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Dissolution rate enhancement of sulfamethoxazole using the gas anti-solvent (GAS) process

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ABSTRACT

The aim of this work was to improve the dissolution rate of a poorly water-soluble antibiotic drug, sulfamethoxazole (SMX), by precipitation and co-precipitation with poly(vinylpyrrolidone) (PVP) using the gas anti-solvent (GAS) process. In the precipitation study, the effects of solvent type (acetone, methanol and ethanol), temperature (35, 40, and 45 °C) and percent drug saturation (25, 50 and 75%) on the particle size were investigated using the Box-Behnken design of experiment. It was found that an increase in temperature resulted in a reduction in particle size. Moreover, smaller precipitates were produced when using ethanol as a solvent. An increase in percent saturation of the drug in acetone yielded larger particle size. It was also found that after passing through a 200 mesh sieve the precipitates obtained from the GAS process exhibited a higher dissolution rate than the micronized starting material. In the co-precipitation study, it was found that when using a mass ratio of drug and PVP polymer of 1:1, at 50% drug saturation in methanol and 35 °C, the highest % drug content (50.0%) was achieved. The dissolution rate of the prepared composites was found to be 10 times greater than that of the GAS precipitates.

1. Introduction

Sulfamethoxazole (SMX) is an effective antibiotic drug used for treating a variety of bacterial infections esp., urinary tract infection. According to the Biopharmaceutical Classification System (BCS), SMX is classified as class IV drug. It has low solubility in aqueous solution, low dissolution rate and low permeability in the gastrointestinal tract. It is suggested that sufficient amount of water intake is needed when administrating this drug in order to prevent crystals forming in the urine. Moreover, lower doses should be used for persons with advanced kidney disease.

In order to minimize the drug dosage required but still maintain the drug effectiveness, it is necessary to enhance the dissolution rate of this drug. Various techniques such as micronization or co-precipitation with a hydrophilic polymer are commonly employed to improve the dissolution rate of poorly water-soluble drugs [1–8]. Chang et al. [9] demonstrated that SMX was successfully micronized using the batch and continuous supercritical anti-solvent (SAS) processes. The mean particle sizes for the unprocessed SMX and the precipitates obtained from the batch and continuous SAS processes were 41.7, 41.2 and 5.1 μm, respectively. It was found that the micronized SMX exhibited a higher dissolution rate than the unprocessed drug and 95% of the drug was dissolved after 10 min. With the addition of 10 wt.% of hydrophilic polymer hydroxypropylcelluouse (HPC) in the co-precipitation study, the obtained composites exhibited a significantly higher dissolution rate than the micronized SAS precipitates. To date, however, there is no report on the precipitation of SMX and production of SMX and poly(vinylpyrrolidone) (PVP) composites using the gas anti-solvent (GAS) process.

In this study, the feasibility to micronize the SMX and produce SMX—PVP composites using the GAS technique was investigated. In the precipitation of SMX study, the effects of solvent type (acetone, methanol and ethanol), temperature (35, 40, and 45 °C) and percent drug saturation (25, 50 and 75%) on the particle size were investigated. A design of experiment combined with response surface methodology analysis is employed in this work in order to understand the simultaneous effects of various parameters on the particle size and the interaction between parameters. For a three-level-three-factor design, the Box–Behnken design offers some advantage in requiring a fewer number of experiments compared to other designs such as a factorial design or central composite design [10]. In the co-precipitation study, the effect of drug to polymer ratio (1:1, 1:2 and 1:3) and percent drug saturation (50 and 75%) on the drug content were investigated, while the operating temperature was kept constant at 35 °C or 45 °C. Methanol was selected as a solvent in the co-precipitation study due to its ability to dissolve both drug and polymer reasonably well compared to acetone or ethanol.

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2. Materials and methods

2.1. Materials

Commercial micronized SMX (Bang Trading Thailand, 100% purity) and unprocessed SMX (Fluka, >99% purity) were used as received. Poly(vinylpyrrolidone) (PVP) (MW = 45,000, Fluka, 99.9% purity) was used as received. Acetone, ethanol and methanol were purchased from Italmar (Thailand) Co., Ltd. (>99.5% purity) and used as organic solvents. Carbon dioxide (high purity grade, TIG) was used as an anti-solvent. Potassium phosphate monobasic (Carlo Erba Reagents, 99% purity) and sodium hydroxide (Sigma, minimum 98% purity) were used to prepare the phosphate buffer solution for the dissolution studies. All chemicals and reagents were used without further purification.

2.2. Precipitation of SMX by the GAS process

The schematic diagram of the GAS process for precipitation and production of drug–polymer composites can be found elsewhere [4,11–13]. Precipitation of drug was conducted by charging the vessel (Jerguson sight gauge series no.32) with 5 mL of the drug in organic solvent. The system temperature was controlled to within 0.1 °C using a recirculation heater (Thermoline Unistat 130). Liquid CO_2 was fed to a syringe pump (ISCO model 260D) and delivered through a preheating coil, which was immersed in the water bath. The precipitation chamber was then brought to the desired pressure by passing CO_2 from the pump through a 0.5 μm filter from the bottom. The rate of pressurization was set at 10 mL/min. The pressure of the system was increased up to 90 bar in order to ensure a complete precipitation. Precipitated samples were then washed with CO_2 at 90 bar for approximately 60 mL of CO_2 to remove residual solvent. After washing, the system was depressurized and a sample was taken for SEM and DSC analyses.

2.3. Experimental design for the precipitation of SMX

In this study, the Box–Behnken design of experiment was used to find the optimal conditions for micronization of SMX. The effects of solvent (S), temperature (T), and % saturation (C) on the particle length and particle aspect ratio (Length/Diameter, L/D) of the final product were investigated in this study. Table 1 shows the experimental range and levels of the independent variables used in this study. The MINITAB Release 14 software was used for statistical analysis of the data obtained. The response variables (particle length and particle aspect ratio) were fitted with a linear + interaction model in order to correlate the particle size to the operating variables. The form of the linear + interaction model is shown in Eq. (1) as follows:

$$Y = \beta_0 + \sum_{i=1}^{3} \beta_i x_i + \sum_{i=1}^{2} \sum_{j=i+1}^{3} \beta_{ij} x_{ij} \quad (1)$$

where Y is the particle length or particle aspect ratio, x_i and x_{ij} are the uncoded independent variables, β_0 is a constant and β_i, β_{ii}, and β_{ij} are regression coefficients.

Table 1
Experimental range and levels of the independent variables.

Variables	Symbol coded	Range and levels		
		−1	0	1
Solvent	*S*	Ethanol	Methanol	Acetone
Temperature (°C)	*T*	35	40	45
% saturation	*C*	25	50	75

2.4. Co-precipitation

The procedure for the production of SMX–PVP composites using the GAS process was similar to the drug precipitation. The amount of predetermined SMX and PVP was dissolved in methanol. Five milliliters of the drug–polymer solution was injected to the vessel for each experiment. The precipitation was carried out at 35 °C or 45 °C in order to avoid the polymer glass transition temperature. The obtained composites were then determined for % drug content using UV–vis (Thermo Scientific model Genesys 10S) at the wave length of 261 nm as follows:

$$\%\ \text{drug content} = \frac{\text{mass of the drug in particles}}{\text{total mass of particles}} \times 100\%. \quad (2)$$

2.5. Dissolution studies

Powder dissolution studies were performed using a magnetic stirrer in 900 mL of phosphate buffer solution at pH 7.4, 37 °C and 200 rpm. Accurately weighed samples (approximately 10 mg) were introduced into the dissolution medium. Aliquots (≈4 mL) were withdrawn at certain time intervals and passed through a 0.45 μm filter. The amount of SMX in the withdrawn samples was determined by measuring the absorbance at λ = 261 nm using a UV spectrometer.

3. Results and discussion

Prior to conducting the GAS experiments, the saturation solubilities of sulfamethoxazole in various organic solvents at room temperature were determined by gravimetric method and found as follows: 2.5 g in 10 mL acetone; 0.8 g in 10 mL methanol; and 0.3 g in 10 mL ethanol. The effects of solvent type, temperature and percent saturation on the precipitates were then investigated using the Box–Behnken design of experiment. The morphology of SMX precipitated by the GAS process within the range of conditions studied was found to be rectangular in shape. Fig. 1 shows the typical morphology of SMX precipitated by the GAS process compared to that of the unprocessed particles. The size of SMX particles was determined by measuring the length and aspect ratio (L/D) of 30–100 particles using the SEM images. Table 2 shows the average particle length and aspect ratio of the precipitates obtained in this study. The particle length of the unprocessed SMX as received from Fluka was found to be 43 ± 11 μm with an average aspect ratio of 1.76, whereas the particle length of the commercial micronized SMX was 32 ± 8 μm with an average aspect ratio of 1.50. It was found that most precipitates obtained by the GAS process were larger than the unprocessed SMX with a broader particle size distribution. As a result, micronization of SMX was not successfully performed using the GAS process. This could be attributed to the fact that the GAS process involved the gradual addition of CO_2 anti-solvent into the system in order to expand the drug solution until the threshold pressure was reached and the drug started to precipitate. The system went across intermediate pressure conditions, resulting in the incomplete mixing and non-uniform nucleation, and thus relatively large particles were obtained [9].

The SMX precipitated from 50% saturation in acetone at 45 °C was used as a representative sample for thermal property analysis, since at this condition the size of the precipitates was comparable to the commercial micronized SMX and sufficient amount of the product could be collected. As is illustrated in Fig. 2, similar melting points were observed for the unprocessed SMX and the precipitates obtained by GAS. This observation revealed that the precipitates obtained after the GAS process were still the SMX particles whose crystal structure remains unchanged. However, the heat of melting obtained from the DSC analysis for the precipitates was found to be 151.9 J/g, which was higher than those of the unprocessed drug and the commercial