Fluid Phase Equilibria 419 (2016) 24–30

Contents lists available at ScienceDirect

Fluid Phase Equilibria

journal homepage: www.elsevier.com/locate/fluid

Solid–liquid phase equilibrium and ternary phase diagrams of ethenzamide-saccharin cocrystals in different solvents

Yao Tong, Zhanzhong Wang, Leping Dang*, Hongyuan Wei

School of Chemical Engineering and Technology, Tianjin University, Tianjin 300072, PR China

ARTICLE INFO

Article history:
Received 24 November 2015
Received in revised form
28 February 2016
Accepted 29 February 2016
Available online 2 March 2016

Keywords:
Ethenzamide
Cocrystal
Solubility product
Solution complexation
Phase diagram

ABSTRACT

The phase equilibrium for ethenzamide (EA) and saccharin (SAC) in ethanol, isopropanol and ethyl acetate were determined at 298.15 and 308.15 K under atmospheric pressure in this work. In ethanol and isopropanol, the two solutes dissolve incongruently and the diagrams are asymmetric, so excessive EA is required to isolate cocrystals. However in ethyl acetate, EA and SAC exhibit similar dissolution behavior, resulting in larger and more symmetric regions for EA-SAC cocrystal, which would be beneficial to enhance the control of EA-SAC cocrystallization process. In addition, the solubility of EA-SAC cocrystal was correlated by using a mathematical model based on both solubility product and solution complexation. The solubility of EA-SAC cocrystal as a function of SAC concentration was calculated. These new findings are of great importance to control the cocrystallization process of EA-SAC.

1. Introduction

Pharmaceutical cocrystals are stoichiometric molecular complexes which contain an active pharmaceutical ingredients (APIs) and an acceptable cocrystal former in crystal lattice via non-covalent interactions such as hydrogen bond, van der walls force, and π-π interaction [1,2]. Cocrystals can substantially improve the important properties of APIs including physical and chemical stability, solubility, dissolution rate, mechanical property and bioavailability without compromising the structural integrity of the APIs [3].

In general, cocrystals can be screened and prepared by using various approaches including solution crystallization, evaporation, co-grinding, supercritical fluid crystallization and spray drying [4–7]. Among them, solution crystallization has been so far the most industrially-preferred process but suffers from the risk of crystallizing the single component phases because of the complicated parameters involved in the cocrystallization process [8,9]. However in solution crystallization, it has been considered that the relationships between any two equilibria among the three phases are more complicated than common phase diagrams. Furthermore, the phase diagram for a system containing cocrystals is more complex than the general ternary system because the region for cocrystals is usually very narrow and asymmetric due to the different solubility values of APIs and coformer. Therefore, sufficient and exact information of ternary phase diagrams is extremely important for efficiently cocrystal screening and the development of solution crystallization processes [10,11]. In this case, detailed investigation on the solute-solute-solvent phase diagram is very necessary to decide the starting point for solution cocrystallization and avoid forming undesired phase [12].

A typical ternary phase diagram for 1:1 cocrystal A-B is illustrated in Fig. 1. Points a and b are the solubilities of component A and B in the specified solvent, respectively; and points c and d are invariant points where cocrystals and pure crystalline component coexist in equilibrium within the solution. The different equilibrium regions are illustrated as unsaturated solution (L), A + solution (A + L), B + solution (B + L), cocrystal + solution (AB + L), cocrystal + A + a solution of the same composition as point c (A + AB + L), cocrystal + and B + a solution of the same composition as point d (B + AB + L).

Ethenzamide (2-ethoxybenzamide, EA) is an extremely poorly water soluble nonsteroidal anti-inflammatory drug mainly used in combination with other ingredients such as acetaminophen, aspirin, dipyrone, allylisopropylacetylurea, caffeine, and ibuprofen for the treatment of mild to moderate pain [13]. EA has been reported to be capable of giving two known 1:1 cocrystal polymorphs with saccharin (1, 1-dioxo-1, 2-benzothiazol-3-one, SAC), which is a

* Corresponding author.
E-mail address: dangleping@tju.edu.cn (L. Dang).

http://dx.doi.org/10.1016/j.fluid.2016.02.047
0378-3812/

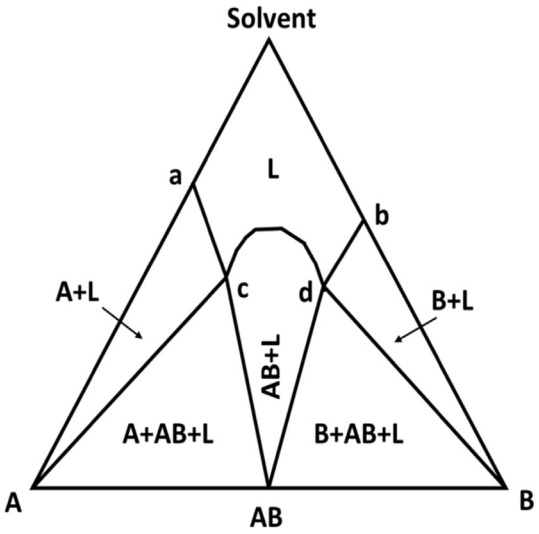

Fig. 1. Schematic ternary phase diagram for a system forming 1:1 cocrystal AB; the stability regions for different crystalline phases are illustrated.

common coformer for pharmaceutical cocrystals [14], and the stable form (named EA-SAC) has been obtained consistently in this study (see Fig. 2). However, to our knowledge, there has been a lack of publication on phase diagram for the EA-SAC cocrystal up to now.

In this paper, phase diagrams of EA-SAC cocrystals in ethanol, isopropanol and ethyl acetate were constructed at 298.15 and 308.15 K under atmospheric pressure. The detail region for forming EA-SAC cocrystals was determined. In addition, the effects of solvent and temperature on solid phase stability were explored systematically. Finally, the solubility behavior of EA-SAC cocrystals was investigated on the basis of a mathematical model considering solubility product and solution complexation.

2. Experimental

2.1. Materials

The EA was purchased from Alfa Aesar. The SAC was purchased from Aladdin Chemistry Co. Ltd. (Shanghai, China). Ethanol, isopropanol and ethyl acetate were purchased from Kewei Chemical Co. Ltd. (Tianjin, China). All the solvents (mass fraction purity >0.995) and chemicals (mass fraction purity >0.990) were used without further treatment. All chemicals were used directly as supplied by the manufacturers without further purification. Mass fraction purity and provenance of the materials are summarized in Table 1.

2.2. Preparation of the EA–SAC cocrystal

The synthesis of EA-SAC cocrystal was conducted by neat grinding, where stoichiometric amounts of EA (100.0 mg) and SAC (110.9 mg) were mixed in a ball mill (MM 400, Retsch, Germany) for 25 min, with a frequency of 30 Hz. Then, the powders were collected for further characterization.

2.3. Determination of the phase diagrams

The phase diagrams were determined by adding excessive EA and SAC into the solvent while varying the EA/SAC ratio from 0 to 1. Experiments were carried out in several 50 ml sealed flasks that were tempered in a constant-temperature water bath with agitation over at least 24 h to make sure that the phase compositions reached thermodynamic equilibrium. The fluctuation of the temperature in the flasks was less than 0.01 K. Then aliquots of solution were withdrawn by a 0.45 μm PTFE filter. The concentrations of EA and SAC in the solution were measured by high-performance liquid chromatography (HPLC), and the solid phase was characterized by powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC) analysis.

2.4. Analytical methods

PXRD experiments were performed using a D/max-2500 diffracometer (Rigku, Japan) at 40 kV, 100 mA with a Cu Kα radiation (λ = 1.54 Å). Data were collected from 2° to 40° in 2θ, with a scan speed of 8° min^{-1}.

Thermal analysis of the solid was carried out by means of DSC (1/500, Mettler Toledo, Switzerland) under protection of a nitrogen atmosphere. Experimental conditions are followed as aluminum crucibles of 40 μL volume, atmosphere of dry nitrogen with flow rate of 150 mL min^{-1}, and heating rate of 10 K min^{-1}.

The solution concentration was analyzed by HPLC equipped with a UV–vis spectrophotometer detector. A C18 column (Extend, 5 μm, 4.6 mm × 250 mm) at T = 298.15 K was used to separate EA and SAC. The eluent phase consisting of 1% w/v glacial acetic acid and methanol with proportions of 39:61, was used with a flow rate of 1 mL min^{-1}. The sample injection volume was 20 μL, and the absorbance of EA was monitored at the wavelength of 280 nm. The calibration was performed as follows. Take the example of saccharin in ethanol, the standard mother solution (2.0 mg/ml) was obtained by adding saccharin (50 mg) to the 25 ml volumetric flask. Then a series of standard solution (0.4, 0.6, 0.8, 1.0, 1.2, 1.4, 1.6, 1.8, 2.0 mg/ml) were obtained by diluting the standard mother solution in the 10 ml volumetric flask using the previous prepared mobile phase. Data collection and processing were performed using the software from Agilent.

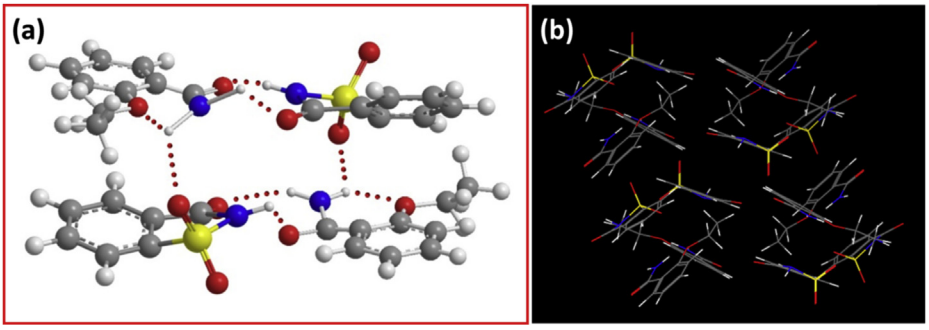

Fig. 2. Diagram of the EA-SAC cocrystal structure.