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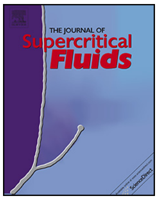

Solid-state property modification and dissolution rate enhancement of tolfenamic acid by supercritical antisolvent process

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ABSTRACT

In this study, the supercritical antisolvent (SAS) process is applied to crystallization of an active pharmaceutical ingredient, tolfenamic acid, using carbon dioxide as the antisolvent. Six operating parameters in the SAS process including solvent system, operating temperature, operating pressure, solution concentration, solution flow rate and nozzle diameter are studied. The effects of operating parameters on solid-state properties of the processed tolfenamic acid including crystal habit, mean particle size and polymorphic form are compared and discussed. The crystal habit of original tolfenamic acid crystals is irregular shape with Form I polymorph. The mean particle size of original powders is about 30 μm. After recrystallization using SAS process, two polymorphic forms of tolfenamic acid with different crystal habits and mean particle sizes are obtained. Form I tolfenamic acid shows a needle-like crystal habit with mean particle size of about 20 μm; while Form II tolfenamic acid shows a rod-like crystal habit with mean particle size of around 10 μm. In addition, the dissolution profiles of original and recrystallized tolfenamic acids are also studied and compared. Experimental results show that the recrystallized Form II tolfenamic acid crystals has an enhanced dissolution rate compared with the original sample, demonstrating that the SAS technology is an efficient process for controlling and modifying the solid-state properties of tolfenamic acid and also produces microparticles with enhanced dissolution behavior.

1. Introduction

The solid-state properties of active pharmaceutical ingredients (API) such as particle size, crystal habit and polymorphic form have been shown to play critical roles in pharmaceutical industry for controlling the dissolution rate, developing suitable administration routes, and designing the appropriate dosage form [1–3]. In conventional API manufacturing process, the solid-state properties of API are frequently controlled by the crystallization process and mechanical milling. However, this conventional route has several disadvantages including residual solvent contamination, batch-to-batch variation and surface property destruction. Thus, in the literature, alternative processes have been designed and developed. Examples of such processes are supercritical fluid crystallization technology, ultrasonic crystallization process and ionic liquid crystallization method [4–9].

Supercritical fluid technology has been widely applied in different fields including extraction, chromatography, chemical reaction and material processing [10,11]. Among these applications, the use of supercritical fluids for the recrystallization of pharmaceutical compounds has been investigated by an increasing number of research groups because of its numerous advantages [12,13]. Depending on the solubility of API in supercritical fluid, different supercritical fluid particle formation techniques have been developed, classified and reviewed. These techniques include rapid expansion of supercritical solution (RESS), supercritical antisolvent (SAS), supercritical assisted atomization (SAA) and particle from gas saturated solution (PGSS) [14], among which SAS and RESS processes are more widely used. In the RESS process, supercritical fluid is used as the solvent while in the SAS process, supercritical fluid is recognized as the antisolvent.

The SAS process is most commonly applied to processing pharmaceutical compounds. For example, Rossmann et al. [15] used the SAS process to manipulate the size, crystal habit and polymorphic form of acetaminophen. The polymorph of acetaminophen crystals

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can be adjusted between monoclinic and orthorhombic by varying the operating parameters. Neurohr et al. [16] used the SAS process to produce the cocrystals of naproxen and nicotinamides, and investigated the effect of initial mixture composition and mixing conditions on production of cocrystals. Sathigari et al. [17] developed a single-step method for deagglomeration of itraconazole microflakes using the SAS process. Su et al. [18] used the SAS process to micronize a steroidal drug, fluticasone propionate, and to overcome the low-yield problem in traditional milling procedure. Chen et al. [19] recrystallized and micronized a sulfa drug, sulfathiazole, to control the mean particle size, polymorphic form and dissolution behavior.

In this study, the SAS process is employed to recrystallize tolfenamic acid for controlling the solid-state properties of mean particle size, crystal habit and polymorphic form. Tolfenamic acid is a non-steroidal anti-inflammatory drug for treating symptoms of migraine. In this study, the effect of six operating parameters in the SAS process including solvent system, operating temperature, operating pressure, solution concentration, solution flow rate and nozzle diameter are studied and compared. The solid-state properties of recrystallized tolfenamic acid are examined and discussed. In addition, the dissolution profiles of tolfenamic acid before and after the SAS process are compared to indicate the potential for further practical use.

2. Materials and methods

2.1. Materials

Carbon dioxide with a minimum purity of 99.9% was purchased from Cheng-Feng Gas and used in this study as the supercritical antisolvent. The non-steroidal anti-inflammatory drug, tolfenamic acid ($C_{14}H_{12}ClNO_2$), with a minimum purity of 99% was purchased from Sigma–Aldrich. For screening the solvent system, 13 organic solvents, namely acetonitrile, acetone, dichloromethane, *N*,*N*-dimethylacetamide (DMAC), *N*,*N*-dimethylformamide (DMF), dimethyl sulfoxide (DMSO), ethanol, ethyl acetate, n-heptane, methanol, methyl ethyl ketone (MEK), *N*-methyl-2-pyrrolidinone (NMP) and tetrahydrofuran (THF) were considered. These organic solvents with a minimum purity of 99.5% were purchased from Sigma–Aldrich, Merck, J. T. Baker, or Macron Fine Chemical. All chemicals were used without further purification.

2.2. Apparatus and procedure

Fig. 1 is the schematic diagram of the SAS apparatus. As can be seen, it comprises two HPLC pumps (SSI, series II), one for CO_2 delivery and the other for pumping the tolfenamic acid solution. The CO_2 flow rate was adjusted by the micrometering valve at the exit of the precipitator and measured by a rotameter at ambient conditions. Pressure in the precipitator was regulated by a back pressure regulator (Tescom) and a micrometering valve. The precipitator with volume of 70 mL was immersed in a water bath. A stainless steel frit with pore size of 0.5 μm was installed at the bottom of the precipitator for collecting the product crystals. The temperature control was achieved by immersing the precipitator into a temperature-controlled water bath. The accuracies in pressure and temperature were estimated as ±0.1 bar and ±0.1 K, respectively. A similar experimental design was also used by Hong et al. [20].

The SAS experiment began with delivering supercritical CO_2 and pure solvent into the precipitator until the temperature, pressure and flow rate reached the steady state. The liquid feed flow was then switched from solvent to drug solution. Rapid recrystallization occurred due to the extremely high supersaturation ratio after the drug solution came in contact with supercritical CO_2. When the amount of solution injected reached the desired level, the injection is stopped. Then, the residual solvent inside the precipitator was removed using a supercritical drying process with supercritical CO_2 delivered continuously for about 30 min. After this drying step, the precipitator was depressurized and the particles precipitated on the stainless steel frit were collected for further analyses.

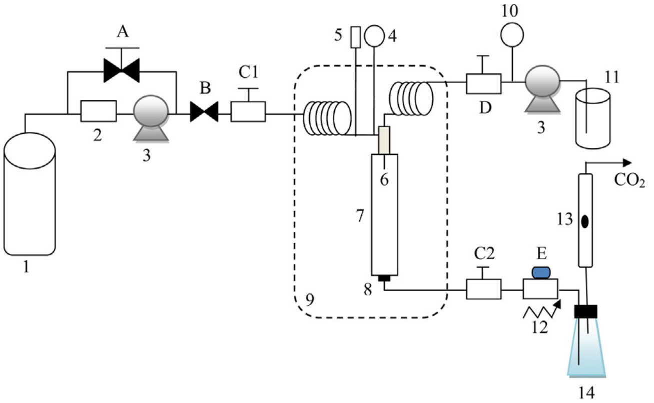

Fig. 1. Experimental apparatus of the SAS process (A: back pressure regulator; B: check valve; C: needle valve; D: ball valve; E: micrometering valve; 1: CO_2 cylinder; 2: cooler; 3: HPLC pump; 4: pressure transducer; 5: thermometer; 6: nozzle; 7: precipitator; 8: filter; 9: water bath; 10: pressure gauge; 11: solution reservoir; 12: heating tape; 13: rotameter; 14: solvent cold trap).

2.3. Analytical method

In order to compare the solid-state properties before and after the SAS process, the generated crystals were analyzed using scanning electron microscope (SEM), optical microscope (OM), powder X-ray diffractometer (PXRD), differential scanning calorimeter (DSC), Fourier transform infrared spectroscopy (FTIR) and thermogravimetric analysis (TGA). To carry out the SEM measurement for comparing the crystal habit, sample of particles were fixed on a conductivity adhesive tape and then sputtered with a thin film of gold. Images of the samples were taken with a SEM instrument (HITACHI, S-3000H). For estimating the particle size of tolfenamic acid crystals, the images of OM were used. For each sample, at least 10 pictures are taken using optical microscope. From these OM images, the mean particle sizes of tolfenamic acid crystals were calculated by counting at least 100 particles using image analysis software. Since needle-like or rod-like particles are produced in our SAS study, the longitude of the rods and needles are used for discussing the mean particles size of produced crystals.

The crystal structures of crystals were detected using the PXRD (PANalytical X'pert) with data collected from 5° to 50° at a scanning rate of 3°/min. To investigate the thermal behavior of crystals, the DSC (PerkinElmer, Jade DSC) and TGA (TA, Dupont 951) were used. For DSC measurement, the samples were heated from 50 °C to 240 °C at a heating rate of 10 °C/min. For TGA analysis, the samples were heated from 50 °C to 680 °C at a heating rate of 20 °C/min. In addition, the spectroscopic property of samples was also confirmed by FTIR (PerkinElmer, Spectrum 100) analysis.

In addition to comparing the solid-state properties of tolfenamic acid, the dissolution profiles of tolfenamic acid before and after the SAS process were also investigated. Dissolution rates of tolfenamic acid were studied in a dissolution tester (Shin Kwang, DT-3) using the paddle method [21]. The dissolution medium was a 0.2 M phosphate buffer with pH value of 7.4. This buffer solution was kept at 37 °C, and the speed of the paddle agitator was 100 rpm. Tolfenamic acid crystals of 25 mg were added into the dissolution medium. At specific time intervals, 3 ml of liquid was withdrawn and filtrated using a 0.45-μm filter. A UV–Vis spectrometry (Thermo, Evolution