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Supplementary Information

Controlled isolation and stabilisation of pure metastable carbamazepine form IV by droplet-confinement via a continuous manufacturing route

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1 Materials and Methods

1.1 Materials

Carbamazepine (CBZ initial) (Sigma-Aldrich CAS number: 298-46-4), Methanol HPLC ≥99.9% (Sigma-Aldrich), IC Millex-LG filter 0.2µm certified with hydrophilic PTFE membrane (Merck).

1.2 Solubility Screening

Anhydrous carbamazepine (CBZ) was added to three sample vials containing 10 ml of methanol at room temperature until the solutions were visually saturated. Excess CBZ was added to each vial to ensure the solution would remain saturated at 25 °C. The vials were sealed and placed in the Polar Bear Plus at 25°C with the stirrer speed set at 300 rpm. The vials were monitored for 1 hour to ensure the solutions remained saturated with CBZ. After 48 hours the vials were removed from the Polar Bear Plus and left to settle. Approximately 2 ml aliquots were taken from the surface of each solution. The aliquots were filtered through a 0.2 µm IC Millex-LG filter into three clean, weighed sample vials. The mass of the vials containing the aliquots was recorded. The open vials were placed in the oven set at 50°C for 24 hours. The samples were re-weighed after all the methanol had evaporated and the solubility was calculated. The results are presented in table S1.

1.3 Slow Evaporation Crystallisation

A 3 ml aliquot was taken from a 10 ml sample of methanol containing an excess amount of CBZ. The aliquot was filtered through a 0.2µm IC Millex-LG filter into a clean sample vial. The three vials were covered with parafilm, holes were punched into the parafilm to allow for solvent evaporation. The vials were left under the fumehood at room temperature for 13 days until the sample had air dried.

1.4 Spray Drying

A Büchi B-290 Mini spray dryer coupled with the Büchi Inert Loop B-295 (Büchi Labortechnik AG, Flawil, Switzerland) was used. A closed loop was set up as an organic solvent, methanol, was used. A two-fluid nozzle with 0.7 mm diameter nozzle tip and 1.4mm nozzle cap was used for each experiment in this investigation. Four experiments were conducted using a 50 mg/mL solution of carbamazepine in methanol as per the solubility investigation. The condenser

temperature was fixed at -20°C. The aspirator was set at 100% (35.0 m^3/h 35000 L/h). The pump was set at 5% (1.5 ml/min). The inlet temperature was adjusted to keep the outlet temperature at ~50 °C.

The atomising gas flowrate was the only parameter altered for each run as shown in table 1. The inlet temperature stayed within +/-1°C of the tabulated values during the period of experiment. This was not altered so that each sample formed under same conditions. The flowrate of the feed stock was set at 1.5 ml/min as it is the minimum flowrate that achieves an optimised drying condition for all samples. Three replicate studies were carried out for each droplet size to check the reproducibility of the results.

1.5 Stability Test

In order to check the stability of the spray dried samples, the Amebis Temperature Controlled Cabinet U062 was used as the stability chamber in this investigation. The stability conditions were chosen in line with ICH guidelines for accelerated stability testing at 40 °C with relative humidity at 75% which was maintained using a saturated solution of sodium chloride (1). The saturated solutions of sodium chloride were placed in open vials in four large sample jars that were sealed with lids. The jars were placed in the stability chamber set at 40 °C 24 hours before introducing the carbamazepine samples into the jars to allow the environment to equilibrate.

1.6 Powder X-Ray Diffraction (PXRD)

The crystalline structure of the samples was analysed using an Empyrean diffractometer (PANalytical, Phillips). The diffractometer was used in reflection mode with Cu Kα radiation (λ=1.5406 Å) at room temperature. The tube voltage and current were set to 40kV and 40mA, respectively. The step size used was 0.006565° with a scan speed of 0.027937°/s. Samples were prepared by lightly pressing the powders on a silicon zero-background disc using a glass slide.

1.7 Scanning Electron Microscopy (SEM)

The morphology of the spray dried particles was analysed using a Hitachi SU-70 Scanning Electron Microscope was used in field-free mode. Samples were loaded on two-sided conductive carbon tapes and mounted on the sample holder. The sample was sputter coated with a thin layer of gold in argon plasma under vacuum before being placed in the SEM instrument under vacuum. The stage was set at 10 mm from the lens. An accelerating beam of 5kV was applied to the sample.

1.8 Fourier-Transform Infrared (FTIR) Spectroscopy

In order to analyse the molecular structure of the samples, the Nicolet™ iS50 FTIR Spectrometer Thermofischer is50 was used in the transmission mode. Spectra were obtained across a wavenumber range of 500 cm^{-1} to 4000 cm^{-1} using 64 scans per spectrum.

1.9 Differential Scanning Calorimetry (DSC)

Thermal properties and solid state of the spray dried samples were analysed using a Perkin-Elmer Pyris 1 DSC equipment. Approximately 3 mg of sample were loaded into the hermetically sealed aluminium pan. Samples were heated at 10 °C/min under the nitrogen flow rate of 30 ml/min.

1.10 Particle Size Analysis (PSA)

The ImageJ java-based image processing program was used to analyse the average particle size based on the obtained SEM images. To determine the average particle size for each sample, the diameter of 100 particles was measured.

2 Results

2.1 Solubility Screening

Table S1 *Solubility screening for CBZ int in methanol at 25 °C*

Sample	Methanol
A	0.0757g/ml
B	0.0750g/ml
C	0.0759g/ml
Average CBZ (σ)	0.0755g/ml (0.000473)
Literature	0.0767g/ml (8)

2.2 Powder X-Ray Diffraction

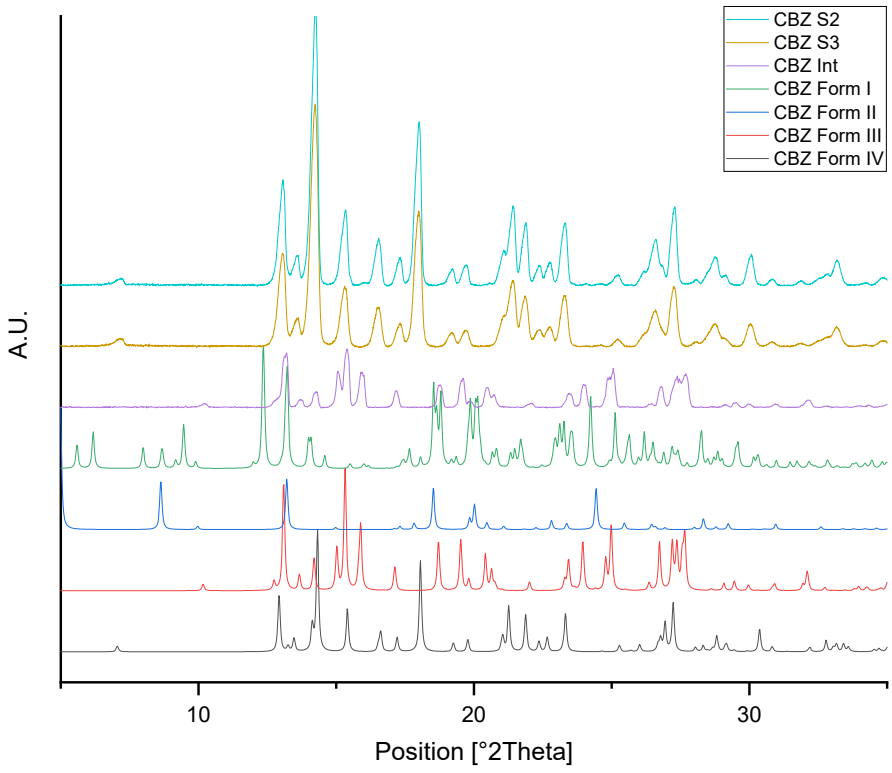

Fig. S1 *PXRD graph of CBZ S2, CBZ S3, CBZ initial (before processing), sample and CBZ polymorphic forms I, II, III, and IV from the CSD.*

According to Cambridge Structural Database (CSD) records, characteristic peaks of form IV obtained are at 2Thetas of 7.0207°, 13.0775°, 14.1800°, 15.2942°, 16.4971°, 17.2471°, 17.8481°, 19.5250°, 21.0090°, 21.3024°, 21.7461°, 22.2956°, 22.6119°, 23.2342°, 23.5265°, 26.4520°, 26.8344° and 27.1406° (2, 3). Characteristic peaks of CBZ form III are obtained at 2Thetas of 10.1438°, 15.8679°, 18.6733°, 20.4313°, 20.7583°, 24.0543°, 25.0827° and 27.7250° (4). Characteristic peaks of CBZ form I are obtained at 5.5699°, 6.1281°, 7.9642°, 8.6776°, 12.3080°, 13.3091°, 13.2031°, 14.0730°, 17.4263°, 18.5375°, 19.9554°, 21.5173°, 23.0754°, 24.1278° (2).

2.3 FTIR

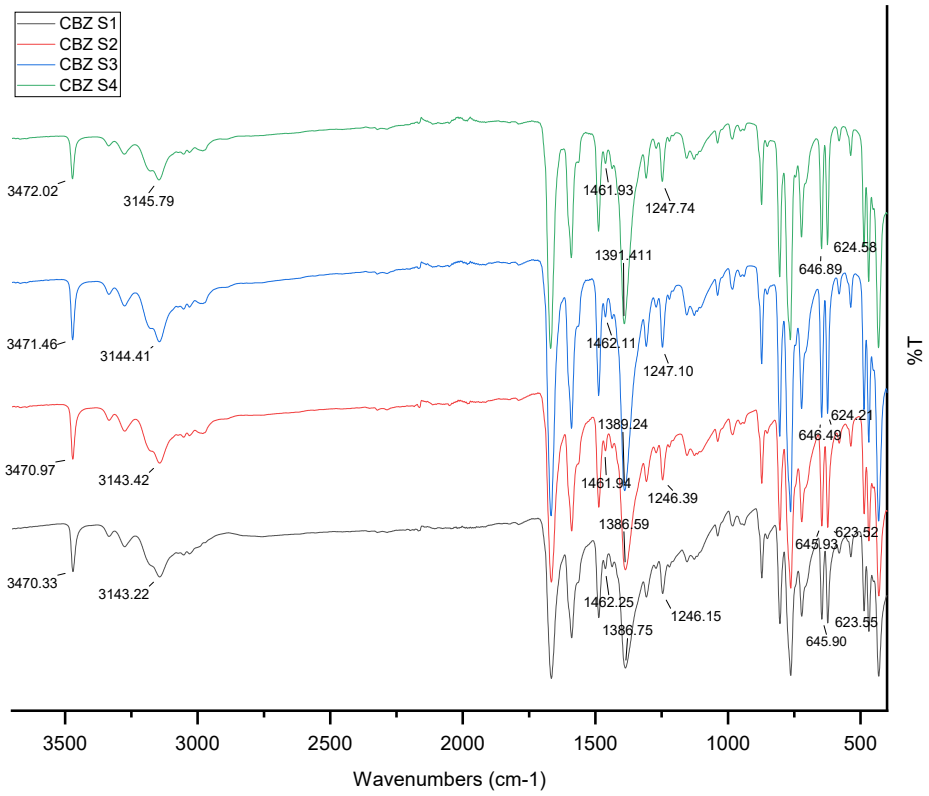

Fig. S2 *FTIR of CBZ S1, CBZ S2, CBZ S3 and CBZ S4*

The IR spectrum of sample S1 confirms the formation of form IV and III in spray dried samples (Fig. S2). Some peaks obtained are characteristic of form III; 1386.75 cm^{-1}, 1307.69 cm^{-1}, 1246.15 cm^{-1} and 623.55 cm^{-1}. Others are characteristic of form IV; 3275.27 cm^{-1}, 3143.22 cm^{-1},1589.43 cm^{-1}, 1487.14 cm^{-1}, 1038.84 cm^{-1}, 872.34 cm^{-1} and 763.23 cm^{-1} (2). For sample S4 with the smallest particle size distributions, only characteristic peaks of form IV are present as follows with the peaks as follows; 3472.02 cm^{-1}, 3276.46 cm^{-1}, 1590.88 cm^{-1}, 1488.03 cm^{-1},

1461.93 cm^{-1}, 1390.99 cm^{-1}, 1308.54 cm^{-1}, 1247.74 cm^{-1}, 1127.52 cm^{-1}, 1039.38 cm^{-1}, 873.19 cm^{-1}, 764.89 cm^{-1}, 722.57 cm^{-1}, 646.89 cm^{-1}, 624.58 cm^{-1}. These results confirm the conclusions made based on PXRD analyses. Table S2 contains explanations for the shifts observed with a comparison between samples S1 and S4.

Table S2 *FTIR shift results*

Literature values	CBZ S1	CBZ S4	Literature explanation
3474 IV 3466 III **(2)** 3472 IV **(5)**	3470.33	3472.26	3467 N-H stretching in primary amine H-bonding (6, 7) N-H in carboxamide group (5)
1463 IV III 1460 II I **(2)**	1462.25	1461.93	C-H stretching C-H C-C (5)
1386 III 1394 IV **(2)**	1386.75	1390.99	1386 C-N amide stretching (6) N-H O-H C-N in carboxamide groups (5)
1246 III 1249 IV **(2)**	1246.15	1247.74	1243 aromatic C-H bending (6) C-H (5)
647 ALL **(2)**	645.90	646.58	646 NH2 bending of all CBZ polymorphs 500-720 Bendings and torsions of the aromatic rings (5) O-H N-H C-H carboxamide (5)
624 I II III 625 IV **(2)**	623.55	624.58	622 NH2 bending of all CBZ polymorphs O-H N-H C-H carboxamide (5)

The transition from a mixture of form III and IV, for larger particles, to pure form IV, for smaller particles, explains the shift observed in positions of specific peaks.

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