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Elusive seed formation via electrical confinement: control of a novel co-crystal in cooling crystallization

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ABSTRACT

Pharmaceutical co-crystals are multicomponent materials formed to enhance the properties of active pharmaceutical ingredients (APIs); they are commercially used to increase the number of drug candidates that successfully make it through the drug discovery pipeline. Nevertheless, the industrial production of co-crystals and other elusive solid forms remains a challenge. The main limitations are due to challenges related to scale up, solid form control and undesirable parameters needed for the preparation method. This study leverages the features of electrospray crystallization to generate elusive co-crystal forms that contain the APIs acetaminophen (paracetamol) and its regioisomer metacetamol. We report the formation of a new co-crystal, held together by van der Waals interactions and the use of the newly electrosprayed co-crystals as seeds to tune the performance of cooling crystallization, allowing this commonly used crystallization method to produce the elusive co-crystal. The electrosprayed co-crystal displays a previously unseen sponge-

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like surface topology and a fourfold solubility enhancement over that of the single component APIs. This new technology expands the accessibility to new solid forms that were previously inaccessible by other crystallization methods.

1. Introduction

One of the greatest challenges in crystallization is to gain a high level of control over the crystallization process and tune the critical quality attributes (CQAs) of a pharmaceutical product. The solid form of an active pharmaceutical ingredient (API) is of vital importance to the pharmaceutical industry, where the majority of phases within drug development depend on the solid form (structural) and particle attributes. Crystal engineering has been previously used to enhance the physical properties of APIs: from the crystallization of co-crystals [1, 2], solvates [2] and the production of metastable polymorphs. Co-crystals are multi-component solid materials with a neutral crystalline single phase; their composition is generally a stoichiometric ratio between two or more different molecular and/or ionic components and neither of the components are solvates nor simple salts.[3] Pharmaceutical co-crystals are particularly attractive since they can be designed to hold the therapeutic properties of two or more APIs and can have superior physical properties to either of the pure single components.

Crystallization is a thermodynamically driven process that consists of two major events, nucleation and crystal growth. Subtle changes in the crystallization process are routinely used to obtain a thermodynamic pathway that gives rise to unique solid forms such as the type of crystallization

method [4-7], solvent [8] and arguably the most critical method used to optimize the crystallization process, seeding [9]. Crystal seeding describes the addition of a homogeneous or heterogeneous crystal (seed) into the crystallization media to promote nucleation and growth of more crystals of the same solid form as the original seed. Crystal seeding can increase control over the crystallization process, product quality, reproducibility and process efficiency. [10] The major drawback of crystal seeding is often the difficulty of obtaining sufficient seed crystals of the solid form with the desired properties, particularly in the case of elusive solid forms, which can often be metastable. There are few methodologies capable of consistently controlling and isolating specific elusive solid forms such as co-crystals. Previous approaches are generally limited to changing the nature of the solvent, stoichiometry of components [11, 12] as well as the implementation of chemical additives[13]. More recent developments have focused on developing non-conventional crystallization techniques such as confinement. Crystallization under a confined environment (micro/nanometer scale) is a promising method for the formation of metastable polymorphs [6, 14-16]; it has been shown to significantly influence the surface and volume free energies of crystals upon crystallization.[17, 18] This work builds upon the method of confinement with the addition of enhanced molecular mobility upon crystallization through an electro-spraying set-up, termed electrical-confinement.

Electrospraying is similar to the widely utilized pharmaceutical process spray drying; however, it utilizes voltage as the driving force for droplet generation. Electrospraying produces an electro-confined crystallization environment by atomizing the crystallization milieu using electrical forces. The droplets produced during electrospraying are highly charged and are typically in the nanometer range. Figure 1 displays an illustration of the electrospray set up. Previous work has highlighted the capability for producing polymorphs and co-crystals by this method. [4, 19, 20]
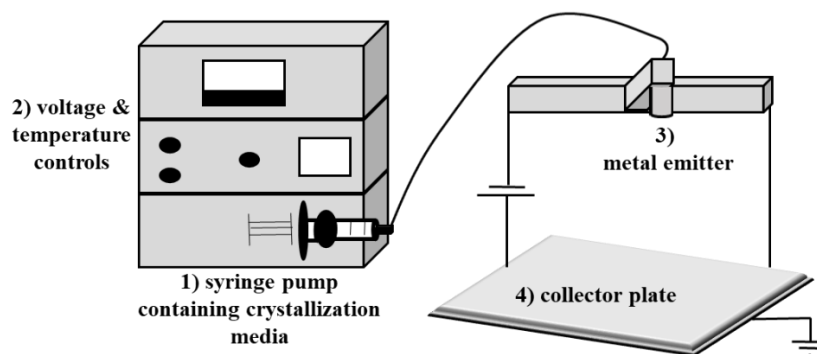
Figure 1. Schematic of the electrospray set up.

This study expands on the capability of electrospraying and highlights its use to produce elusive crystal seeds in an unconventional way. In particular, it was discovered that electrospraying was able to form a novel paracetamol (PCM) / metacetamol (MCM) co-crystal. Figure 2a displays the molecular structure of PCM, an API used to treat moderate pain relief and 2b the structure of MCM, a non-toxic regioisomer of PCM. The electrosprayed co-crystal was then used as crystal seeds in conventional cooling crystallization to yield the new solid form, which otherwise has not been accessed in extensive unseeded conventional crystallisation trials.
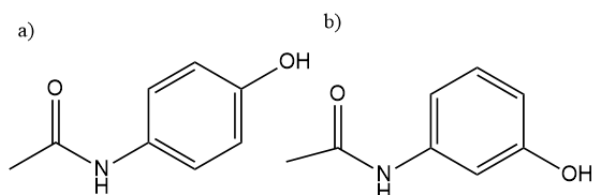
Figure 2. The structure of a) paracetamol and b) metacetamol.

2. Experimental Methods

Paracetamol (Sigma-Aldrich), Metacetamol (Tokyo Chemical Industry) and Isopropanol (VWR) were used as obtained without further purification. Several mixtures of PCM and MCM, with a total weight of 0.75 g, were dissolved in 13 mL of a binary solvent mixture containing isopropanol

(IPA) and water (4:6). As shown in Figure 1, a SPRAYBASE electrospray unit was used to conduct the crystallization experiments. The unit consisted of a syringe pump, which was used to feed the crystallization solution at a set flow rate of 0.5 mL h^{-1}. The solution was sent to a 0.55 mm (I.D.) metallic emitter connected to a power supply. A continuous voltage of 16 kV was supplied to the metallic emitter to atomize the crystallization solution and generate microdroplets. The droplets were electrodynamically sprayed in an environmental chamber held at 40°C and atmospheric pressure. The droplets dried to generate crystals which were collected onto an anodic metallic collector. The distance between the emitter and the anodic collector was 120 mm. The complete details of the electrospray experiments can be found in the Supporting Information (SI Table 1 and SI Figures 1-2).

Seeded cooling crystallization. A Cambridge Reactor Design Polar Bear Plus crystallizer was used to control the heating/cooling profiles and magnetic bottom stirring rates for batch crystallization. A solution containing MCM and PCM (1:1) in a binary solvent system of IPA and water (4:6) was placed into a sealed glass vial. The solution was saturated at 40°C, based on the solubility curves of MCM and PCM (1:1) in IPA and water (4:6) (SI Figure 3). Figure 3 displays the seeded cooling profile used for successful co-crystallisation, Table 2 in the supporting information displays the experimental details for the development and optimization of the seeding protocol. The system was heated to 50 °C at 1°C/min and held for 10 minutes under 700 rpm stirring to ensure complete dissolution of the starting materials. Upon dissolution, the stirring was stopped, and the system was cooled to 40°C at 1°C/min and left to dwell for 1 h to ensure the solution was at the desired starting temperature. The system was cooled to 30 °C at 1°C/min and dwelled for 2 h, then 2 percent of 150 µm crystal seeds were added to the solution after 1 h. Seeds

were prepared from the electrosprayed solid product using a stainless-steel sieve from Endecotts, certified to align to the ISO3310-1 specification. After further cooling to 4°C, again at a cooling rate of 1°C/min, the seeded crystallization media was left for 72 h. The product obtained from crystallization was filtered and dried at room temperature before analysis. Note that PXRD characterization was performed on the solid extracted from the crystallization media at 12, 24 and 72 hours (SI Figure 4).
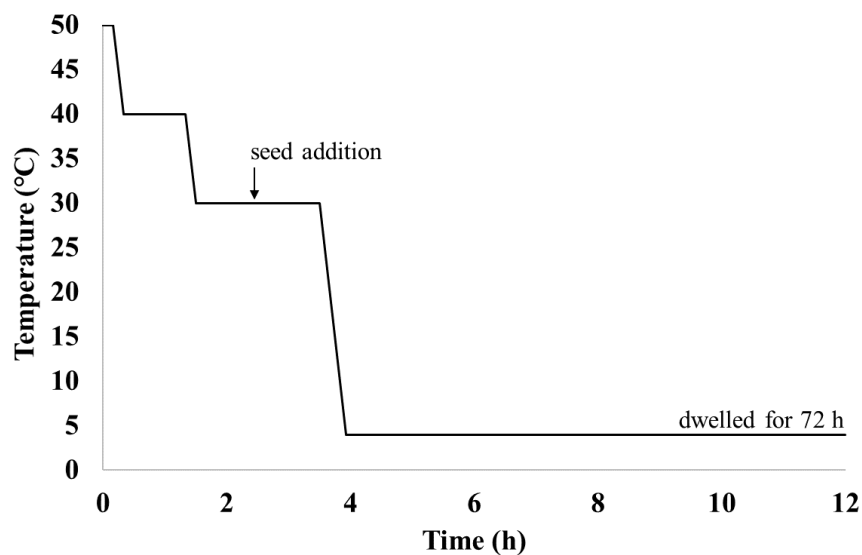
Figure 3. The temperature profile used under seeded cooling crystallization methods for co-crystal production.

Characterization. All samples were characterized by powder X-ray diffraction (PXRD) on a STOE STADIP in transmission mode, with Cu as the X-ray source. Further characterization techniques were used on some of the samples to gain further insights on their structural, thermal and morphological characteristics. These include differential scanning calorimetry (DSC) on a Thermal Advantage Q20 DSC from TA Instruments; scanning electron microscopy (SEM) on a JEOL JSM-6480LV, for which sample preparation was performed on a Edwards 150B splutter

coater; proton nuclear magnetic resonance (^{1}H NMR) on an Agilent Technologies 300 MHz ^{1}H NMR instrument; and single crystal X-ray diffraction (SCXRD) on a Rigaku Oxford Diffraction Gemini A Ultra single crystal X-ray diffractometer, equipped with a four-circle kappa goniometer with a Mo-Kα source of X-rays and a graphite monochromator. Data were collected at 150 K, the temperature was controlled with an Oxford Diffraction Cryostream.

3. Results

Materials consisting of various weight percentages of MCM (0-100%) and PCM (0-100%) were investigated under electro-confined conditions with the electrospray (SI Table 1). A novel 1:1 co-crystal of MCM and PCM was discovered from a 50:50 w/w ratio of the APIs. Other weight percentages yielded a mixture of the starting materials apart from a 75:25 w/w ratio of MCM:PCM, where trace amounts of the MCM:PCM co-crystal were formed amongst starting material. The new co-crystal was confirmed by PXRD (Figure 4) and DSC (SI Figure 5). A significantly lower melting point of 104°C was observed for the MCM:PCM co-crystal in comparison to those of the pure API forms (169°C for PCM and 148°C for MCM). Further characterization via ^{1}H NMR confirmed a 1:1 multicomponent ratio (SI Figure 6). The new co-crystal displayed a surface topology that resembled a sponge (SI, Figure 7), while the other methodologies produced samples with a smooth crystal surface. The electrosprayed particle sponges seem to have a higher surface area, higher porosity, and roughness than those particles produced through alternative methodologies, which should enable faster dissolution and hence release of the active molecules. The solubility of the new co-crystal in IPA: water (4:6) was determined using observational methods, showing a four-fold enhanced solubility of the APIs when compared to PCM-I and MCM-I at 37°C (SI Figure 8). This demonstrates that electrospraying is a technology capable of

influencing the CQAs of small molecules. It is important to mention that although the solubility enhancement, experimentally shown in this work, is a good indicator that the new co-crystal will outperform PCM and MCM in biological settings; this enhancement still requires validation through *in vitro* and *in vivo* tests. Furthermore, the electrosprayed co-crystal was found to be stable after six weeks of being enclosed in a chamber held at a heightened temperature of 70°C and a relative humidity of 70 and 80% (SI Figure 9).

The formation of this new solid form was successfully translated into cooling crystallization, leveraging the elusive crystal seeds gained via electrospraying. Large single co-crystals were obtained via seeded cooling crystallization and characterized by SCXRD to gain crystallographic information, which is displayed in the supporting information (SI Figure 10). Other non-seeded crystallization methods failed to deliver the formation of the new MCM:PCM co-crystal including evaporative, cooling, slurry, vapor diffusion and grinding crystallization (SI Table 2 and SI Figure 11). Beyond the screening experiments carried out in this work, there have been extensive studies on the MCM:PCM system, until now no reports of co-crystal formation have been reported. [21-24] As consequence, we present electrospraying as a unique crystallization technique capable of generating new solid forms that seem unreachable through other crystallization methods. Beyond producing new crystal morphologies, electrospraying can be used for crystal seed manufacture, in this case of a highly elusive co-crystal form not accessible by other methods. In other words, newly electrosprayed crystals can be readily used as seeds and implemented in batch crystallization systems, which are commonly used in industry settings.
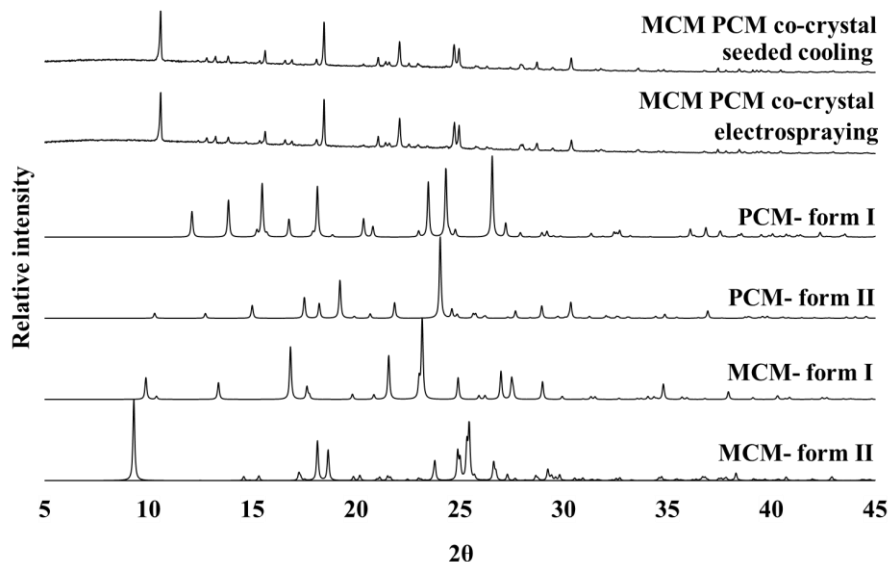
Figure 4. The PXRD pattern of the MCM PCM co-crystal obtained from electrospraying and seeded cooling crystallization, compared against the PXRD patterns of starting material: MCM-II, CSD code = MENSEE04; MCM-I, CSD code = MENSEE; PCM-II, CSD code = HXACAN and PCM-I, CSD code = HXACAN01.

4. Discussion

An overview of a novel electrospray produced MCM PCM co-crystal.

The novel electrosprayed co-crystal has a crystal structure with an asymmetric unit containing one molecule of each API (Figure 5a). The molecular arrangement, displayed in Figure 5b, shows that the PCM molecules pack in a herringbone arrangement sandwiched between MCM molecules that pack in a cross-like arrangement. Likewise, PCM form I packs in a herringbone arrangement as a single entity. In contrast, MCM form I has a zig zag like packing arrangement as a single entity (SI Figure 12).
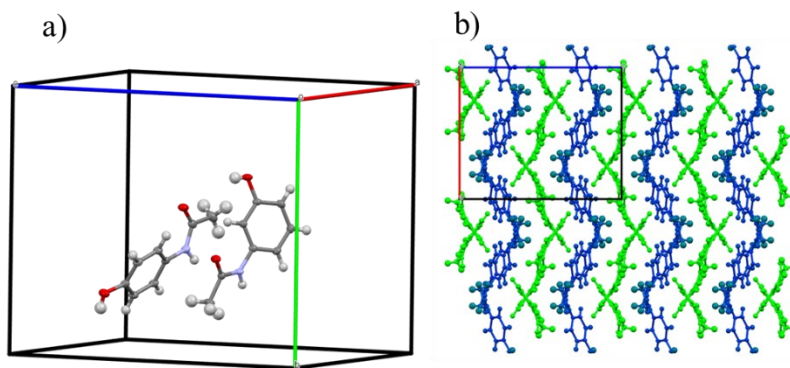
**Figure 5.** The asymmetric unit, within the unit cell (a) and the packing arrangement (b) of the MCM PCM co-crystal viewed along the *b* axis. MCM is highlighted in green and PCM in blue.

Hydrogen bonds are a key intermolecular interaction for most solid forms, including pure PCM and MCM; however, that is not the case for the formation of the new co-crystal. Figure 6 depicts the intermolecular interaction framework for the co-crystal; where two components in the co-crystal are linked by van der Waals interactions. The hydrogen bonding present within the co-crystal, is solely between the single component molecules (PCM-PCM and MCM-MCM), as displayed in SI Figure 13 and 14. Figure 7 displays the hydrogen bond framework between the starting materials - PCM and MCM. Upon comparison, it was observed that the PCM molecules in the co-crystal mimic the framework observed in both PCM form I and II (SI Figure 13) Similarly, the hydrogen bond framework present between the MCM molecules was observed to be similar to a mixture of MCM-form I and MCM-form II.
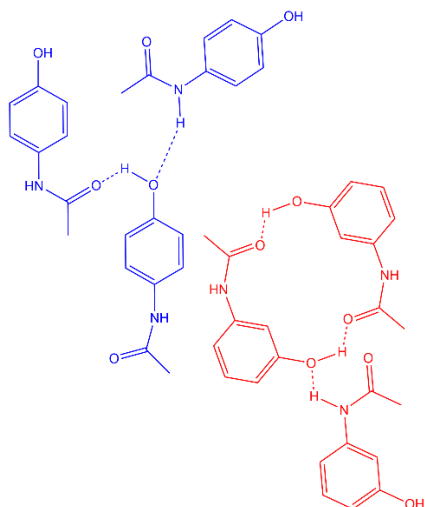
Figure 6. The hydrogen bonding framework in the MCM PCM co-crystal. PCM is highlighted in blue and MCM in red.
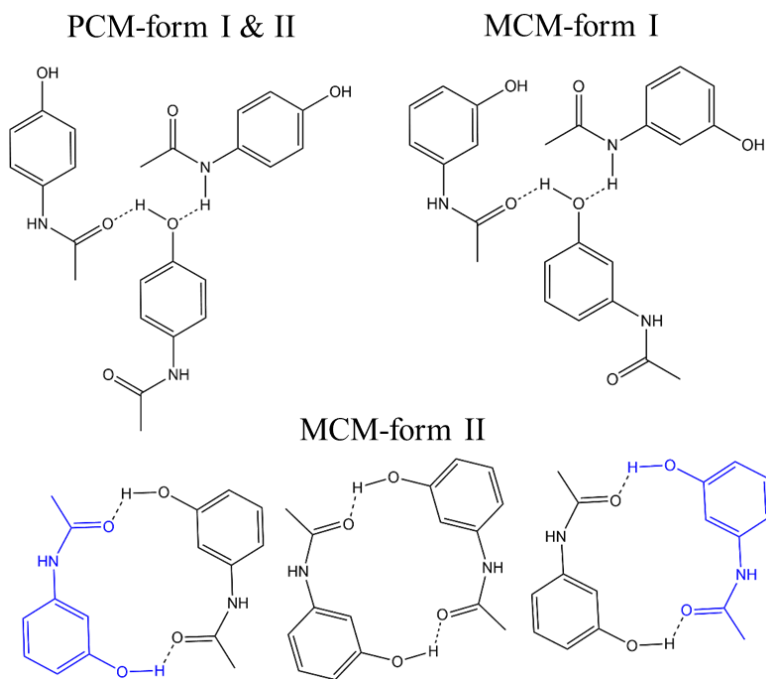

Figure 7. The hydrogen bonding framework for PCM-form I & II (CSD= HXACAN01 & HXACAN), MCM-form I (CSD=MENSEE) and MCM-form II (CSD=MENSEE04). The asymmetric unit cells are shown in black for all forms.

Formation of PCM-MCM co-crystals

Electrospraying is a unique crystallization method that can produce elusive crystal seeds in an unconventional way.[4, 19, 20] We hypothesize that the electro-confined environment allows stabilization of the interaction between the APIs, effectively reducing the probability for hydrogen bond formation. As described by Etter's hydrogen bond formation rules [25], the presence of good proton donors and acceptors is key for hydrogen formation. However, the presence of electrical charges on the surface of each electrosprayed crystallization droplet seems to neutralize the electronegativity of PCM and MCM. The lack of negatively charged proton acceptors inhibits hydrogen formation and enables other intermolecular forces to become relevant. In fact, in this work, the new solid form is structurally held together by van der Waals interactions.

The most common method for co-crystal formation exploits hydrogen bonding interactions, arguably the strongest and most directional intermolecular interaction for crystal structure formation. Another common interaction that drives crystal structure formation is the π-stacking interaction which exploits flat-ring molecular moieties; an interaction dominated by the delocalized electron system that exists between the two components. Co-crystal systems that contain multicomponents unable of interacting by hydrogen bond formation are common, many accounts can be found in the Cambridge Structural Database.[26] However, these systems are mostly reliant on π-π stacking interactions of flat molecular moieties. In this study, a less common multicomponent system linked by van der Waals interactions is observed that does not rely on the π-π stacking interactions of flat molecular moieties. Figure 8 illustrates the simple van der Waals interaction frame that connects the two components in the MCM:PCM co-crystal. Indeed, these results indicate that the addition of molecular mobility and confinement upon electrospraying allows the crystallization media to inhibit the formation of complexes that are built from a framework of stronger intermolecular interactions, such as hydrogen bonds.

The successful translation of electrosprayed co-crystal seeds into cooling crystallization suggests that the proposed technique could be deployed for pharmaceutical manufacturing. Unconventional seed manufacturing technologies – such as electrospraying - could be used for discovering and producing crystal seeds with a quality-by-design (QbD) approach, while seeded conventional methods could then be integrated downstream for large scale manufacturing. In this manner, regulatory agencies could continue using "conventional standards" to evaluate and regulate production, while allowing industry to accelerate product innovation.
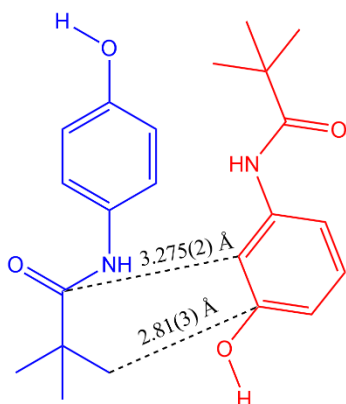
Figure 8. The van der Waals interaction framework in the MCM PCM co-crystal. A C-C short contact of 3.275(2) Å and a H-C contact of 2.81(3) Å is displayed. PCM is highlighted in blue and MCM in red.

Conclusion

Electrospray crystallization was used to yield a novel MCM:PCM co-crystal, a structure in which distinct networks of hydrogen bonded MCM and PCM components are held together by van der Waals interactions. Although various conventional crystallizations methods were implemented to generate this new crystal form, none were able to produce this structure. We conclude that the electric charge used for electrospraying inhibits the electronegative features of proton acceptors, enabling other forces – such as van der Waals interactions – to be the main drivers for structure

formation. Indeed, increasing the diversity of structure directional forces could instill a new wave of pharmaceutical product innovation. Finally, the new electrospray-produced co-crystal was successfully utilized as a crystal seed in cooling crystallization to produce the PCM:MCM form by this seeded method, effectively decoupling crystal nucleation from crystal growth and enabling the rigorous characterization of the new co-crystal.

SUPPORTING INFORMATION

The Supporting Information is available, containing the following: experimental data sets containing process parameters, description of the protocol and outcomes; experimental XRD patterns; solubility curves; DSC profile; ^{1}H NMR spectrum; SEM images; and crystallographic data.

ACKNOWLEDGMENTS

ABBREVIATIONS

CQAs, critical quality attributes; API, active pharmaceutical ingredients; PCM, paracetamol; MCM, metacetamol; IPA, isopropanol; PXRD, powder X-ray diffraction; DSC, differential scanning calorimetry; SEM, scanning electron microscopy; SCXRD, single crystal x-ray diffraction; ^{1}H NMR, proton nuclear magnetic resonance; QbD, quality-by-design.

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TABLE OF CONTENT SYNOPSIS

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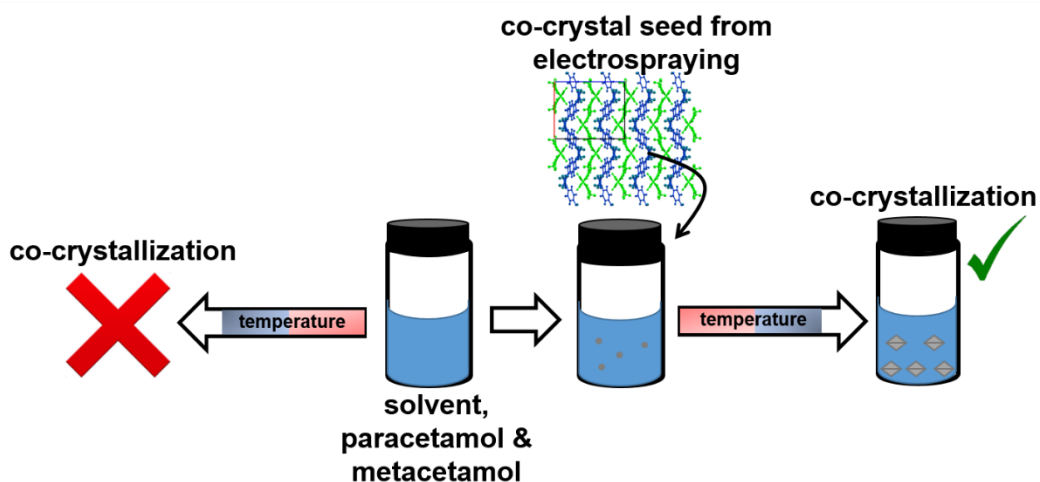
Synopsis: By harnessing the features of electrical confinement, this work shows a new approach to access crystal structures previously inaccessible. An elusive co-crystal was formed and found to be held together by van der Waals interactions, while displaying a sponge-like surface topology and a fourfold solubility enhancement.