Reply to "comment on "Trimorphs of a pharmaceutical cocrystal involving two active pharmaceutical ingredients: potential relevance to combination drugs" by S. Aitipamula et al., CrystEngComm, 2009, 11, 1823"

Srinivasulu Aitipamula,*[a] Pui Shan Chow,[a] and Reginald B.H. Tan*[ab]

[a]*Crystallization and Formulation Science, Institute of Chemical and Engineering Sciences, A*STAR (Agency for Science, Technology and Research), 1 Pesek Road, Jurong Island, Singapore, 627833.*

[b]*Department of Chemical & Biomolecular Engineering, National University of Singapore, 4 Engineering Drive 4, Singapore 117576.*

Email: srinivasulu_aitipamula@ices.a-star.edu.sg; reginald_tan@ices.a-star.edu.sg

Electronic supplementary information (ESI)

1. Experimental

a. Preparation of polymorphs

Forms I and III of the EA-GA cocrystal were prepared by solvent-evaporative crystallization experiments. In a typical experiment, 1:1 stoichiometric amounts of EA (1.652 g, 0.01 mol) and GA (1.541 g, 0.01 mol) were dissolved in a minimum amount of solvent (approximately 10-15 ml). While ethyl acetate yielded pure samples of Form I, Form III was obtained from a crystallization experiment using methanol.

In an attempt to explore alternative techniques for preparation of the polymorphs, rotavap method, which has recently been established as a method of choice for selective preparation of metastable polymorphs (*CrystEngComm*, 2011, 13, 5650−5652), was found suitable for preparation of Form II and hence the bulk sample for slurry experiments was prepared by this method. In a typical experiment, EA and GA in 1:1 molar ratio (0.01 mol each) were completely dissolved in methanol (50 ml)

and the solvent was rapidly removed using BÜCHI rotary evaporator at 60 °C, 100 mbar, and 100 rpm. The recoved powder sample was analyzed by PXRD.

b. Slurry experiments

A physical mixture of all the three polymorphs of the EA-GA cocrystal was slurried in deionized water at RT for 24 h. The solid was filtered using vacuum and dried in open air. The resulting dried powder was analyzed by PXRD and DSC.

c. Powder X-ray diffraction (PXRD)

The powder materials of the crystallization, rotavap and slurry experiments were identified by D8 Advance powder X-ray diffractometer (Bruker AXS GmbH, Germany), with Cu-Kα radiation (λ = 1.54056 Å). The voltage and current applied were 35 kV and 40 mA, respectively. Samples were placed on the sample holder of 1mm thickness and 1.5 cm diameter. The sample was scanned within the scan range of 2θ = 5° to 50° continuous scan, with a scan rate of 2 deg min^{-1}. The PXRD patterns were plotted using OriginPro 9.1 and compared with that of the standard materials to confirm the cocrystal identity.

d. Differential scanning calorimetry (DSC)

DSC was performed with a Mettler Toledo DSC 1 STAR^e System. The sample which was recovered from the slurry experiment was placed in crimped aluminium sample pan. The sample size was typically 2–3 mg and analyzed in the temperature range of 30–150 °C @10 °C min^{-1}. The DSC instrument was calibrated using indium as the reference material.

2. DSC analysis

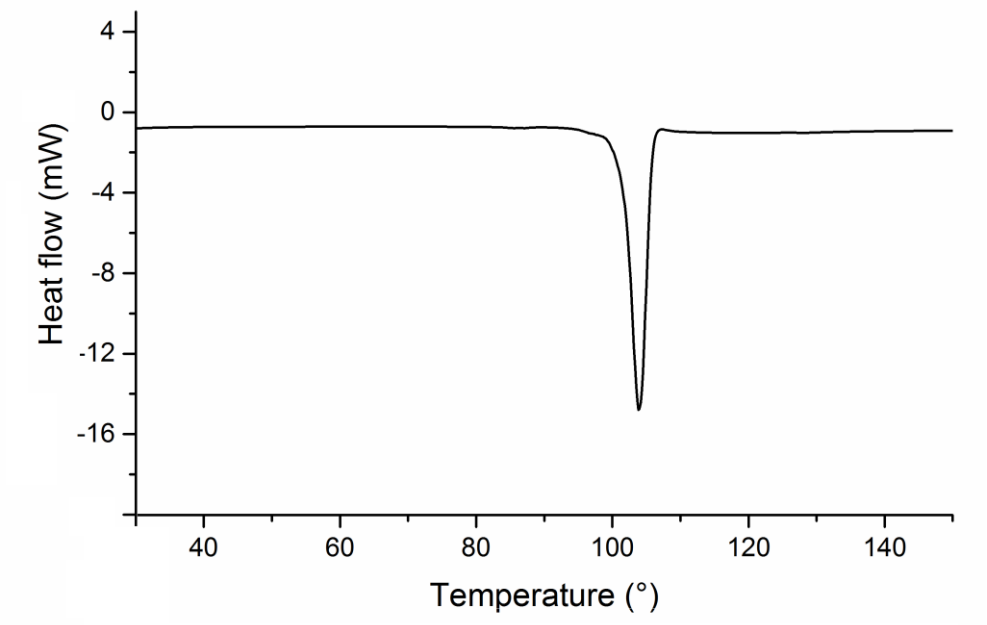

Fig. S1 DSC curve of slurry product from 30-150 °C (melting point (T_{on}) = 101.49 °C). Heating rate was 10 °C min^{-1}.