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Nanosizing of sodium ibuprofen by SAS method

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ABSTRACT

The micro/nanosizing of drug particles has been identified as a potentially effective and broadly applicable approach. Sodium ibuprofen is a chiral nonsteroidal anti-inflammatory drug. This work aimed to recrystallize particles of sodium ibuprofen, reducing its particle size, using a Supercritical Anti-solvent (SAS) technique performed in a modified supercritical fluid extraction unit. For this purpose, the phase equilibrium of the system sodium ibuprofen + acetone + CO_2 was also investigated at temperatures ranging from 35 to 55 °C. Phase equilibrium data exhibited solid–vapor–liquid and vapor–liquid transitions. The average particle sizes of the SAS-precipitated ibuprofen were below 380 ± 84 nm for all the SAS conditions tested, reducing the original dimension of the samples from micrometric to nanometric order. The best SAS operational conditions, in order to produce the lowest estimated particle size and higher crystallinity were, respectively, using 0.5 and 1.0 $mg_{ibuprofen}$/mL, and 1 $mL_{solution}$/min, 1 kg_{CO2}/h, 110 bar and 35 °C. The DSC results indicated that, besides reducing the ibuprofen particle size, the SAS process appears to have changed the original sodium ibuprofen to the acid form. The PXRD and RAMAN results indicated that the SAS process at 1 $mg_{ibuprofen}$/mL, 1 $mL_{solution}$/min, 1 kg_{CO2}/h, 110 bar and 35 °C is the best condition to obtain ibuprofen particles with higher crystallinity.

1. Introduction

Ibuprofen is a nonsteroidal anti-inflammatory drug (NSAID) used to reduce fever and to treat pain or inflammation. It is presented in many formulations (powders, capsules, tablets, etc.), and it is available over the counter in most countries as one of the core medicines listed in World Health Organization's "Essential Drugs List" [1].

The nanosizing of drug particles has been identified as a potentially effective and broadly applicable approach. For example, smaller-diameter particles have a faster dissolution rate, with potentially higher activity and easier absorption. Other distinct advantages include tissue or cell-specific targeting of drugs, easier dispersion throughout the body, higher stability against enzymatic degradation, and the reduction of unwanted side effects [2–5]. Disadvantages related to nanoscale drug particles are the difficulty in their production, and also their physical instability, which may lead to particle aggregation, causing problems related to drug storage and administration [3,5]. Traditional techniques for particle size reduction such as mechanical milling and precipitation–condensation present considerable success in the nanosizing of drug particles, but concerns including the broad particle size distribution and the excessive use of organic solvent remain to be addressed [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 material production for pharmaceutical applications [7–12]. Supercritical fluids present low viscosity, permitting matrix penetration as gas-like characteristic; liquid-like density, promoting 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 due to its relatively low critical conditions ($T_c = 31.1$ °C, $P_c = 7.38$ MPa), nontoxicity, nonflammability, 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 because, besides the novelty related to process characteristics, it also accommodates 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) [35], Supercritical Antisolvent (SAS) processes [18–20], and Solution-enhanced Dispersion by Supercritical fluids (SEDS) [21].

In the SAS process, the $scCO_2$ and the liquid solution are simultaneously introduced into the high-pressure vessel using or not a specially

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designed coaxial nozzle. When the solution droplets reach the $scCO_2$, a rapid mutual diffusion at the interface of the droplets and the $scCO_2$ instantaneously takes place, inducing phase separation and supersaturation of the solute in $scCO_2$, leading to its nucleation and precipitation [14]. The supercritical fluid is used both as anti-solvent for its chemical properties and as a 'spray enhancer' by mechanical effects. The temperature and pressure, together with accurate metering of flow rates of solution and supercritical fluid, provide uniform conditions for particle formation. Morphology and particle size of the product (formed particles) can be adjusted by means of the process parameter optimization [13,22].

Considering the cited literature information, this work aimed to recrystallize sodium ibuprofen particles by means of the Supercritical Anti-solvent (SAS) technique performed in a modified/adapted supercritical fluid extraction unit. For this purpose, the phase equilibrium of the system sodium ibuprofen + acetone + CO_2 was also investigated in order to suggest adequate conditions for the precipitation SAS assays. Therefore, the present study also seeks to evaluate the adaptation of the extraction unit to perform a SAS process, by studying the process parameters on the recrystallized particles of sodium ibuprofen.

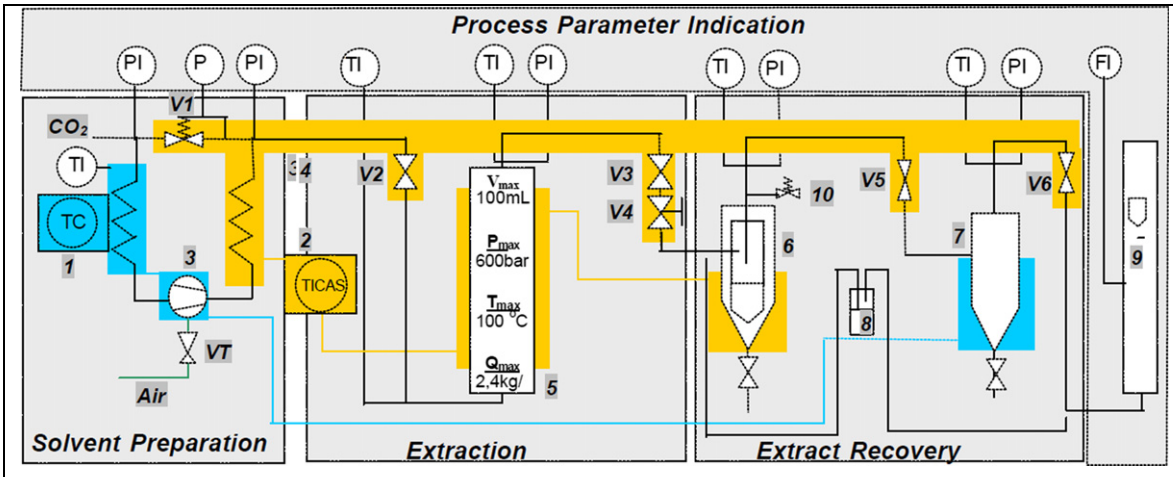
2. Materials and methods

2.1. Materials

Sodium ibuprofen (Sigma Aldrich, Brazil) was used as the solute to perform the precipitation processes and phase equilibrium assays. In order to prepare 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 min) until a complete solute solubilization was reached. The processes 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 (SFE) unit previously detailed by Zetzl et al. [23], and presently shown in Fig. 1, was adapted to perform a Supercritical Anti-solvent (SAS) process. Both techniques (SFE and SAS) require the use of a pump (M111, Maximator, Germany), used to provide the solvent or the antisolvent (CO_2) at the desired high pressure conditions. In order to warrant the correct functioning of the pump, CO_2 must be supplied in liquid form, which requires the use of a heat exchanger (cooler — C10-K10, TermoHaake) (1 from Fig. 1) in order to condense the gaseous fluid from the CO_2 bottle outlet. The oscillation frequency of the piston is controlled by the throttle valve (VT from Fig. 1). The gear ratio of the booster piston is 1:130. The system pressure is controlled by the spring-loaded backpressure regulator (Tescom Cat. nº 26-1761-24-161 — V1 from Fig. 1). The piston sensor opens when the required pressure is reached. Subsequently, the preheated fluid flows from the valve box (4 from Fig. 1) back to the sucking section inside the condenser (1 from Fig. 1). Consequently, the pump continuously produces a compressed CO_2 flow in a closed loop. The closed loop assembly allows constant solvent supply with low-pressure fluctuation. Before and behind 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 from Fig. 1). Changing the original configuration, the extraction/precipitation chamber was heated in a second tempered heating bath, regulated at the operational temperature desired.



1 Cooler (Condenser), CO_2cooling 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

Fig. 1. Flow sheet of the supercritical fluid extraction [23].