

Supplementary Information

Self-templating accelerates precipitation of a soluble carbamazepine cocrystal

Hiroyuki Yamashita,^{1, 2} and Changquan Calvin Sun^{2,*}

¹ Analytical Research Laboratories, Technology, Astellas Pharma Inc., Tsukuba-shi, Ibaraki, 305-8585, Japan

² Pharmaceutical Materials Science and Engineering Laboratory, Department of Pharmaceutics, College of Pharmacy, University of Minnesota, Minneapolis, MN 55455, USA

Materials and methods

Material

Carbamazepine (CBZ) (anhydrate, form III, p-monoclinic, the most stable form at r.t.), glutaric acid (GLA), nicotinamide (NCT), ethanol, and acetonitrile were purchased from Sigma–Aldrich (St. Louis, MO, USA). Hydroxypropyl methylcellulose acetate succinate (HPMCAS) MF were received from Ashland (Covington, KY, USA). Potassium phosphate and sodium hydroxide were purchased from Avantor Performance Materials (Center Valley, PA, USA) and Mallinckrodt Chemicals (St. Louis, MO, USA), respectively. Phosphate buffer (pH 6.8) was prepared by

dissolving 68.06 g of potassium phosphate and 8.96 g of sodium hydroxide in 10.0 L deionized water.

Methods

Preparation of CBZ cocrystal

CBZ-NCT and CBZ-GLA cocrystals were prepared following a method previously published.^{1, 2} A physical mixture of 3.85 g of CBZ and 1.95 g of NCT was suspended in 100 mL of ethanol in a covered glass beaker and stirred with a magnetic stirring bar under ambient conditions for 24 h. The resulting solid was then recovered by vacuum filtration and dried in oven at 45°C for 2 h. Similarly, a physical mixture of 4.72 g of CBZ and 1.32 g of GLA was suspended in 50 mL acetonitrile to prepare for CBZ-GLA cocrystal.

Powder X-Ray Diffraction (PXRD)

Powders were analyzed on a powder X-ray diffractometer (D5005, Bruker AXS, Karlsruhe, Germany) with Cu K α radiation (1.54056 Å). Two-theta was calibrated using a silicon standard. Samples were scanned from 5 to 25 or 30° two theta with a step size of 0.02° and a dwell time of 0.5 s/step. The tube voltage and amperage were set at 45 kV and 40 mA, respectively.

Preparation of physical mixture of a cocrystal and a polymer

Physical mixtures (PM) of each cocrystal and HPMCAS was prepared by grinding gently with a mortar and pestle for 30 seconds. Mixtures in three different ratios (w/w) were prepared at 3:1 (25% HPMCAS), 1:1 (50% HPMCAS), and 1:3 (75% HPMCAS).

Intrinsic dissolution rate

The intrinsic dissolution rate (IDR) was measured **in triplicate** using the rotating disc method.^{3, 4} Powder was compressed at a force of 1000 lb, using a custom-made stainless steel die, against a flat stainless steel disc for 2 min to prepare a **round** pellet (6.39 mm in diameter). The resulting pellet had a visually smooth surface that was coplanar with the surface of the die. While rotating at 300 rpm, the die was immersed in 300 mL of the dissolution medium at 37 °C in a water-jacketed beaker. An UV-Vis fiber optic probe (Ocean Optics, Dunedin, FL) was used to continuously monitor the UV absorbance of the solution at $\lambda=300$ nm, which was used to obtain concentration-time profiles based on a previously constructed concentration – absorbance standard curve. This wavelength does not correspond to the peak absorbance of CBZ but it avoids interference from UV absorbance by cofomers.

Analysis of crystal packing similarity

Mercury CSD 3.8 (The Cambridge Crystallographic Data Centre (CCDC), Cambridge, England) was used **to analyze crystal structures**. CIFs of CBZ dihydrate (FEFNNOT03), CBZ-NCT (UNEZES), and CBZ-GLA (MOXVOL) were **obtained** from Crystal Structure Database (CSD). Size of molecular cluster compared was 20 molecules. Geometric tolerances of distance and angle were **set at** 20% and 30 degrees, respectively. Molecular components **other than CBZ** were ignored.

Lattice matching analysis using GRACE

Lattice matching was evaluated using GRACE software (Prof. Ward Research Group, <http://wardresearchgroup.com/ResearchSoftware>) installed on a desktop computer (Windows XP). The parameters used for the calculations were: cut-off distance $d_c = 0.5 \text{ \AA}$, $d_0=0.3 \text{ \AA}$; θ range was from -90° to 90° with increments of 0.5° over a search area of $400 \text{ \AA} \times 400 \text{ \AA}$. The substrate crystal planes of $-1 \leq h,k,l \leq 1$ was surveyed in turn with the range of over layer hkl plane of $-3 \leq h,k,l \leq 3$. For both cocrystals, the (1

1 0) plane had the highest E score (Figure S1). In the cases of (0 1 1) plane in CBZ-GLA and (1 0 1) plane in CBZ-NCT, calculation errors occurred due to the narrow α angle.

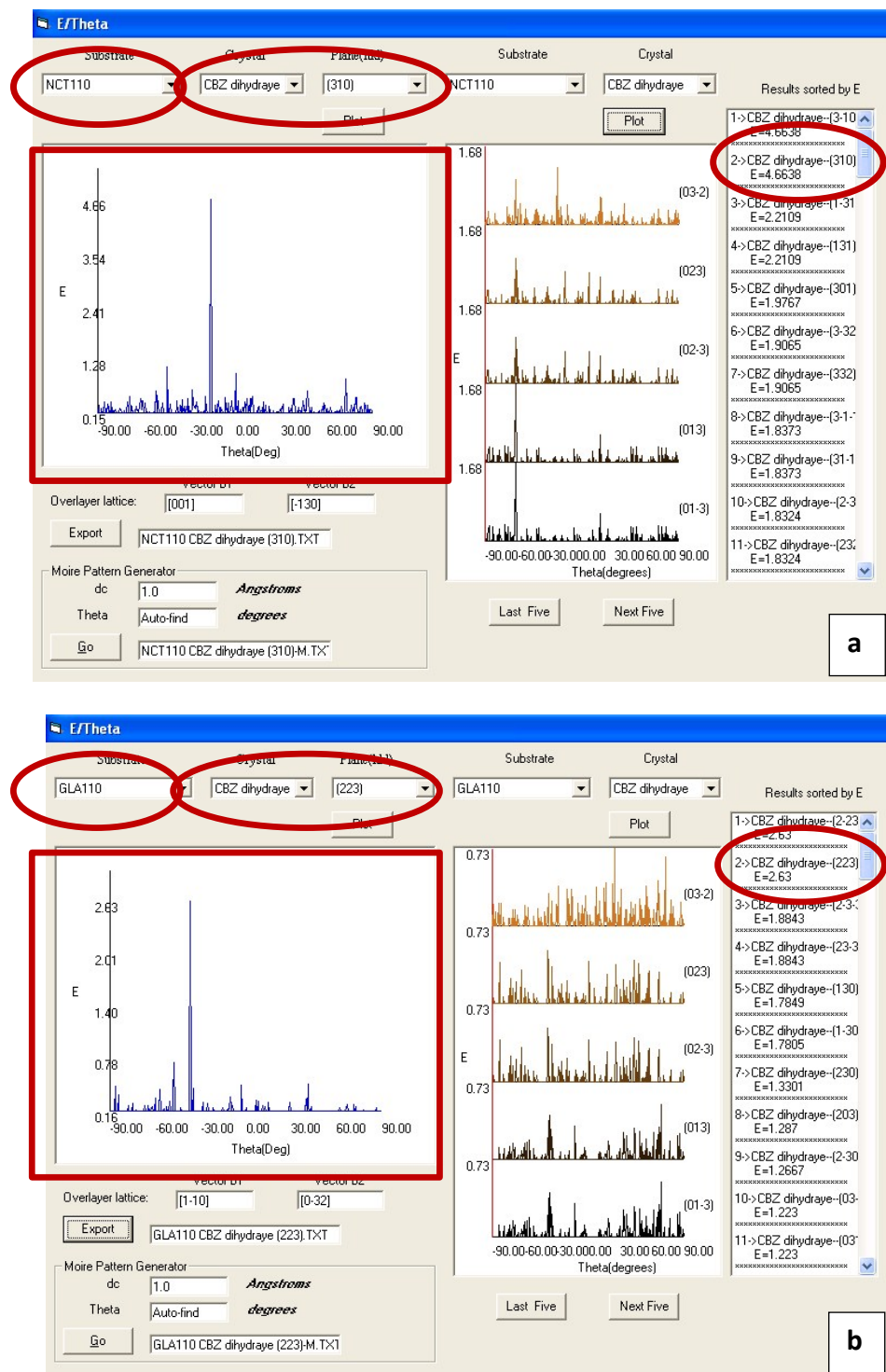


Figure S1. GRACE analysis results for the (1 1 0) planes of a) CBZ-NCT, and b) CBZ-GLA, which yielded the best matching (highest E scores among all planes attempted).

References

1. N. Rodriguez-Hornedo, S. J. Nehru, K. F. Seefeldt, Y. Pagan-Torres and C. J. Falkiewicz, *Mol Pharmaceut*, 2006, 3, 362-367.
2. S. L. Childs, N. Rodriguez-Hornedo, L. S. Reddy, A. Jayasankar, C. Maheshwari, L. McCausland, R. Shipplett and B. C. Stahly, *Crystengcomm*, 2008, 10, 856-864.
3. C. G. Wang, S. R. Perumalla, R. L. Lu, J. G. Fang and C. C. Sun, *Cryst Growth Des*, 2016, 16, 933-939.
4. S. F. Chow, L. M. Shi, W. W. Ng, K. H. Y. Leung, K. Nagapudi, C. C. Sun and A. H. L. Chow, *Cryst Growth Des*, 2014, 14, 5079-5089.