



## Short communication

## Gas anti-solvent processing of a new sulfamethoxazole–L-malic acid cocrystal

Rawin Imchalee<sup>a</sup>, Manop Charoenchaitrakool<sup>a,b,\*</sup><sup>a</sup> Department of Chemical Engineering, Faculty of Engineering, Kasetsart University, Bangkok 10900, Thailand<sup>b</sup> Center for Advanced Studies in Nanotechnology for Chemical, Food and Agricultural Industries, Kasetsart University, Bangkok 10900, Thailand

## ARTICLE INFO

## Article history:

Received 26 June 2014

Received in revised form 3 November 2014

Accepted 10 November 2014

Available online 15 November 2014

## Keywords:

Crystallization

Co-precipitation

Cocrystal

Sulfamethoxazole

L-Malic acid

## ABSTRACT

The objective of this work was to enhance the dissolution rate of a poorly water-soluble antibiotic drug, sulfamethoxazole (SMX), by forming cocrystal with L-malic acid (MA) using gas anti-solvent (GAS) process. The effect of SMX to MA mass ratio (2:1, 1.5:1 and 1:1) on drug content and dissolution rate was investigated. The GAS cocrystallization was carried out at 45 °C using the drug concentration of 50% saturation in acetone. It was found that cocrystals produced from SMX to MA ratio of 2:1 had higher drug content than those produced from the ratios 1.5:1 and 1:1. In the dissolution studies, it was found that 90% of SMX in the cocrystals could be dissolved within 4.2 min, whereas the times required to dissolve 90% of the drug in the physical mixtures were 8.2 min (ratio 1:1) and 25 min (ratio 2:1), and up to 28 min for the micronized SMX.

© 2014 The Korean Society of Industrial and Engineering Chemistry. Published by Elsevier B.V. All rights reserved.

## Introduction

In pharmaceutical practice, many drugs exhibit poor solubility in water, thus presenting problems with regards to dissolution and bioavailability [1]. Cocrystallization is a relatively recent technology which is considered as a potential method for enhancing the bioavailability of drugs with low aqueous solubility [2–6]. The formation of cocrystals involves hydrogen bonding between the active pharmaceutical ingredients (APIs) and highly water soluble coformers. The altered properties of cocrystal such as solubility, melting point, crystallinity, hygroscopicity, stability, compression property are highly beneficial for tailoring the properties of an API in drug formulation [7–14]. Many new drug–coformer cocrystals have been explored and synthesized, for examples, itraconazole–L-malic acid [15], itraconazole–succinic acid [16], carbamazepine–cinnamic acid [17], naproxen–nicotinamide [18].

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. Various techniques have been used to increase the dissolution rate of SMX, for

examples, micronization [19], co-precipitation with polyvinylpyrrolidone (PVP) [20]. However, the possibility of cocrystal formation between SMX and L-malic acid (MA) for dissolution rate enhancement has not been reported.

In this letter, the feasibility to synthesize cocrystal of SMX–MA using the gas anti-solvent (GAS) technique was explored. The effect of SMX to MA mass ratio (2:1, 1.5:1 and 1:1) on drug content and dissolution rate was also investigated. Production of SMX–MA cocrystal by a slow evaporation technique was also conducted in order to compare the obtained results.

## Experimental

Commercial micronized SMX (Bang Trading Thailand, 100% purity) and L-malic acid (Acros, 99.9% purity) were used as received. Acetone (Carlo Erba Reagents, 99.9% purity) was used as organic solvent. 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.

The schematic diagram of the GAS process is shown in Fig. 1. Production of SMX–MA cocrystal was conducted by charging the vessel (Jerguson sight gauge series no.32) with 5 mL of the drug and coformer solution in acetone. Three different SMX to MA mass ratios (2:1, 1.5:1 and 1:1) with a fixed drug concentration of 50%

\* Corresponding author at: Department of Chemical Engineering, Faculty of Engineering, Kasetsart University, Bangkok 10900, Thailand.  
Tel.: +66 2 797 0999x1216; fax: +66 2 561 4621.

E-mail address: [manop.c@ku.ac.th](mailto:manop.c@ku.ac.th) (M. Charoenchaitrakool).

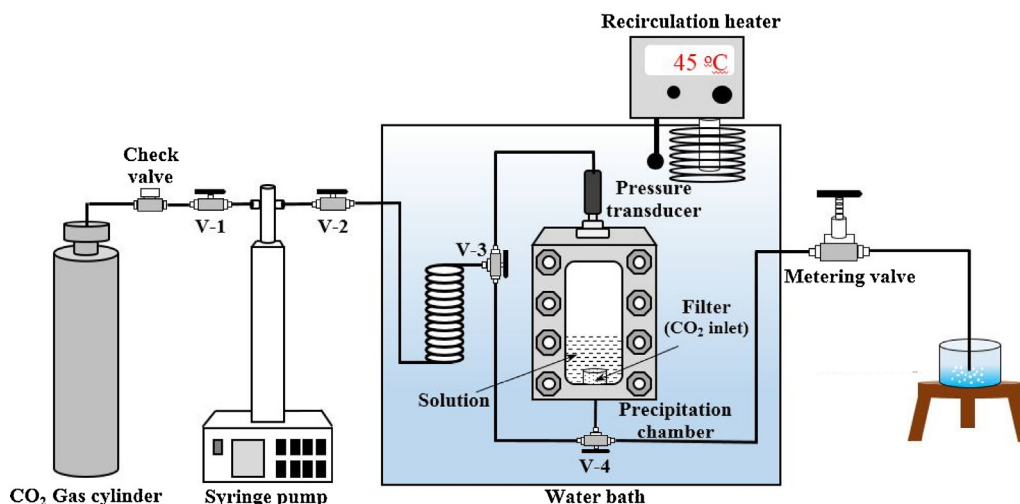


Fig. 1. Schematic diagram of the GAS apparatus.

saturation in acetone were used in this study. The system temperature was controlled to within 0.1 °C using a recirculation heater (Thermoline Unistat 130) and set to 45 °C (note that 45 °C approaches the upper limitation of the water bath material, and from the preliminary studies the cocrystals produced at lower temperatures such as 25 °C and 35 °C had lower dissolution rates compared to 45 °C). Liquid CO<sub>2</sub> was fed to a syringe pump (ISCO model 260D) and delivered through a preheating coil, which was immersed in the perspex water bath. The initial pressure prior feeding to the system was set to be 40 bar for each experiment. The precipitation chamber was then brought to the desired pressure by passing CO<sub>2</sub> from the pump through a 0.5 µm filter from the bottom. The flow rate of CO<sub>2</sub> delivered to the vessel for 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 approximately 80 mL of CO<sub>2</sub> at 90 bar to remove residual solvent. After washing, the system was depressurized and a sample was taken for analyses.

Powder X-Ray Diffraction (PXRD) and Fourier Transform Infrared Spectroscopy (FTIR) were used as the primary means of detecting cocrystal formation. The drug content was determined

using UV–vis at the wave length of 261 nm. The drug content can be calculated using the following equation:

$$\text{drug content} = \frac{\text{mass of the drug in product}}{\text{total mass of product}} \times 100\%$$

Powder dissolution studies were performed in 900 mL of phosphate buffer solution at pH 7.4 and 37 °C, using a magnetic stirrer at 200 rpm. Accurately weighed samples 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 were determined by measuring the absorbance at  $\lambda = 261$  nm using UV spectrometer (Shimadzu, Anthelie advance 5).

## Results and discussion

### Characterization of SMX–MA cocrystal

Prior to the production of SMX–MA cocrystal, independently precipitation of SMX and MA were carried out by GAS. Conditions for the cocrystallization were then selected to give a small difference in the threshold pressures of the drug and cofomer.

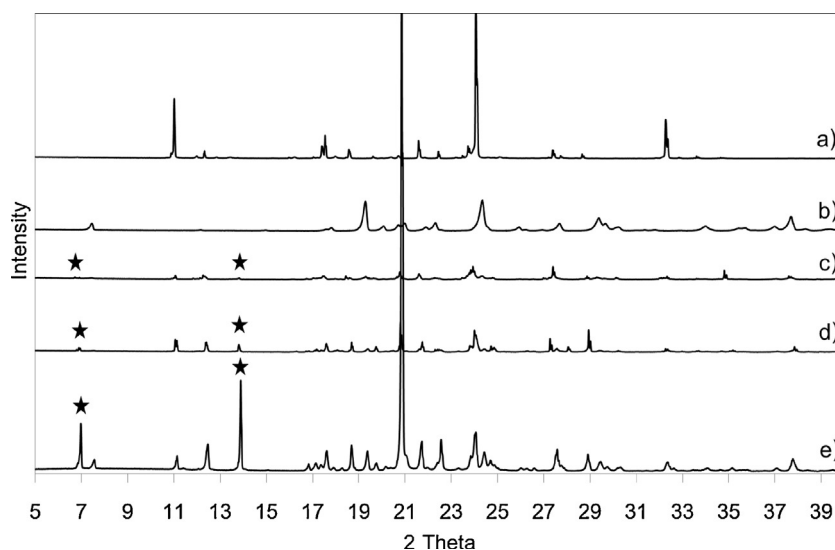


Fig. 2. PXRD patterns of (a) SMX after the GAS process, (b) MA after the GAS process, (c and d) cocrystals by GAS using SMX to MA ratio of 1.5:1; (c) white crystal (d) pale yellow crystal, and (e) cocrystal by slow evaporation using SMX to MA ratio of 1.5:1 (each \* denotes a new peak found in the cocrystal).

Download English Version:

<https://daneshyari.com/en/article/227083>

Download Persian Version:

<https://daneshyari.com/article/227083>

[Daneshyari.com](https://daneshyari.com)