Understanding solid-state processing of pharmaceutical cocrystals via milling: Role of tablet excipients

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ABSTRACT

Discovery of novel cocrystal systems and improvement of their physicochemical properties dominates the current literature on cocrystals yet the required end-product formulation is rarely addressed. Drug product manufacturing includes complex API solid state processing steps such as milling, granulation, and tableting. These all require high mechanical stress which can lead to solid-state phase transformations into polymorphs and solvates, or lead to dissociation of cocrystals into their individual components. Here we measured the effect of tablet excipients on solid-state processing of a range of pharmaceutical cocrystal formulations. Our findings were rationalised using Density Functional Theory (DFT) calculations of intermolecular binding energies of cocrystal constituents and co-milling excipients. A 1:1 stoichiometric ratio of API Theophylline (THP) and co-former 4-Aminobenzoic acid (4ABA) was co-milled with five different excipients: hydroxypropylmethylcellulose (HPMC), polyvinylpyrrolidone (PVP), polyethylene glycol (PEG), lactose, and microcrystalline cellulose (MCC). The experiments were carried out in 10 and 25 ml milling jars at 30 Hz for different milling times. Co-milled samples were characterised for formation of cocrystals and phase transformation using powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC). Our data shows that co-milling in the presence of PEG, HPMC or lactose yields purer cocrystals, supported by the calculated stronger excipient interactions for PVP and MCC. We identify a suitably-prepared THP–4ABA pharmaceutical cocrystal formulation that is stable under extended milling conditions.

1. Introduction

Pharmaceutical product manufacturing is complex, requiring challenging unit operations such as milling, dry mixing, blending, dry granulation, and tablettting. In some cases, solid processing may have undesired effects on drug substances such as amorphisation of active pharmaceutical ingredients (APIs) which makes the drug molecules thermodynamically unstable due to high unfavourable free energy (Curtin et al., 2013a). Another issue for solid-state processing is change in solid form of materials that remain crystalline, i.e., possibility of displaying polymorphism via formation of solvates and hydrates (Healy et al., 2017; Newman and Zografi, 2014).

In the pharmaceutical manufacturing chain, milling is primarily used for size reduction of APIs (Lyszczarz et al., 2020), as it is challenging to obtain API crystals with desired size distribution in the crystallization step. However, milling can induce the solid state transformation of API molecules which can significantly alter the physicochemical properties of drug formulations (Curtin et al., 2013b). Milling can also be used for production of drug substances with improved properties such as solubility, compressibility, and tablettability (Szafraniec et al., 2017). Among different properties of APIs, solubility is of great importance, as it can affect the drug bioavailability. It has been recognized that improving bioavailability of the poorly water-soluble APIs is a major challenge for the pharmaceutical industry (Abuzar et al., 2018; Loh et al., 2015; Riikonen et al., 2019). Different approaches have been developed for improving the solubility of APIs, among which solid-state modification...
has attracted much attention for improving the physicochemical properties of drugs. Various pathways can be used for solid-state modification of drugs including formation of salts, solvates, polymorphic drugs, and cocrystals. These methods not only improve the solubility of APIs, but can also improve the physicochemical properties of drug formulations, such as compressibility, flowability, and stability. However, a thorough understanding of the drug modification process during solid-state processing is lacking yet of great importance for drug development. For example, it has been reported that the inclusion of low glass transition temperature (Tg) polymers as an excipient can lower the amorphisation of some APIs during the co-milling process (Curtin et al., 2013b).

The cocrystallisation method is a promising technique for improving the solubility and other properties of oral solid dosage formulations (Shaikh et al., 2018b). A pharmaceutical cocrystal is a crystalline single phase material composed of a drug (API) with a pharmaceutically approved co-former molecule, i.e., two or more different molecular and/or ionic compounds generally in a stoichiometric ratio, which is neither a solvate nor a simple salt (Aitipamula et al., 2012). The interaction between API and co-former is through hydrogen bonding, in which one component is donor and the other one is acceptor. Cocrystals offer unique characteristics that can improve drug properties, and have been used to overcome the poor solubility of poorly water soluble drugs (Shaikh et al., 2018b).

Different methods have been proposed for the preparation of pharmaceutical cocrystals, which are divided into two main approaches, i.e., solution-based and solvent-less approach. Slow solvent evaporation, slow cooling crystallization, and slurry conversion are examples of solution-based approaches for pharmaceutical cocrystallization. Neat grinding, ball milling, and hot melt extrusion are examples of solvent-less approaches. Recently, some hybrid methods have been developed for pharmaceutical cocrystallization including sonic-slurry, supercritical assisted crystallization, and ultrasound (Berry et al., 2008; Childs et al., 2008; Padrela et al., 2010). The conventional solution-based approach has some drawbacks such as consumption of high amount of solvent, contamination of end product by organic solvent residue, and lower cocrystal purity.

Recently, mechanochemical processing has attracted much attention and there is a growing demand for this approach in pharmaceutical processing, as it is greener and more sustainable. Mechanochemical processing via ball milling is a viable process for pharmaceutical cocrystallization, as it is a simple process which requires no solvent or minimal solvent (Chadwick et al., 2007; Friscic et al., 2006; Hollingsworth et al., 1994; Trask et al., 2004). The milling process has also been used to reduce particle size for lung delivery and other dry powder formulations such as hypoglycemic (diabetes) and anti-viral medicines (Mitragotri et al., 2014; Santos Caviola and Edelman, 2014). Dry powder inhaler formulations are made of co-milled API and excipients, with the excipients used to improve the drug formulation efficiency, dispersibility, and flowability. Mechanochemical preparation of cocrystals using ball milling has been investigated in several studies (Arabiani et al., 2019; Bysouth et al., 2011). Few studies have characterised the thermodynamic stability of the cocrystals during solid-state milling, and competitive milling reactions were conducted in the presence of functional groups to identify stable cocrystal systems (Fischer et al., 2015, 2016). Chow et al. demonstrated that jet milling was more effective than ball milling in preserving solid state integrity for caffeine-glutamic acid (1:1) cocrystals (Chow et al., 2017). In another study by Hasa et al., polymer-assisted grinding (POLAG) was used to investigate the cocrystal formation and to control polymorphic selection of the organic molecules (Hase et al., 2016, 2015). Furthermore, various studies also reported the use of matrix-assisted cocrystallization (MAC) with hot melt extrusion (HME) processing, where co-processing of cocrystal components with polymer or inert substances was performed to produce cocrystals (Boks et al., 2014; Gajda et al., 2018; Li et al., 2016; Shaikh et al., 2018a). Recently Korde et al. investigated a scalable continuous solid state shearing milling (SSM) for polymer assisted cocrystallization (Kor et al., 2018).

The current research on pharmaceutical cocrystals has focused on the discovery of novel cocrystals with improved properties (Guerain et al., 2020; Tomar et al., 2020). However, there is little research on understanding the solid processing of cocrystals during various downstream processing steps (unit operations) such as milling. API properties may be altered due to high mechanical stress in the milling environment during solid processing. The mechanical stress may change API from a crystalline to amorphous phase, or trigger polymorphic transformation, or dissociation of the cocrystal into its primary components. Moreover, the presence of an excipient during co-milling may also have a significant effect on the formation of cocrystals again potentially leading to amorphization, dissociation or a change in solid form. These phenomena can affect the properties of a formulation significantly, which makes understanding the formation of cocrystals in the milling process crucial for the successful production of pharmaceutical cocrystal products. It needs to be controlled, not only to minimise the amorphisation of the drug, but also to enhance the purity of the cocrystal.

Theophylline-4-amino benzoic acid (THP-4ABA) cocrystal has been chosen as a model compound for this study. THP is a challenging drug to formulate because mechanical processing can affect the polymorphic transition, which complicates the design of a robust and reproducible manufacturing process. Herein, we study THP solid state processing during milling (Fig. 1). The aim of the current study is to provide thorough understanding of the co-milling process, using THP and 4ABA as the API and co-former, respectively, and five different commonly-used excipients: semi-crystalline PEG, MCC and lactose, and amorphous excipients PVP and HPMC. Co-milling experiments are conducted by milling a 1:1 stoichiometric ratio of THP and 4ABA with various ratios of excipients using a ball mill. This allows us to compare the effect of the excipients on THP-4ABA cocrystal formation in the co-milled mixture. Density functional theory (DFT) binding energy calculations supported the experimental observations of purity and stability of the cocrystals.

2. Materials and methods

2.1. Materials

Theophylline (anhydrous) was purchased from Alfa Aesar (Lancashire, UK). 4-Aminobenzoic acid (4ABA) was obtained from Acros Organics, (Geel, Belgium). Polyethylene glycol was obtained from Sigma Aldrich (Arklow, Wicklow, Ireland). Metolose 60SH 10,000 (HPMC) was kindly provided by Shin-Etsu Chemical Co., Ltd. (Livingstone, UK). α-lactose monohydrate was purchased from Sigma-Aldrich (Dorset, UK). Microcrystalline cellulose (Avicel PH101) was obtained from Pharmatrans Sanaq AG (Basel, Switzerland). Polyvinylpyrrolidone (PVP 10) was purchased from Sigma-Aldrich (Dorset, UK).

2.2. Preparation of THP/4ABA cocrystals using solvent evaporation

In order to prepare the cocrystal sample as a reference for characterizations, a pure cocrystal was prepared by dissolving a 1:1 stoichiometric molar ratio of THP and 4ABA in 20 ml of methanol and stirring the mixture at a temperature of 64 °C until complete dissolution of API and coformer in the solvent was achieved. The solvent of the resulting clear solution was slowly evaporated under a fume hood for 48 h. The obtained solid sample was further dried in an oven at 40 °C for 12 h to remove any residual solvent. The dried sample was stored in a vacuum desiccator prior to characterization.

2.3. Manufacturing of the cocrystals via ball milling

Milling of the pharmaceutical cocrystals was carried out using a ball milling apparatus (MM 400, Retsch, Germany) equipped with 10 and 25
ml milling jars. 1.76 g of equimolar material of THP and 4ABA were placed in 10-ml grinding jars (with one grinding ball of diameter 8.74 mm, 4.06 g) and 25-ml sized grinding jars (containing one grinding ball of diameter 13.72 mm, 13.64 g). The mixture was milled at 30 Hz for set periods of time (2, 5, 10, 15, 20, and 25 min). The obtained samples were then collected and tested for formation of cocrystals using powder X-ray diffraction (PXRD) and differential scanning calorimetry (DSC).

2.4. Co-milling with use of tablet excipients

In order to understand the influence of excipients on the formation of cocrystals, a tablet excipient was included in the formulation. Co-milling with various ratios of the tablet excipients HPMC, PVP, PEG, MCC, and lactose, with 1.76 g of equimolar material of THP and 4ABA, was carried out in a 25 ml grinding jar containing one grinding ball of 13.72 mm (13.64 g) for 10 min at 30 Hz. The milled samples were characterised for formation of cocrystal using PXRD and DSC.

2.5. Milling stability

To examine the effects of over-milling, the formed cocrystals with or without excipient were further milled. The milling stability test of cocrystals (1.76 g) and cocrystals with excipient (1.84 g) were conducted in a 25 ml grinding jar containing one grinding ball of 13.72 mm (13.64 g) for 15 min, at 30 Hz. The milled samples were characterised for formation of cocrystal using PXRD and DSC.

2.6. Differential scanning calorimetry (DSC)

Thermal analysis of Theophylline and 4-Aminobenzoic acid and the ball milled cocrystal was performed using a 214 Polyma DSC (NETZSCH Group). Accurately weighed the powder materials loaded into crimped DSC aluminum pans. The samples were scanned at a heating rate of 10 °C min⁻¹ over the temperature of 35–280 °C and flow rate of 30 ml·min⁻¹ of dry nitrogen atmosphere. Analysis was carried out using Proteus® software version 7.

2.7. Powder X-ray diffraction (PXRD)

Powder XRD patterns of obtained materials was performed using PANalytical Empyrean diffractometer with Cu Kα radiation. The tube voltage and tube current used were 40 kV and 40 mA, respectively. X-ray diffraction patterns were collected over the 2θ range of 5–50°, with a step size of 0.026° and a step time of 56 s. In this technique, the powder sample was exposed to a beam of monochromatic X-ray radiation, which was diffracted and recorded by an X-ray detector. The diffracted data was processed and an X-ray powder pattern was plotted.

2.8. Molecular modelling

All calculations were carried out using the Vienna Ab initio Simulation Package (VASP) (Hafner, 2007), with plane wave basis sets (Kresse and Furthmüller, 1996) and the projector augmented-wave (PAW) method (Kresse and Joubert, 1999). Exchange-correlation effects were treated using density functional theory (DFT) (Argaman and Makov, 2000) via the Perdew, Burke, and Ernzerhof (PBE) implementation of the Generalised Gradient Approximation (GGA) (Perdew et al., 1996) with Grimme D3 dispersion corrections (Grimme et al., 2010). Single Γ-centred k-point relaxations were carried out using a plane wave cut-off of 600 eV and Fermi smearing with smearing width of 0.1 eV.

The smallest chemically relevant representation of each excipient molecule was used. For PEG, for example, this was a monomer, for MCC this was two units. Molecules were placed within 1.6 Å of each other and possible binding configurations sampled at rotations of 10° (see Fig. 1 for axes of rotation) to determine the most favourable binding orientations (based on the lowest ground state energy, similar to previous binding energy studies (Song et al., 2018)). Each complex was pre-optimised using Avogadro (Hanwell et al., 2012), and then fully optimised in VASP as described above. Once the most favourable molecular orientations were determined, binding energies (Ebinding) were calculated as the total ground state energy of the complex minus the ground state energies of each isolated component. For example, to calculate the binding energy between Lactose and THP, three calculations are required: Optimisation of the lactose and THP complex, optimisation of lactose alone, and optimisation of THP alone. The binding energy in this case is:

\[ E_{\text{binding}} = E_{\text{Lactose:THP}} - E_{\text{Lactose}} - E_{\text{THP}} \]
3. Results

3.1. Synthesis and characterization of the theophylline cocrystals

3.1.1. PXRD analysis

The X-ray diffraction patterns of THP, 4ABA, and the reference cocrystal powders are indicated in Fig. 2. The diffraction pattern of THP exhibits characteristic peaks at 2θ values of 12.7°, 14.4°, 24.2°, while 4ABA shows characteristic diffraction peaks at 2θ values of 13.9°, 15.4°, 21.9°. The THP–4ABA cocrystal displays distinct peaks, not present in the patterns of its primary components, at 2θ values of 12.3°, 14.0°, 15.5°, 26.4°, 27.5°, 28.6°, which shows good agreement with the calculated X-ray diffraction pattern. The calculated PXRD pattern of the pure THP–4ABA cocrystal and the pattern obtained from the experiment are included in the supporting information (Fig. S1). The distinct PXRD peaks for THP–4ABA confirm formation of a new solid-state phase, formed by interaction between the two primary components.

3.1.2. DSC analysis

In order to determine the thermal properties of the primary components and the reference cocrystal, DSC analysis was carried out on the samples. The DSC patterns of THP, 4ABA and THP–4ABA cocrystals are depicted in Fig. 2. THP pattern shows a single endothermic peak at temperature of 274 °C, whereas 4ABA indicates a single melting point at 187 °C. Also, a single endothermic melting at 170 °C with a melting enthalpy of 114.7 kJ mol⁻¹ is observed in the thermogram of the THP–4ABA reference cocrystal.

3.2. Ball milling

THP–4ABA 1:1 cocrystallization experiments were conducted via ball milling using 10 ml and 25 ml steel vessels. The PXRD patterns of the milled (10 ml) THP–4ABA crystals are shown in Fig. 3. With increased milling duration a decrease was observed in characteristic peak intensities of the primary components. The distinct PXRD cocrystal peaks become more prominent, and ball milling at 25 min leads to the new solid forms of THP–4ABA. Milling carried out in a 25 ml grinding jar of a 1:2 physical mixture of THP:4ABA for 5 mins leads to the new solid forms of THP–4ABA with unique diffraction pattern distinguishable from THP and 4ABA (Fig. 4). To verify the PXRD results, DSC was performed for the cocrystals.

The DSC thermograms for a 1:1 physical mixture of THP:4ABA subjected to ball milling in 10 ml grinding jars for 5, 10, 15, 20 and 25 min are shown in Fig. 3. Examination of the thermal behaviour of the material recovered from 5 to 20 min shows two endothermic peaks at approximately 168 °C and 171 °C, demonstrating the possibility of eutectic melting and some quantity of pure cocrystals of THP–4ABA. Formulations milled at 25 mins showed cocrystal melt and the absence of a thermal event attributable to eutectic melting. The melting endotherm peak at 171 °C corresponds to a highest obtained ΔH of 99.58 J/g. Thus, increased milling periods lead to decreasing eutectic melting and increasing melting enthalpy, suggesting complete cocrystal formation. THP–4ABA 1:1 cocrystallization in a 25 ml grinding jar after 2 min of milling showed two melting endotherms at 161.2 °C and 168.2 °C and their respective ΔH were found to be 3.97 J/g and 21.75 J/g (Fig. 4). On the other hand, the 1:1 physical mixture of THP: 4ABA milled for 5 mins showed a single melting endotherm at 169.7 °C with high ΔH of 103.8 J/g, with this single melting endothermic peak corresponding to the melting point of THP–4ABA cocrystals. The DSC result supports the interpretation of the PXRD results. It was found that faster cocrystallization occurred after only 5 mins of milling in 25 ml jars in comparison to 25 mins in 10 ml grinding jars. This is most likely due to interaction between the larger grinding ball with the mill wall generating higher shear forces and friction. Thus, increasing mechanical energy leads to increase in reactivity and resulting formation of cocrystals, and degradation of cocrystals can be avoided by using low residence times (Korde et al., 2018).

3.3. THP–4ABA cocrystal co-milling and effects of excipients

The effect on cocrystallization was studied of co-milling physical mixtures containing 1:1 THP: 4ABA in the presence of various excipients (HPMC, PEG, PVP, MCC, and lactose). The excipient co-milled samples were characterised by PXRD and DSC. The PXRD patterns of the co-milled and individual cocrystal components using HPMC concentrations ranging from 2 to 50% w/w are shown in Fig. 5. The characteristic peaks of the THP–4ABA cocrystal were observed with all the HPMC co-milled formulations, indicating that cocrystals can be obtained in the presence of varying HPMC content. While we did not perform quantitative analysis, it can be noted that on increasing the HPMC polymer

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Fig. 2. PXRD patterns and DSC thermograms of starting materials and reference cocrystal prepared using solvent evaporation.

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content, the intensity of the characteristic cocrystal peaks decreased, with THP peak counts observed at $2\theta = 12.7^\circ$. Hence, the purity of the cocrystals decreases with increasing HPMC concentration in the co-milled THP–4ABA mixtures.

Fig. 5 shows the DSC curves of THP–4ABA co-milled with various percentages of HPMC. When 2% and 5% HPMC is co-milled with cocrystal components, single endothermic peaks at 168.7°C and 167.4°C, respectively are observed, which is similar to pure cocrystals. The enthalpy of melting for 2% and 5% HPMC are 96.46 J/g and 81.86 J/g, which are less than that of the THP–4ABA cocrystal. The DSC thermograms of milled formulation of the THP–4ABA with 10% and 20% HPMC showed single melting endotherms at 165.5°C and 165.2°C, with $\Delta H$ of 65.7 J/g and 47.3 J/g, respectively. It is clear that increasing the HPMC content from 10 to 20% results in a slight decrease in melting point, with high variation in enthalpy. Increasing the HPMC content from 20 to 50% significantly decreases the cocrystal melting point to 155.2°C and enthalpy of melting to 10.5 J/g (Fig. 5). These observations suggest that at higher HPMC percentages, a possible interaction between the HPMC and cocrystal components yielding less pure cocrystals (Gajda et al., 2018).

Fig. 6 shows the powder XRD patterns of co-milled cocrystal components with PVP. The co-milled cocrystal formulation containing 2%
PVP demonstrated a similar intensity of characteristic peaks of the co-crystalline phase, which proves it to be complete cocrystallization of THP–4ABA. However, PXRD patterns also evidence a very small THP peak at 12.7°. Increasing the PVP content from 2 to 30% with the co-milled cocrystal components resulted in a reduced number of cocrystal peaks and more peak counts of characteristic THP at 12.7°. When 30% PVP was used, an increased peak intensity of THP was observed compared to the cocrystal peaks. These results suggest that co-milling at a higher PVP percentage did not lead to complete cocrystallization. It is likely that partial amorphisation of cocrystals at higher PVP
concentration hindered complete cocrystal formation upon milling. DSC thermograms of the physical mixtures of the THP–4ABA with 2%, 5%, 10%, 20%, and 30% PVP showed reduction (167.6 °C to 150.6 °C) in the cocrystal melting temperature with increasing concentration (Fig. 6). Furthermore, the melting enthalpies of PVP co-milled cocrystals were significantly reduced (97.7 J/g to 8.8 J/g) as polymer concentration increased. Lowest enthalpy values at higher PVP concentration suggest partial dissolution of cocrystal components in already molten polymer (Coleman and Painter, 1995).

Results of PXRD for co-milling using PEG are shown in Fig. 7. Co-milling 2% to 20% PEG with cocrystal components resulted in diffraction patterns characteristic of cocrystals. The appearance of cocrystal peaks suggests the formation of cocrystals in the presence of PEG. Increasing the concentration of PEG in the co-milled mixtures results in a slight decrease in characteristic THP–4ABA cocrystal peaks at 14.0° and 27.5°, with a very low intensity of THP at 12.7° detected. This can be attributed to unreacted THP. DSC analysis of different amounts of PEG co-milled with individual cocrystal components shows two endothermic transitions (Fig. 7). The first endothermic peak (melting point of PEG) spans from 60.4 °C to 58.2 °C. The second melting endotherms of the THP–4ABA cocrystal decreases with increasing content of the PEG (168.9 °C to 164.2 °C). The decrease in the enthalpy of fusion from 94.86 to 30.73 J/g with increasing content of the polymer is also observed. This is most likely due to the increased miscibility of cocrystal components in PEG at higher concentrations.

For THP–4ABA 1:1 mixtures co-milled using MCC, PXRD showed large decrease in the intensity of the characteristic peaks of cocrystals with MCC (50 and 67.7%) (Fig. 8). Peak broadening is also observed, potentially due to the interaction between MCC and the primary components of the cocrystal and may be also associated with high degree of amorphisation due to crystal surface defects induced by the milling process. The DSC thermogram for THP–4ABA/MCC cocrystals shows melting point depression (from 170 °C to 162 °C) and broader melting peaks (Fig. 8), with significant reduction in the melting enthalpies (from 114.7 kJ to 41.1 J/g). Increase of the MCC content from 50% to 67.7 wt % leads to increase in the glass transition temperature (Tg) of MCC from 119.8 °C to 125 °C and a decrease of the cocrystal melting peak from 162 °C to 160.8 °C. Based on the thermal analyses, the enthalpy of the cocrystal peak reduced from 41.10 J/g to 20.88 J/g. This can be explained by potential dissolution of cocrystal components in molten polymer. Fig. 9 shows the PXRD patterns of co-milled cocrystal components with lactose. When 50% of lactose is co-milled with cocrystal components, PXRD reveals a spectrum characteristic of the pure cocrystal along with lactose peaks. On increasing lactose concentration to 67.7% a decrease in the peak of cocrystals is observed. The change in the cocrystal peak intensity clearly demonstrates a reduction in purity of the cocrystallization product. The DSC curve of THP–4ABA/lactose cocrystals (Fig. 9) shows the endothermic peak varied between 152 °C and 137.3 °C, with corresponding enthalpy of 95.63 J/g and 95.17 J/g, respectively. However, it is not possible to measure the exact melting enthalpy for the formed cocrystals, as the dehydration endotherm of lactose overlaps with cocrystal melting.

3.4. The stability of THP–4ABA cocrystals with and without tablet excipients

Milling stability testing was conducted to check the integrity of cocrystals formed under mechanochemical conditions. Prepared THP–4ABA cocrystals (in the absence of excipients) after a further 15 mins of milling showed a similar normalised energy of 105.5 J/g, indicating high purity and crystallinity (Fig. 10), i.e., cocrystals that are robust and maintain their integrity. Milling stability tests for cocrystals co-milled with excipients (15 mins further milling with 5% HPMC, PEG, or PVP) showed PXRD intensity peaks that still resemble the original cocrystal and the thermograms showed melting peaks and enthalpies that were similar to cocrystals (Fig. 11). Therefore, no phase separation or dissociation of cocrystals occurred, suggesting optimal co-milling conditions.

3.5. Density functional theory (DFT) modelling

In order to rationalise the experimental results at the nanoscale, intermolecular binding energies were calculated using dispersion-
corrected DFT. Binding energies between pairs of excipient molecules were first calculated, as well as binding energies between the excipient molecules and the API, the co-former, and the cocrystal molecular complex (Fig. 12), respectively (Table 1).

Generally speaking, smaller-magnitude binding energies with the excipient result in more stable cocrystal formation. If either the co-former, the API, or the hydrogen-bonded complex bind too strongly to the excipient molecules, crystallisation will be inhibited via dissociation or amorphization (Fig. 13a and b) (Alhalaweh et al., 2012; Seaton and Parkin, 2011).

Fig. 8. PXRD patterns and DSC thermograms of MCC co-milled material samples.

Fig. 9. PXRD patterns and DSC thermograms of lactose co-milled material samples.
The binding energies calculated by DFT show a clear trend in the affinities of the excipient molecules for the THP–4ABA complex, in the order PEG < HPMC < lactose < MCC < PVP. Fig. 13 shows the most favourable molecular orientations that were used to calculate the intermolecular interactions. As the binding energies shown in Table 1 are for the strongest possible interactions in each case, it is important to note that in a standard ball-milling process multiple molecular geometries will interact. Here we discuss the strongest molecular interactions for both the API and co-former with each excipient, representing their interactions prior to forming the molecular complex. For studying the interactions between excipients and the THP–4ABA complex the known optimised configuration is used, where two hydrogen bonds are formed between the API and co-former i.e. (O–H—O and N–O—H, shown as dashed yellow lines in Fig. 12). It is possible that less probable geometries will interact in a large scale process, but the results demonstrate that the strongest/most probable interactions successfully predict co-crystal stability.

PEG consistently has the lowest binding energy with all molecules, due to the low number of interaction sites available for this small molecule. The intermolecular PEG-PEG binding energy is 28.4 kJ/mol, which is half the strength of the HPMC intermolecular binding energy (60.9 kJ/mol), and one third of that of PVP (91.1 kJ/mol). We see an almost identical trend in binding energy between the excipients and the THP–4ABA complex, with binding energies of 17.0 kJ/mol, 32.9 kJ/mol, and 54.6 kJ/mol for PEG, HPMC, and PVP, respectively.

Lactose has weaker binding energies than MCC for both the intermolecular and THP–4ABA interactions, correlating with more stable cocrystal formation when using lactose as an excipient (measured enthalpies from above). The difference in binding energies between these molecules for each instance is relatively small. The intermolecular interactions...
dynamics simulations of hundreds of API/co-former molecules and large key design rules for effective cocrystal-excipient interactions in large-netics of these binding interactions. Based on this study we identify some excipient surfaces, similar to Verma et al. (2018), to investigate the kinetic strengths. Recommended future work includes classical molecular

Fig. 12. Example unit cell showing a starting geometry between THP-4ABA and MCC. The excipient molecule is oriented so that the molecular backbone is parallel to the arbitrary a axis (shown by the black line). The edge of the complex is brought within less than 2 Å of the excipient backbone. The central axis of the molecular complex, shown as a purple line, is rotated about each excipient interface to determine the strongest molecular interactions. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Table 1

Intermolecular binding energies (kJ/mol) calculated by DFT.

| Molecule | HPMC | Lactose | PEG | MCC |
|----------|------|---------|-----|-----|
| THP      | –47.6| –33.9   | –20.4| –39.2| –43.9|
| 4ABA     | –40.6| –66.9   | –30.9| –38.3| –44.6|
| Cocrystal| –32.9| –35.8   | –17.0| –54.6| –39.6|

Table 1 shows the intermolecular binding energies (kJ/mol) calculated by DFT. The computed structures show that only HPMC and lactose form hydrogen bonds with the API/co-former complex. PEG has the weakest binding with THP-4ABA, with just van der Waals contacts, and d) which is also the case for MCC and PVP. Given the experimentally measured superior performance of lactose relative to MCC, our data emphasises that some low level of hydrogen bonding between the excipient and component molecules is necessary for stable cocrystal formation, coupled with overall mild excipient-API/co-former interaction strengths. Recommended future work includes classical molecular dynamics simulations of hundreds of API/co-former molecules and large excipient surfaces, similar to Verma et al. (2018), to investigate the kinetics of these binding interactions. Based on this study we identify some key design rules for effective cocrystal-excipient interactions in large-scale processing (Fig. 13c). To reduce the probability of amorphisation a weak binding energy between the cocrystal complex and the excipient molecule is recommended. This can be due to exclusively vdW contacts or minimal hydrogen bonding. The easiest way to achieve this is to use an excipient with a lower molecular weight than the cocrystal complex, but this is not a requirement for stable cocrystal formation.

4. Discussion

Successful development of pharmaceutical cocrystal drug products remains something of a “black art” (Shaikh et al., 2018b) despite decades of intense research on pharmaceutical cocrystals. In the pharmaceutical manufacturing process, active pharmaceutical ingredients (APIs) and excipients undergo various mechanical operations such as milling, mixing, granulation and compaction which are responsible for causing potential interactions of the drug with the excipients. On the other hand, solid-state phase transformations can affect the quality and performance of the final product. The pharmaceutical milling process is the most common unit operation to achieve uniform size reduction for better solid oral products (Shaikh et al., 2018a). Milling and co-milling of pharmaceutical cocrystals can often result in solid-state phase transformations and dissociation into its individual components. Therefore, this study attempts to create an understanding of cocrystal API solid state processing with a variety of excipients in milling environment.

Cocrystal formation occurred in the presence of all five commonly used excipients. However, the purity of the cocrystals varied according to the type of excipient and the concentration used in the formulation. 2% of polymer excipients PVP, HPMC, PEG all showed increased cocrystal peak intensities and higher melting enthalpies. Increasing the polymer excipient concentration in the cocrystal formulation from 20 to 50% wt. leads to significant broadening in cocrystal peaks that lower the observed melting temperature, and greatly reduced intensities of cocrystal peaks that lower the enthalpy. This suggests that when less polymer excipient is co-milled with the cocrystal components, the intermolecular interaction between API and co-former is stronger than the interaction with the excipients, thus producing purer cocrystals. Increasing the co-milled polymer concentration (20 to 50% wt.) allowed for a higher probability of interaction between the excipient and the cocrystal components which leads to partial amorphisation of cocrystals and may further inhibit the molecular interaction between the API and co-former (Shaikh et al., 2019). PXRD and DSC results revealed that cocrystal formulations co-milled with HPMC or PEG produced high-purity cocrystals compared to PVP. This may be because the cocrystal components are less miscible in HPMC and PEG in comparison with PVP during the co-milling process. Diluents (lactose and MCC) were co-milled at increased ratios to evaluate the maximum concentration at which cocrystals would form. API and co-former co-milled with lactose diluent retained cocrystal characteristics with increased intensity suggesting highest purity cocrystals. This is further supported by the higher enthalpy values of the samples co-milled with lactose in comparison with MCC. Therefore, co-milling with crystalline lactose has the potential to control the crystalline form of the cocrystal. Although co-milling of cocrystals in the presence of excipients can cause amorphization and polymorphism, co-milling with HPMC, PEG and lactose has the potential to significantly inhibit these changes.

DFT calculations confirm that PEG, HPMC, and lactose are the most suitable excipients based on their weaker binding to the cocrystal complex. The generally low-magnitude binding energies of all excipients (both amorphous and semi-crystalline) with the cocrystal complex and subcomponents reduces the probability of dissociation and amorphisation during processing and increases the probability of stable cocrystal formation.

A thorough characterisation of cocrystal physicochemical properties was achieved, substantiated by computational modelling of potential interactions between the excipient and cocrystal components that can affect the cocrystal product performance. Our studies in model cocrystal
formulation co-milling (THP–4ABA) have demonstrated that the type of excipient, excipient crystallinity, molecular weight, and concentration greatly influence cocrystal purity. The results showed that amorphization is reduced and purity of cocrystals is enhanced by co-milling with PEG HPMC, or lactose. Future work could further consider the possible role of adsorbed water on the structures, using for example, more detailed DFT models, X-ray diffraction studies, and thermogravimetric analysis (TGA) of both the pure excipients and the milled reaction mixture.

5. Conclusions

In the present study we investigated the robustness of a theophylline pharmaceutical cocrystal (with 4-aminobenzoic acid co-former) during
a milling process with a variety of excipients. Using DSC and PXRD, the formation of cocrystals during co-milling has been investigated. Our results indicate that co-milling with excipients generally leads to cocrystallization, with amorphization more likely in the presence of PVP and MCC. Cocrystal co-milling with an excipient showed the limiting excipient concentration required to get the highest purity of cocrystals, and MCC. Cocrystal co-milling with an excipient showed the limiting crystallization, with amorphization more likely in the presence of PVP.

CRediT authorship contribution statement

Rahamatullah Shaikh: Conceptualization, Data curation, Formal analysis, Writing - original draft, Writing - review & editing. Saeed Shirazian: Investigation, Writing - review & editing. Sarah Guerin: Software, Validation, Writing - review & editing. Eoin Sheehan: Data curation. Damien Thompson: Methodology, Software, Validation, Writing - review & editing. Gavin M. Walker: Supervision, Funding acquisition. Denise M. Croker: Supervision, Writing - review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary material

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