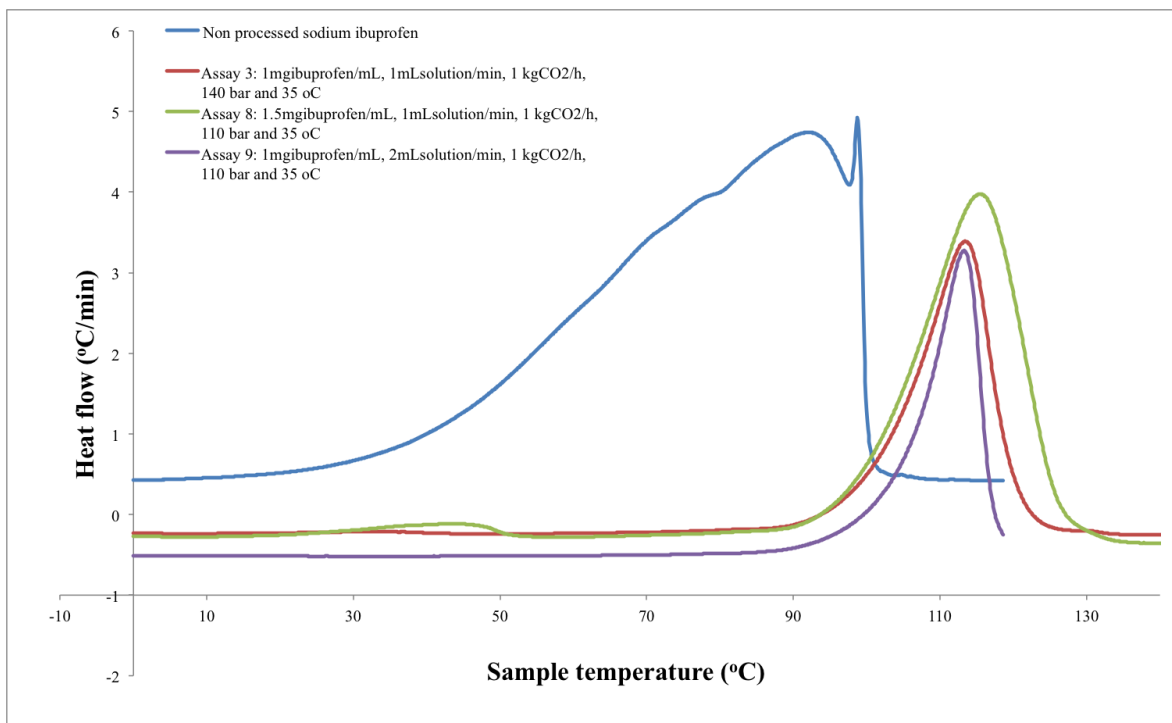
Figura 4. Calorimetry of ibuprofen processed by Supercritical Anti-Solvent process and of original sodium ibuprofen (non-processed)

4. Conclusions

Micronization of ibuprofen was successfully performed by SAS using CO_2 as supercritical solvent. The average particle sizes of the SAS-precipitated ibuprofen were below 380 ± 84 nm for all the conditions tested in the experiments, which means that the size of the original particles was reduced from micrometric to nanometric order. The best SAS operational conditions, in order to produce the lowest ibuprofen particle size, were: 0.5 $mg_{ibuprofen}$/mL, 1 $mL_{solution}$/min, 1 kg_{CO2}/h, 110 bar and 35 ^{o}C. Ibuprofen is poorly soluble in water, and its bioavailability for gastrointestinal absorption is limited by its dissolution rate. Since smaller particle size, or larger surface area, increases the dissolution rate of a drug, it can be concluded that smaller particles produced by the SAS process enhance the bioavailability of ibuprofen. Besides reducing the ibuprofen particle size, the SAS process appears to have purified the original sodium ibuprofen, according to the thermal analysis of processed and non-processed ibuprofen particles.

Acknowledgements

References

[1] D. Kayrak, U. Akman, O. Hortacsu. Micronization of Ibuprofen by RESS, The Journal of Supercritical Fluids 26 (2003) 17-31.
[2] S. Stolnik, L. Illum, S.S. Davis, Long circulating microparticulate drug carriers, Advance in Drug Delivery Reviews 16 (1995) 195-202.
[3] C. Leuner, J. Dressman, Improoving drug solubility for oral delivery using solid dispersions, European Journal of Pharmaceutics and Biopharmaceutis 50 (2000) 47-52.
[4] S.M. Moghimi, A.C. Hunter, J.C. Murray, Long-circulating and targetspecific nanoparticles: theory to practice, Pharmacology Reviwes 53 (2001) 283-290.

[5]   O. Kayser, A. Lemke, N. Hernandez-Trejo, The impact of nanobiotechnology on the development of new drug delivery systems, Current Pharmaceutical Biotechnology 6 (2005) 3-6.

[6]   P. Pathak, M. J. Meziani, T. Desai, Y. Sun. Formation and stabilization of ibuprofen nanoparticles in supercritical fluid processing,The Journal of Supercritical Fluids 37 (2006) 279–286.

[7]   A.I. Cooper, Polymer synthesis and processing using supercritical carbon dioxide. Journal of Materials Chemistry 10 (2000) 207-234.

[8]   I. Kikic, F. Vecchione, Supercritical impregnation of polymers, Current Opinion in Solid State and Materials Science 7 (2003) 399-405.

[9]   D.L. Tomasko, H. Li, D. Liu, X. Han, M.J. Wingert, L.J. Lee, K.W. Koelling, A Review of CO_2 Applications in the Processing of Polymers, Industrial & Engineering Chamistry Research 42 (2003) 6431-6456.

[10] S.P. Nalawade, F. Picchioni, J.H. Marsman, L.P.B.M. Janssen, The FT-IR studies of the interactions of CO_2 and polymers having different chain groups, The Journal of Supercritical Fluids 36 (2006) 236-244.

[11] J.X. Jiao, Q. Xu, L.M. Li, Porous TiO_2/SiO_2 composite prepared using PEG as template direction reagent with assistance of supercritical CO_2, Journal of Colloid Interface Science 316 (2007) 596-603.

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

[13] J. Jung, M. Perrut, Particle design using supercritical fluids: Literature and patent survey, The Journal of Supercritical Fluids 20 (2001) 179-219.

[14] S.D. Yeo, E. Kiran, Formation of polymer particles with supercritical fluids: A review, The Journal of Supercritical Fluids 34 (2005) 287-308.

[15] P.G. Debenedetti, J.W. Tom, S.D. Yeo, Rapid expansion of supercritical solutions (RESS): fundamentals and applications, Fluid Phase Equilibria 82 (1993) 311-318.

[16] P.M. Gallagher, M.P. Coffey, V.J. Krukonis, Gas anti-solvent recrystallization of RDX: Formation of ultra-fine particles of a difficult-to-comminute explosive, The Journal of Supercritical Fluids 5 (1992) 130-142.

[17] J. Thies, B.W. Müller, Size controlled production of biodegradable microparticles with supercritical gases, European Journal of Pharmaceutics and Biopharmaceutis 45 (1998) 67-74.

[18] E. Weidner, Z. Knez, Z. Novak, Int. Pat. Publ. WO 95/21688 (1995).

[19] P. Chattopadhyay, R.B. Gupta, Protein nanoparticles formation by supercritical antisolvent with enhanced mass transfer, AIChE Journal 48 (2002) 235-244.

[20] E. Reverchon, G. Caputo, I.D. Marco, Role of Phase Behavior and Atomization in the Supercritical Antisolvent Precipitation, Industrial & Engineering Chemistry Research 42 (2003) 6406-6414.

[21] N. Elvassore, T. Parton, A. Bertucco, V.D. Noto, Kinetics of particle formation in the gas antisolvent precipitation process, AIChE Journal 49 (2003) 859-868.

[22] M. Hanna, P. York, B.Y. Shekunov, Proceedings of the 5th Meeting on Supercritical Fluids, France, March 23–25, 1998, p. 325.

[23] R. Adami, E. Reverchon, E. Järvenpää, R. Huopalahti. Supercritical AntiSolventmicronization of nalmefeneHCl on laboratory and pilot scale, Powder Technology 182 (2008) 105-112.

[24] M. Charoenchaitrakool, F. Dehghani, N.R. Foster, H.K. Chan. Micronization by rapid expansion of supercritical solutions to enhance the dissolution rates of poorly water-soluble pharmaceuticals. Industrial & Engineering Chemistry Research 39 (2000), 4794-4806.

[25] T.J. Young, S. Mawson, K.P. Johnston, I.B. Henriksen, G.W. Pace, A.K. Mishra. Rapid expansion from supercritical to aqueous solution to produce submicron suspensions of water-insoluble drugs.BiotechnologyProg., 16 (2000) 402-408.

[26] C. Zetzl, G. Brunner, M. A. A. Meireles, Proceedings of the 6th International Symposium on Supercritical Fluids 1 (2003) 577-582.