Re-crystallization and Micronization of Sulfaphenazole Using the Supercritical Anti-Solvent Process

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Abstract

Supercritical anti-solvent (SAS) process provides a useful method to re-crystalize and micronize the active pharmaceutical ingredients (API). After the SAS treatment, the particle size of the pharmaceutical compound can be decreased to less than one tenth of its original value. The particle morphology can also change with enhanced pharmaceutical effects.

This study presents our experimental results for the micronization of sulfaphenazole, a sulfonamide drug, using the continuous SAS process. Acetone was used as solvent and supercritical carbon dioxide was used as the anti-solvent. The experimental temperature and pressure were 308 K and 100 bar, respectively. The re-crystallization process was carried out in a stainless steel tube with volume of 75 mL. The micronized sulfaphenazole particles were collected at the bottom of the precipitation cell. The SAS treated particles were analyzed by SEM, DSC and XRD to investigate the micronization effects. It is also observed that the micronized sulfaphenazole showed enhanced dissolution rate in a simulated intestinal fluid.

Keywords: Supercritical anti-solvent (SAS), Micronization, Sulfaphenazole, Dissolution rate.

1. Introduction

Supercritical fluid (SCF) technology is widely employed in materials processing, and the micronization of particles is one of the important topics. The SCF technology has been applied in pharmaceutical processing [1-2] to produce smaller particles with narrow size distribution. Carbon dioxide is the most commonly used SCF owing to its low critical properties and the safety concern.

When supercritical CO_2 is taken as the anti-solvent for particle formation, it is recognized as the supercritical anti-solvent (SAS) method.

In this study, the continuous SAS processes were employed to re-crystalize and micronize sulfaphenazole which is an antibacterial drug. The particle size and morphology of sulfaphenazole after the SAS process were investigated in this study. The dissolution rates of the micronized sulfaphenazole particles were also measured using a simulated intestinal fluid to test its further application in pharmaceutical industry.

2. Experimental section

2.1 Materials

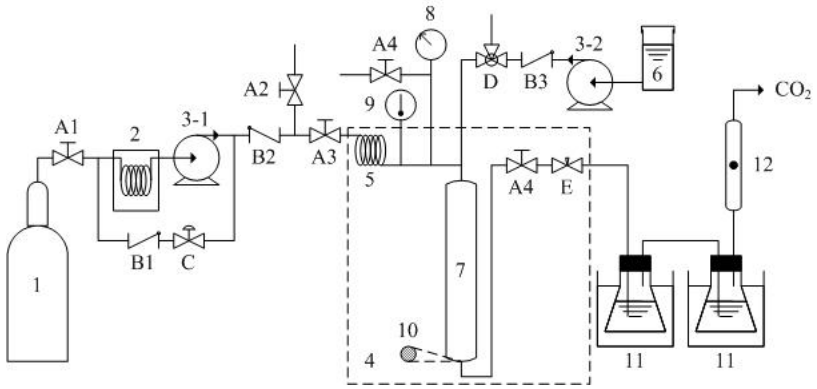
Sulfaphenazole ($C_{15}H_{14}N_4O_2S$) was purchased from Sigma with a purity better than 99 %. Acetone (Merck, 99.8 %) was used as the solvent in this study. Carbon dioxide with a purity better than 99.8 % (San Fu, Taiwan) was used as the anti-solvent. Potassium phosphate monobasic (Sigma, 99.0 %) and sodium hydroxide (Merck, 99.0 %) were used in preparing the dissolution medium to measure the dissolution rate of sulfaphenazole.

2.2 Apparatus and procedures

(a) Continuous SAS process

The schematic diagram of our experimental apparatus is shown in Fig. 1. A high flow rate HPLC pump (SSI, Prep 100) was used to deliver CO_2. A HPLC pump (SSI, series II) was used for pumping the solution of sulfaphenazole. The stainless steel precipitator had a volume of 75 mL. The micronized particles were collected on the frits with pore size of 0.5 μm at the bottom of the precipitator. The flow rate of CO_2 was measured by a rotameter and was adjusted to 4 L/min (measured at the ambient conditions) using the micrometering valve at the exit of the precipitator. The constant operation pressure in the precipitator was maintained by a back pressure regulator (Tescom). The precipitator was immersed in a water bath at a desired temperature. The accuracies for pressure and temperature were controlled at 0.1 bar and 0.1 K, respectively. The continuous SAS experiment was started by delivering supercritical CO_2 into the precipitator until the pressure and flow rate attained the steady values. The solution of sulfaphenazole in acetone was then pumped into the precipitator through a nozzle that was a 20 cm long stainless steel capillary tube with an internal diameter of 127 μm. The solution of sulfaphenazole and the supercritical CO_2 contacted through the coaxial flow in the precipitator. Due to the rapid supersaturation of the solute, re-crystallization and micronization of sulfaphenazole occurred in a short period of time. After the SAS process, supercritical drying using

CO_2 was proceeded for 1 hour to remove the residual solvent inside the precipitator. The precipitator was then depressurized and the particles precipitated on the stainless steel frits were collected for further analyses.



Valve description	Element description		
A : Two way needle valve	1：CO_2 cylinder	5：Pre-heater	9：Thermometer
B : Check valve	2：Cooler	6：Solution reservoir	10：Stainless frit
C : Back pressure regulator	3：HPLC pump	7：Precipitator	11：Solvent trap
D : Three way ball valve	4：Water bath	8：Pressure transducer	12：Rotameter
E : Micrometering valve			

Fig. 1 Experimental apparatus for the continuous SAS process.

(b) Characterization of products

The scanning electron microscope (SEM, JOEL JSM-5600) was used to examine the morphologies of sulfaphenazole particles. Particle size and its distributions were determined using image analysis software ImageJ [3]. The crystal structures of particles were detected using the X-ray diffractometer (XRD, Philips X'pert diffractometer) where data were collected between $2\theta = 5^{o}$ and 40^{o} with a scanning rate of 5^{o}/min. Thermal behavior of the particles was investigated using the differential scanning calorimetry (DSC, DuPont TA 2010) with a heating rate of 5 K/min.

(c) Dissolution rate measurement

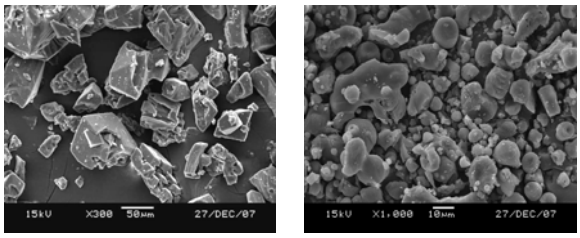
Dissolution rates of the original and micronized sulfaphenazole particles were performed according to the USP paddle method [4]. These experiments were conducted in a dissolution medium of 900 mL. The dissolution medium was a simulated intestinal fluid (pH = 6.8) prepared from an aqueous solution of potassium phosphate monobasic and sodium hydroxide. The temperature of the dissolution medium was kept at 37 ^{o}C, and the speed of the agitator was at 100 rpm. Accurately

weighed samples of sulfaphenazole were added into the suspended basket inside the dissolution medium. A small amount of the liquid was withdrawn over certain time intervals and the dissolved amount of sulfaphenazole was detected using an UV spectrophotometer (Varian Cary100) by measuring the absorbance at wavelength of 249 nm.

3. Results and discussion

3.1 Micronization of sulfaphenazole using the continuous SAS process

Acetone was used as the solvent in this study. The solubility of sulfaphenazole in acetone at room temperature was determined by gravimetric method as 205.10 mg/mL. The experimental temperature and pressure were set at 308 K and 100 bar, solution flow rate and concentration were set at 1 mL/min and 30 % saturation. The SEM images of the original and micronized sulfaphenazole are shown in Fig. 2. The untreated sulfaphenazole showed irregular block mophorlogy with particle size up to 80 μm in Fig. 2(a). After the SAS process, smaller and irregular block particles were obtained as shown in Fig; 2(b). Fig. 3 illustrates the particle size distribution for sulfaphenazole before and after the SAS process. The mean particle sizes for the original and micronized sulfaphenazole were 81.6 and 10.3μm, respectively. It is observed that the particle size after the SAS treatment decreased significantly.



(a) (b)

Fig. 2 SEM images of sulfaphenazole: (a) Original (b) After the SAS process.

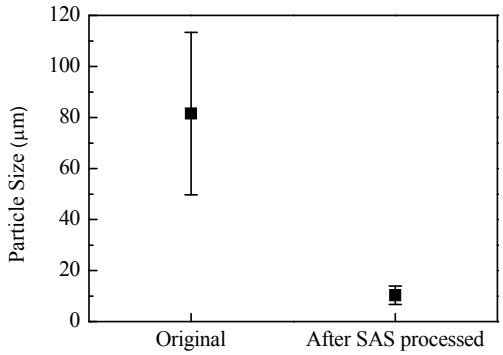


Fig. 3 Comparison of the particle size distribution for sulfaphenazole

The comparisons of the crystal structures for sulfaphenazole before and after the continuous SAS process were examined using DSC and XRD. The DSC results for the original and micronized sulfaphenazole are shown in Fig. 4 where the same endothermic peaks at 185 ^{o}C are observed. The XRD patterns are presented in Fig. 5. Two characteristic peaks at 12.4 ^{o} and 21.0 ^{o} are observed, and the intensity apparently decreased after mocrinzation. From the DSC and XRD results, no polymorphism of sulfaphenazole was obtained at our experimental conditions.

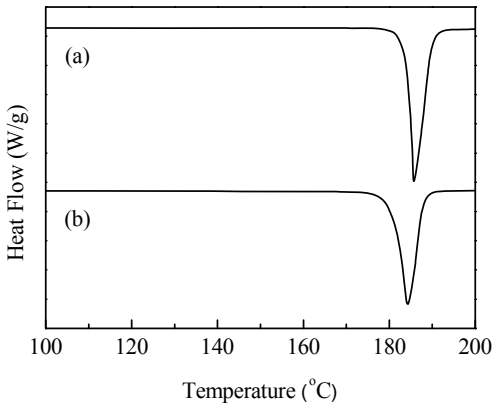


Fig. 4 DSC analysis for sulfaphenazole: (a) Original (b) After the SAS process.

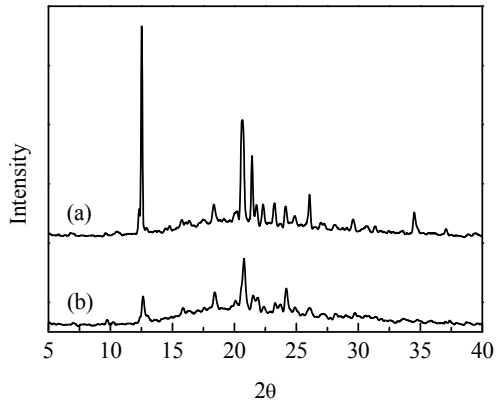


Fig. 5 XRD pattern for sulfaphenazole: (a) Original (b) After the SAS process.

3.2 Results for the dissolution rate of sulfaphenazole

The original and SAS treated sulfaphenazole particles were employed in the dissolution rate test. Modeling and comparison of the dissolution profiles for sulfaphenazole in a simulated intestinal fluid are shown in Fig. 6. In this study, a general empirical equation, the Weibull equation [5], was applied to describe the dissolution profile. This equation is expressed as:

$$m = 1 - \exp\left[\frac{-t^b}{a}\right] \tag{1}$$

where m is the accumulated fraction of sulfaphenazole in the dissolution medium at time t. Two empirical parameters a and b were regressed from the experimental data of the dissolution profile. For the Weibull equation, the dissolution rate coefficient (k_w) can be adopted for comparing the dissolution profile [6]. It is calculated from the model parameters in the Weibull equation:

$$k_w = \frac{1}{\sqrt[b]{a}} \tag{2}$$

In this study, the calculated dissolution rate coefficients for the original and micronized sulfaphenazole were 0.0444 min^{-1} and 0.0169 min^{-1}, respectively. The dissolution rate coefficient of micronized sulfaphenazole is almost 2.6 times higher than that of the original material. This result confirms that the enhanced dissolution rate is attributed to the reduction of the mean particle size from 81.6 to 10.3 μm.

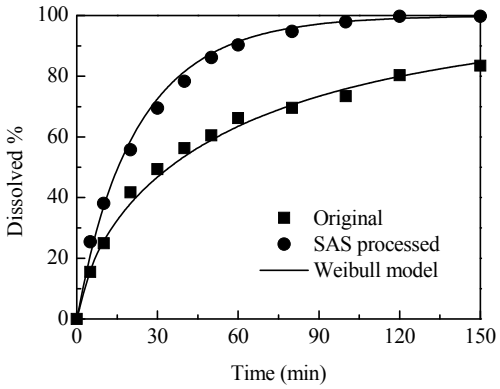


Fig. 6 Dissolution profiles for sulfaphenazole before and after the SAS process.

4. Conclusion

In this study, micronized particles of sulfaphenazole were satisfactorily obtained from the continuous SAS processes. The mean particle size of sulfaphenazole was reduced from its original 81.6 μm to 10.3 μm. Modeling and comparison of dissolution profiles between original and micronized sulfaphenazole in a simulated intestinal fluid were investigated. After the SAS process, the dissolution rate of sulfaphenazole was significantly enhanced about 2.6 times higher than that of the original compound.

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