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 CO₂ (scCO₂) is the most widely used supercritical fluid because of its relatively low critical conditions (T_c = 31.1 °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 scCO₂ 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 scCO₂ and the liquid solution are simultaneously introduced into the high-pressure vessel using a specially designed coaxial nozzle. When the solution droplets contact the scCO₂, 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. Charoenchitrakool 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. Charoenchitrakool 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 morphology, 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 °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 CO₂ 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 (Tescam 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.

**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.
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 °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 CO₂. 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 CO₂ at the operational conditions.

The experiments started by pumping pure CO₂ into the precipitator vessel. When the desired operating conditions (temperature, pressure and CO₂ 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 CO₂ 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 °C and protected from light to avoid the decomposition of the product.

2.4 Particles analysis

Scanning electron 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 micrometric 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.

<table>
<thead>
<tr>
<th>Assay</th>
<th>Ibuprofen concentration (mg/mL)</th>
<th>Solution flow rate (mL/min)</th>
<th>CO₂ flow rate (kg/h)</th>
<th>Pressure (bar)</th>
<th>Temperature (°C)</th>
<th>Average particle diameter (nm)</th>
</tr>
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<tr>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>80</td>
<td>35</td>
<td>240 ± 87</td>
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<tr>
<td>2(a)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>110</td>
<td>35</td>
<td>173 ± 34</td>
</tr>
<tr>
<td>2(b)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>110</td>
<td>35</td>
<td>173 ± 34</td>
</tr>
<tr>
<td>2(c)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>110</td>
<td>35</td>
<td>173 ± 34</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>140</td>
<td>35</td>
<td>380 ± 84</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>110</td>
<td>55</td>
<td>153 ± 47</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>110</td>
<td>45</td>
<td>127 ± 9</td>
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<tr>
<td>6</td>
<td>0.5</td>
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<td>1</td>
<td>110</td>
<td>35</td>
<td>87 ± 28</td>
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<tr>
<td>7</td>
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<td>110</td>
<td>55</td>
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<tr>
<td>8</td>
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<td>1</td>
<td>110</td>
<td>35</td>
<td>209 ± 15</td>
</tr>
<tr>
<td>9</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>110</td>
<td>35</td>
<td>207 ± 47</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>3</td>
<td>1</td>
<td>110</td>
<td>35</td>
<td>156 ± 67</td>
</tr>
<tr>
<td>Original sodium ibuprofen (non-processed)</td>
<td>144 ± 87 (x 10³)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Assays: (1): 1mg_{ibuprofen}/mL, 1mL_{solution}/min, 1 kg_{CO2}/h, 80 bar and 35 °C; (2): 1mg_{ibuprofen}/mL, 1mL_{solution}/min, 1 kg_{CO2}/h, 110 bar and 35 °C; (3): 1mg_{ibuprofen}/mL, 1mL_{solution}/min, 1 kg_{CO2}/h, 140 bar and 35 °C; (4): 1mg_{ibuprofen}/mL, 1mL_{solution}/min, 1 kg_{CO2}/h, 110 bar and 45 °C; (5): 1mg_{ibuprofen}/mL, 1mL_{solution}/min, 1 kg_{CO2}/h, 110 bar and 55 °C; (6): 0.5mg_{ibuprofen}/mL, 1mL_{solution}/min, 1 kg_{CO2}/h, 110 bar and 55 °C; (7): 0.5mg_{ibuprofen}/mL, 1mL_{solution}/min, 1 kg_{CO2}/h, 110 bar and 35 °C; (8): 1.5mg_{ibuprofen}/mL, 1mL_{solution}/min, 1 kg_{CO2}/h, 110 bar and 35 °C; (9): 1mg_{ibuprofen}/mL, 2mL_{solution}/min, 1 kg_{CO2}/h, 110 bar and 35 °C; (10): 1mg_{ibuprofen}/mL, 3mL_{solution}/min, 1 kg_{CO2}/h, 110 bar and 35 °C; (11) Commercial sodium ibuprofen (original without processing).

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

Micronization of ibuprofen was successfully performed by SAS using CO\textsubscript{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\textsubscript{ibuprofen}/mL, 1 mL\textsubscript{solution}/min, 1 kg\textsubscript{CO2}/h, 110 bar and 35 °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

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References