Cocrystal Polymorphic Control by Nanodroplet and Electrical Confinement

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Electronic Supporting Information (ESI)

Conventional Spray-drying

Samples produced via conventional spray-drying were generated utilizing a commercial Büchi B-290 mini spray-dryer, described in detail in the literature \cite{1}. The unit contained a 2-fluid nozzle with 0.7 mm cap, which was used for atomization. Solid particles were collected by a high efficiency cyclone. All the powders generated were transferred to a desiccator immediately before their characterization.

Electrospraying

All electrospraying work was carried out on a custom built electrospraying/electrospinning device as shown in Figure S1. The electrospraying units consisted of a 25 ml plastic syringe with a stainless steel metallic needle of 0.43 mm in diameter. A syringe pump was used to continuously push the precursor solution out of the syringe while the syringe needle was connected to a high voltage power supply (Bertan, Series 230). Aluminium foils were ground-connected and used to collect the electrosprayed co-crystals. The foils were positioned at a distance of 14 cm from the tip of the needle.

\textbf{Figure S1:} The electrospraying/electrospinning unit utilised for electro-confinement of the crystallization precursor and a graphic of the process (insert).
**Supercritical CO$_2$ nano spray-drying**

A custom built unit was utilized to nano spray-dry the precursor solution containing CBZ and SAC. Figure S2 represents a schematic of the unit, where supercritical CO$_2$ was produced by pressurizing the gas into a vessel regulated by a metering valve. Gas was compressed by a Teledyne ISCO 260D pump and the pressure was determined using a pressure transducer (Omega model PX603). The CO$_2$ was then allowed to flow into a high-pressure stainless steel storage vessel to reach the set temperature inside the temperature-controlled (monitored by a T-type thermocouple) air chamber. Afterwards, the supercritical CO$_2$ flowed to the high-pressure nozzle in the spray drying apparatus where it mixed with the CBZ-SAC solutions. A coaxial nozzle was used to mix the supercritical fluid and the precursor solution into the precipitator vessel. The products were collected in a filter located at the outlet of the precipitator. All samples were stored in a desiccator prior to characterization.

![Figure S2: Schematic of the supercritical CO$_2$ nano spray-dryer.](image)

**Powder X-ray diffraction**

An X'pert PRO X-ray diffractometer (PANalytical,) with mono-chromatized Cu Kα radiation ($\lambda =$ 0.15405 nm) was used for XRD analysis. The High Score Plus software was used for post analyses. The employed X-ray generator setting was 40 kV and 40 mA. Data were collected over the 2θ range of 5-50°, with a step size of 0.02°.step$^{-1}$ and a step time of 40 s.step$^{-1}$.

**Differential scanning calorimetry**

A PerkinElmer DSC 8500 equipped with a refrigerated cooling accessory (PerkinElmer, Workingham) using nitrogen (30 mL·min$^{-1}$) as the purge gas was used to study all the samples. The instrument was calibrated at heating rates of 5 °C·min$^{-1}$ using high purity indium and zinc to standardise the temperature and heat flow signals. Samples (~5.0 mg) were weighed and placed in crimped DSC pans, then ramped from 20 to 190 °C at 5 °C·min$^{-1}$. Figure S3 shows the DSC profiles of all the
samples generated in this work. Diverse polymorphs show different decomposition energies at different temperatures. For instance, the onset temperature of Form I occurred at 172 \(^\circ\)C, while the onset of Form II at 168 \(^\circ\)C; as shown before in the pertinent literature.\(^2\) In addition there was no indication of residual solvent in any of the CBZ-SAC samples. Figure S3 shows the lack of polymorphic exclusivity and selectivity of the solvent evaporation and the conventional spray-drying methods. Furthermore, the presence of exclusive Form I or II in nano spray-drying and electrospraying is clearly observed.

**Figure S3:** DSC of CBZ-SAC cocrystal samples produced using different methods.

### Fourier transform infrared spectroscopy (FTIR)

A Perkin-Elmer Spectrum 100 FTIR spectrometer was used to obtain the spectra of the samples generated. The spectra was collected at room temperature at wavelengths of 4000–650 cm\(^{-1}\). The samples were placed and 128 scans were collected for each sample at a resolution of 4.00 cm\(^{-1}\). Figure S4 shows the spectra of CBZ-SAC cocrystals synthesized via evaporation and electrospraying from a methanol solution.

**Figure S4:** FTIR spectra of CBZ-SAC cocrystals synthesized via solvent evaporation and electrospraying from a methanol solution.
Electron mapping

The structure of the carbamazepine and saccharin molecules were optimized via Gaussian 09 software package\(^2\). Density functional theory (DFT) was used to optimize the molecular structures. The 6-311 G basis set\(^3\) was applied to all atoms in the optimization process. Avogadro software suit\(^4\) was employed in mapping the electron densities. Ab initio simulations were carried out on Irish Centre for High End Computing (ICHEC).

References