Supporting information for

Cooling Cocrystallization of Acetazolamide & *p*-Aminobenzoic Acid in Continuous Slug Flow Crystallizer

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S1. Materials:

ACZ (CAS number: 59-66-5, purity > 99.8%) procured from Nakoda Chemicals Ltd., Hyderabad, India and PABA (CAS number: 150-13-0, purity ≥ 99%) procured from Sigma-Aldrich, St. Louis, Missouri, USA was used without further purification. Throughout the process, the crystallizing solvent was deionized water (DI), which was generated with Rions Ultra Plus UV/VF (RIONS, India).

S2. Solubility:

Solubility data of ACZ in water are limited in the literature.[1,2] Hence, the solubility of ACZ in water at 5 ˚C was measured through the gravimetric method. The solubility of ACZ and PABA in water at 25 ℃ and 5 ℃ are provided in Table S1.

Table S1. Solubility of ACZ and PABA.

Temperature	ACZ (mg/mL)	PABA (mg/mL)
5 °C	0.35 ± 0.02 (measured)	2.5 ([3])
25 °C	0.72 ([1])	5.3 ([3])

S3. Crystal filtration:

A vacuum filtration assembly was used for filtration of crystals from the mother liquor. For this, a vacuum filter assembly (Glassco, Haryana, India and Tarsons, India) with a cellulose filter paper (Grade 1, Whatman (Cytiva), Sigma Aldrich, Bengaluru, India) was used. Crystals were washed with cold water to wash off any layer of impurities and feed solution. The crystals were then kept for 24-48 hours at 45-50 °C to dry, before further characterization. In case of batch cocrystallization, after crystallization the whole slurry was poured into filter assembly. In case of slug flow crystallization, the filter assembly was connected at the outlet of the crystallizer to

continuously separate the crystals and mother liquor. The filtered crystals were regularly washed and removed for drying while the operation continues.

S4. Crystal Morphology:

The dried crystals were observed under the microscope to determine the shape and size of the crystals. Crystal images were captured using an inverted microscope (Eclipse ti2, Nikon, Japan).

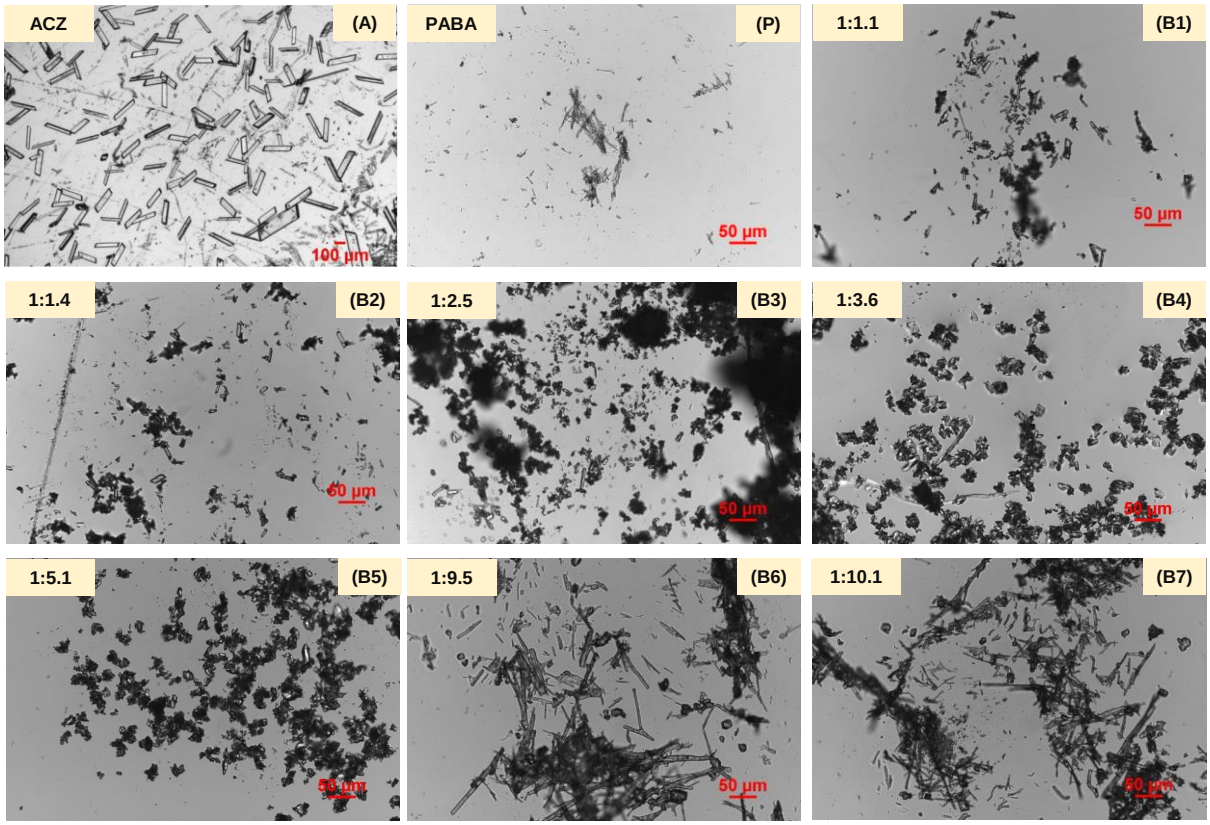

Figure S1: Microscopic images of crystal produced in batch experiments mentioned in table 1. A: pure ACZ, P: pure PABA, B1-B7: batch experiments having different ratio of ACZ and PABA mentioned on top left of each image.

In Figure S1, A and P are the microscopic images of pure ACZ and PABA is for comparison with the crystal produced in the different ratios. Pure ACZ has rectangular block shape crystals while PABA has needle shape crystals. Figure S2, shows the comparison of microscopic images of crystals produced from batch for 1:3.6 and 1:5.1 ACZ:PABA ratio to the crystals produced from CSFC at same ACZ:PABA ratio. Crystals produced through CSFC are larger in size as compared to those obtained from the batch crystallization.

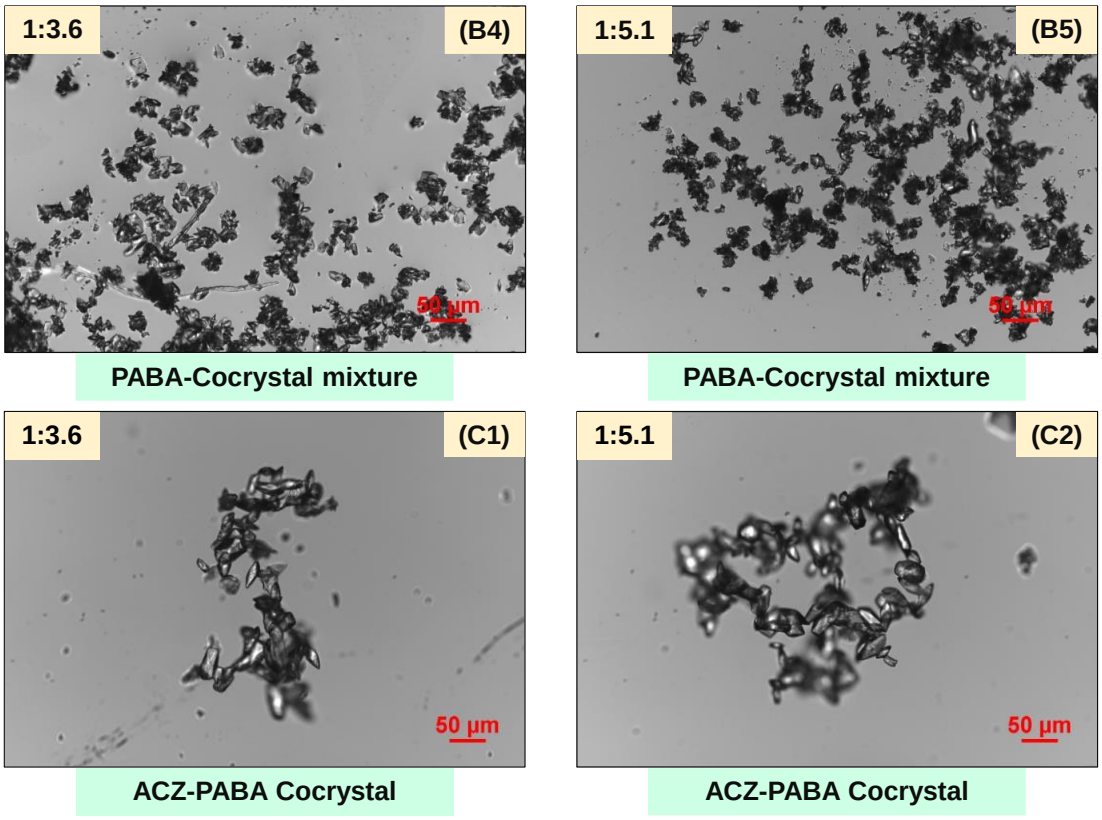

Figure S2: Comparison of microscopic images of crystals produced from batch for 1:3.6 and 1:5.1 ACZ:PABA ratio to the crystals produced from CSFC at same ACZ:PABA ratio. All scale bars correspond to 50 µm length.

S5. Polymorphic purity:

Empyrean X-ray diffractometer (Malvern Panalytical, Malvern, United Kingdom) for Powder X-ray Diffraction (PXRD) measurement with Cu Kα radiation (λ = 1.5406 Å) at 45 kV, 40 mA in the 2θ range of 5-45 at a scan rate of 2 °/min was used to analyze the produced crystals to confirm the polymorphic purity. The filtered and dried crystals were grinded to form a fine powder and this powder then used for PXRD analysis. PXRD pattern of produced crystals and source solute was compared with the simulated PXRD pattern generated utilizing Cambridge Structural Database (CCDC) to confirm the polymorphic purity. Figure S3 shows the PXRD patterns of batch

conditions and their comparison with the simulated PXRD pattern of PABA, ACZ and ACZ:PABA pure cocrystal.

S6. Configuration and working of continuous slug flow crystallizer (CSFC):

The slug flow crystallizer consists of a Tygon tubing (ID = 4.8 mm, Tarsons, India) with a length of 1000 cm. Slugs were produced by using air with the help of an air compressor (Hyco, New Delhi, India) with pressure regulator. Tygon tubing was wrapped around a PVC pipe in a vertical coiled pattern. This coiled tubular crystallizer was immersed in an acrylic bath (290 mm diameter) containing 10 L of coolant (distilled water). Temperature controlled external recirculators (Corio CD-200F, Julabo, Germany) were utilized to provide a continuous supply of chilled water at the required temperature in the acrylic jacket and bath to maintain the crystallizer temperature. Feed solution was pumped through a peristaltic pump (Masterflex L/S Digital Miniflex, Masterflex,

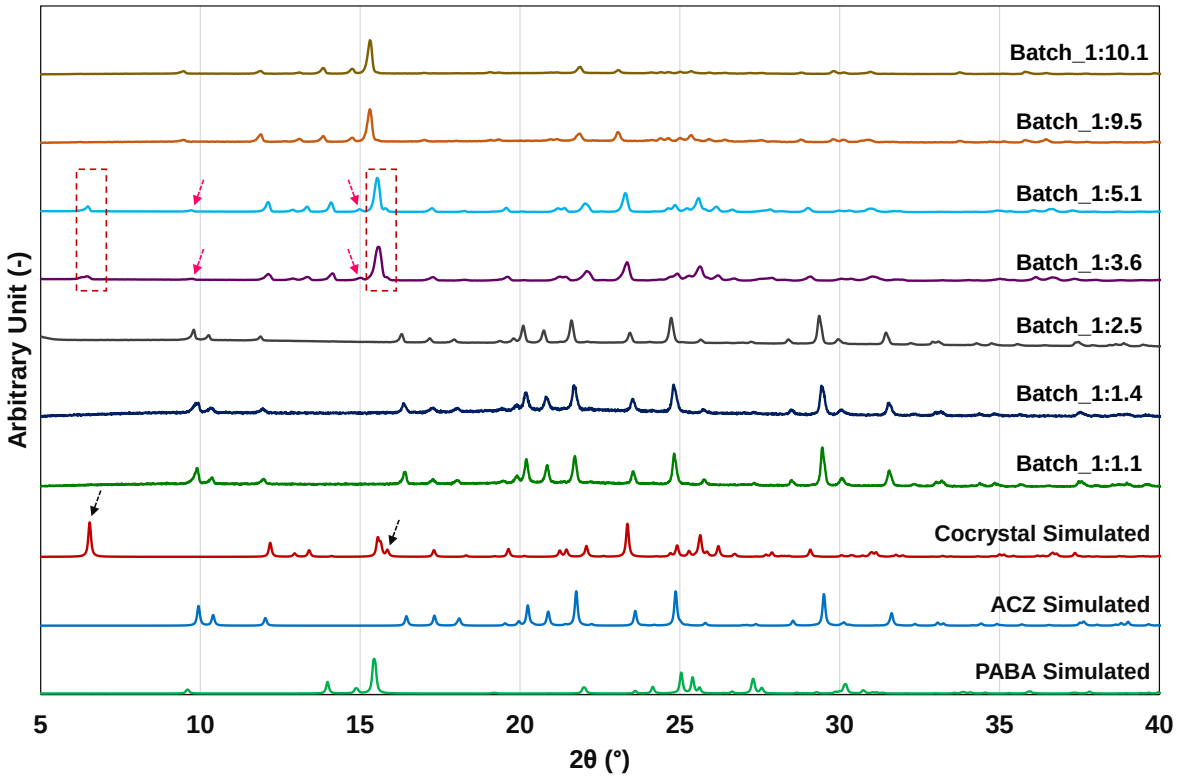

***Figure S3**: PXRD pattern of simulated PABA, ACZ, and pure co-crystal, obtained from CCDC (Cambridge Structural Database ID: AMBNAC01, ATDZSA, and DACBIW01 respectively) and crystals produced through batch for various ratios of ACZ and PABA as mentioned in Table 1. Characteristic unique peaks for pure co-crystals are highlighted with black arrow (simulated) and red dotted box (experimental). And presence of PABA with cocrystal in batch are highlighted with pink arrows.*

USA) and airflow is controlled with a rotameter (Cole Parmer, USA) at different flow rates connected coaxially through a needle (Dispovan, 18 gauge, Hindustan Syringes & Medical Devices Ltd., Faridabad, India) in a T-connector (polypropylene, ID = 4.8 mm, Tarsons, India). All experiments were conducted with the same temperature (5 ˚C) and constant flow rates of feed sample (2 mL/min) and air (15 mL/min). The operating flowrate of feed and air provides a residence time of 15 minutes for each slug inside the tubular crystallizer.

The absolute flow rate of solution sample and air and their relative flow rates were fixed based on a number of preliminary experiments. As the flow rates decrease, the residence time in the crystallizer increases, as the crystallizer length was maintained constant. Additionally, when the flow rates are low, the crystals tend to attach to the tube surface, thereby resulting in encrustation. Further, when the sample to air flow rate ratio increases, the separation between the liquid slugs decrease. At low flow rates, this leads to nearby liquid slugs to join with each other, causing non-ideal back mixing and inconsistent slug flow. However, when high flow rates and low sample to air flow rate ratio are maintained, the slug formation is uniform, the liquid slugs are well separated, and there is no mixing or joining of liquid slugs. Moreover, high flow rates keep the crystals suspended within the liquid slugs and no encrustation is observed within the experimental duration. Hence, near ideal plug flow conditions are observed for the slugs under the CSFC conditions reported in this study.

S7. Crystallization Output:

Each experimental condition was performed at least three times to obtain accurate values and standard deviations. The mass yield is defined as the ratio of the dry mass of the cocrystal produced (crystal mass measured after filtration and drying) to the total mass of the coformers used in crystallization.

Table S2: Consolidated details of the experiments (both batch and CSFC) with quantity of the solutes, experimental conditions, induction and retention times, mass of crystal yield, and the final mass yield.

Expt. No.	ACZ:PABA Ratio	ACZ & PABA Quantity (mg)	Crystallization Conditions	Induction Time (s)	Dry Mass of Crystals (mg)	Mass Yield (%)
A	Pure ACZ	100 mg (ACZ)	**BATCH** Sample volume: 50 ml	869 ± 51	78 ± 0.6	78
P	Pure PABA	250 mg (PABA)		756 ± 81	198 ± 0.6	79

B1	1:1.1	54 & 37 mg	Crystallization Temperature: 5 ± 0.2 °C Stirring: 300 ± 10 RPM	924 ± 70	64 ± 0.4	70
B2	1:1.4	54 & 45 mg		905 ± 30	70 ± 0.3	71
B3	1:2.5	37 & 57 mg		918 ± 70	67 ± 0.4	71
B4	1:3.6	54 & 120 mg		749 ± 25	122 ± 0.4	70
B5	1:5.1	54 & 170 mg		746 ± 50	157 ± 0.6	70
B6	1:9.5	54 & 316 mg		747 ± 56	259 ± 0.4	70
B7	1:10.1	54 & 335 mg		672 ± 85	273 ± 0.3	70
C1	1:3.6	162 & 360 mg	**CSFC** Sample volume: 150 ml Crystallization Temperature: 5 ± 0.2 °C Air flow rate: 15 mL/min Sample flow rate: 2 mL/min	Retention time = 900 ± 6 s (~15 min)	127 ± 0.3	24
C2	1:5.1	162 & 510 mg			166 ± 0.1	25

S8. References:

1 J. Parasrampuria, in *Analytical Profiles of Drug Substances and Excipients*, Academic Press, 1993, vol. 22, pp. 1–32.

2 M. J. Mora, L. I. Tártara, R. Onnainty, S. D. Palma, M. R. Longhi and G. E. Granero, *Carbohydr. Polym.*, 2013, **98**, 380–390.

3 S. Gracin and Å. C. Rasmuson, *Cryst. Growth Des.*, 2004, **4**, 1013–1023.