Influence of Excipients on Cocrystal Stability and Formation

Marwah Aljohani,[1] Patrick McArdle,[1,2,*] and Andrea Erxleben[1,2,*]

[1] School of Chemistry, National University of Ireland, Galway, Ireland

[2] Synthesis and Solid State Pharmaceutical Centre (SSPC), Ireland

*Corresponding author email address: andrea.erxleben@nuigalway.ie (AE);

p.mcardle@nuigalway.ie (PM)

Abstract

Cocrystal formation is widely used to modify and optimise the physicochemical properties of an active pharmaceutical ingredient (API). However, the stability of cocrystals towards formulation with excipients is little investigated. In this work the effect of grinding in the presence of the common excipients polyvinylpyrrolidone (PVP) and microcrystalline cellulose (MCC) on 11 cocrystals and a salt of the sulfonamide diuretic chlorothiazide (ctz) was studied (ctz-bipy, ctz-ebipy, ctz-pbipy, ctz-pyr, ctz-hyp, ctz-hma, ctz-bza, ctz-nia, ctz-ina, ctz-cbz, ctz-aca, ctz-ppa, ($bzamH^+$)(ctz^-); bipy = 4,4'-bipyridine, ebipy = 1,2-di(4-pyridyl)ethylene, pbipy = 1,3-di(4-pyridyl)propane, pyr = pyrazine, hyp = 2-hydroxypyridine, hma = hexamethylenetetramine, bza = benzamide, nia = nicotinamide, ina = isonicotinamide, cbz = carbamazepine, aca = acetamide, ppa = propionamide, $bzamH^+$ = benzamidinium). Except for ctz-ppa and ctz-aca, all cocrystals were stable towards milling with one weight equivalent PVP or MCC. It was also shown that the cocrystals ctz-bipy, ctz-ebipy, ctz-pbipy, ctz-pyr, ctz-hma, ctz-bza, ctz-ina, ctz-cbz and the salt ($bzamH^+$)(ctz^-) formed *in situ*, when ctz was milled with the respective coformer in the presence of PVP or MCC. The stability and formation of ctz-cbz, ctz-nia and htz-nia (htz = hydrochlorothiazide) towards grinding with a wider range of excipients (HPC, α-lactose, deoxycholic acid and sodium taurocholate) was also investigated and the results are discussed with regard to the heterosynthons of the ctz cocrystals and competing H bonding with the excipients.

1. Introduction

Cocrystallization of an active pharmaceutical ingredient (API) with a biologically acceptable coformer or a second complementary drug has become a well-established strategy to optimise the physicochemical properties of the API without chemically modifying the drug molecule.[1-4] Several cocrystals have recently entered the market, examples are Entresto, a cocrystal of sacubitril and valsartan for the treatment of chronic heart failure, Lexapro, a cocrystal of escitalopram oxalate and oxalic acid for the treatment of depression and anxiety and tramadol-celecoxib that has completed phase III clinical trials to treat acute pain. A large number of studies are reported in the literature that systematically explore heterosynthons and hydrogen bonding patterns and that apply crystal engineering concepts to rationally design new cocrystals.[5,6]

The majority of studies on cocrystals are aimed at improving the dissolution behaviour and thus the bioavailability of poorly soluble drugs, as more than 70 % of the drugs currently in the development pipeline are Biopharmaceutics Classification System (BCS) class II or IV, i.e. have low aqueous solubility.[7] However, modifying the dissolution properties through cocrystal formation presents a dilemma, as cocrystals with a high lattice energy and strong drug-coformer H bonding often fail to give a dissolution advantage,[8] while a lower lattice energy and weaker interactions may lead to a low cocrystal stability. Various studies on the stability of 'as-is' cocrystals have been published. In particular, cocrystal stability on heating,[9,10] exposure to high relative humidity[10-13] and on addition of a competing coformer[14-16] or additive[17] was investigated. The stability of cocrystals in supersaturated solutions and suspension formulations has recently been reviewed.[18] However, the literature on the stability of cocrystals during formulation as solid dosage forms and under processing conditions is scarce.[19-25] Secondary processing involves mixing or blending with excipients which have H bond donor and acceptor groups that can compete with the coformer for the H bonding sites of the API. Chow *et al*. studied the effect of milling on the caffeine-glutaric acid cocrystal.[25] Duggirala *et al.* reported that the caffeine-oxalic acid cocrystal, while being stable under high relative humidity, dissociates in the presence of ionic excipients under pharmaceutically relevant storage conditions.[21] The reaction is water-mediated and is due to a proton transfer from oxalic acid to an anionic group of the excipient. It was further shown by Kaur *et al*. that the dissociation of the caffeine-oxalic acid cocrystal is

accelerated by milling.[23] In the absence of excipients the cocrystal is stable towards milling and it was suggested that the water-mediated dissociation is initiated in regions having processing-induced lattice defects at the interface of cocrystal and excipient particles. Koranne *et al*. investigated the effect of a range of excipients in tablets containing the theophylline-glutaric acid or theophylline-isonicotinamide cocrystals.[22,24] The cocrystal stability during storage of the tablets at 40 °C and 75 % relative humidity was found to depend on the hygroscopicity and ionizability of the excipient, the solubility of the coformer and the ability of the coformer to ionize in the pH microenvironment generated by the excipient.

We have recently reported a series of cocrystals of the sulfonamide diuretic and antihypertensive chlorothiazide (ctz, Figure 1) and analysed the heterosynthon formation and H bonding preferences with a variety of coformers with different functional groups.[26] Ctz is an interesting model API as it contains a primary as well as an imidic sulfonamide group. We have now evaluated the robustness of the different heterosynthons found in the crystal structures towards grinding with a range of common excipients as competing H bond donors or acceptors. We also show that in the majority of cases formulations of the cocrystals can be directly prepared by grinding chlorothiazide and the coformer in the presence of an excipient. The combination of cocrystallisation and blending with excipients in a one-step process which would reduce the number of required unit operations is rarely reported.[27-30]

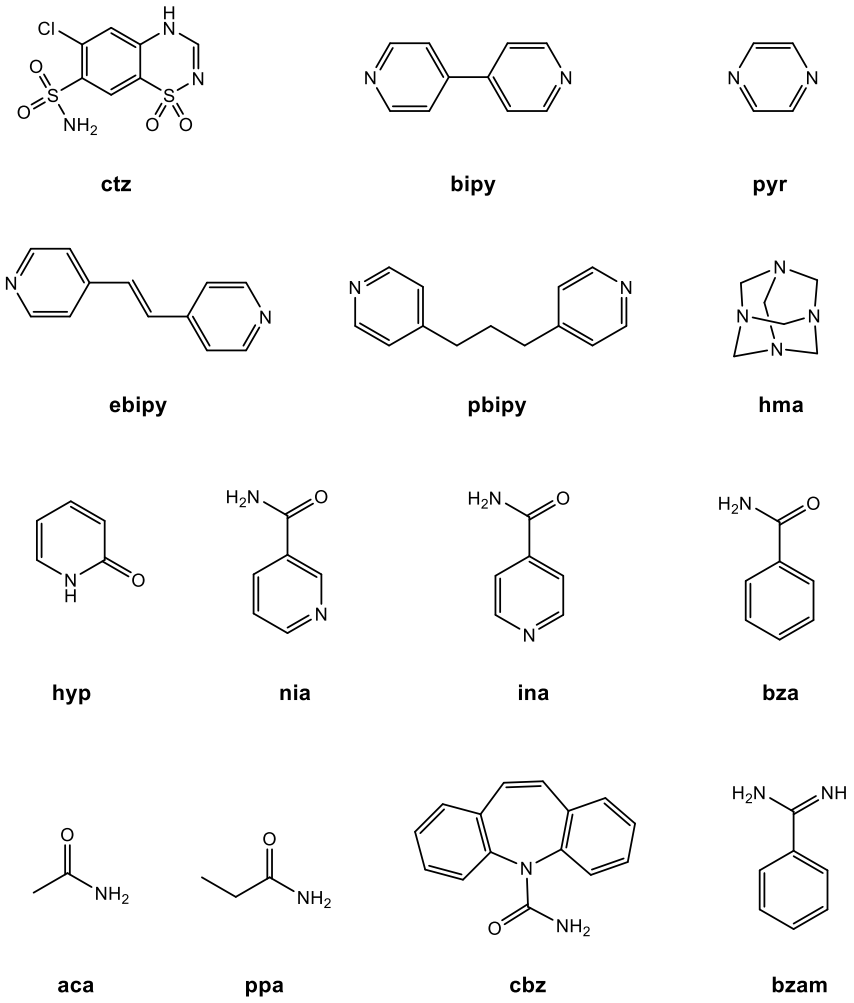


Figure 1. Chemical structures of ctz and the coformers used in this study.

2. Experimental

2.1. Materials

Chlorothiazide (ctz), hydrochlorothiazide (htz), pyrazine (pyr) and nicotinamide (nia) were purchased from Tokyo Chemical Industry (TCI Europe). The coformers 4,4'-bipyridine (bipy), 1,3-di(4-pyridyl)propane (pbiby), 1,2-di(4-pyridyl)ethylene (ebipy), 2-hydroxypyridine (hyp), benzamidine (bzam), hexamethylenetetramine (hma), isonicotinamide (ina), acetamide (aca) and propionamide (ppa) were purchased from Sigma Aldrich. Carbamazepine (cbz) and benzamide

(bza) were purchased from Alfa Aesar. The excipients deoxycholic acid (DA, ≥ 98 %) and α-lactose monohydrate (batch #018K00651) were purchased from Sigma Aldrich. Polyvinylpyrrolidone (PVP, MW ~10,000, batch #FZZRD-HC) and hydroxypropyl cellulose (HPC, batch #G102-GI$C) were obtained from TCI Europe. Microcrystalline cellulose (MCC, batch #7130-8C) was purchased from FMC Biopolymer and sodium taurocholate (NaTC, ≥ 98 %, batch # 0000008775) was supplied by Biosynth.

2.2. Milling Experiments

Milling experiments were carried out at room temperature using an oscillatory ball mill (Mixer Mill MM400, Retsch GmbH & Co., Germany) and a 25 mL stainless steel milling jar containing one 15 mm diameter stainless steel ball.

Preparation of the cocrystals by milling. The cocrystals ctz-ebipy, ctz-pyr, ctz-hyp, ctz-hma·CH_3CN, ctz-bza, ctz-nia·H_2O, ctz-ina, ctz-aca, ctz-ppa and the salt ($bzamH^+$)(ctz^-) were prepared by milling equimolar mixtures of ctz and the respective coformer (0.25 – 0.5 g in total) in the presence of traces of acetonitrile at 25 Hz for 60 min with a cool down period of 15 min after 30 min. following the procedure described previously.[26] In the case of the ctz-cbz and ctz-pbipy cocrystals, ctz and the coformer were mixed in a 1:2 molar ratio. A 2:1 molar ratio was used for ctz-bipy. The htz-nia cocrystal was obtained by milling htz and nia in a 1:1 molar ratio (0.25 g sample in total) in the presence of 50 µL of methanol. Details of the compositions of the reaction mixtures are given in the Supporting Information (Table S1). The formation and identity of the cocrystals was confirmed by X-ray powder diffraction.

Milling of the cocrystals in the presence of excipients. The prepared cocrystals were mixed with the respective excipient in a 1:1, 1:3 or 1:10 (weight excipient : weight ctz, Table S2) ratio and 0.5 g of the mixtures was milled at 25 Hz for 60 minutes with a 15 minute break after 30 minutes to avoid overheating.

Formation of the cocrystals in the presence of excipients. Ctz, the coformer and the excipient were mixed. The ctz : coformer molar ratio was 1:1 for ctz-ebipy, ctz-pyr, ctz-hyp, ctz-hma·CH_3CN, ctz-bza, ctz-nia·H_2O, ctz-ina, ctz-aca, ctz-ppa and ($bzamH^+$)(ctz^-), 1:2 for ctz-cbz and ctz-pbipy and 2:1 for ctz-bipy and the ctz : excipient weight ratio was 1:1 (Table S3). 0.5 g

of the sample was placed in a milling jar and 100 μL of acetonitrile was added to the milling jar prior to milling at 25 Hz for 60 minutes with a 15 minute break after 30 minutes.

2.3. Stability Studies

The milled samples were stored at 20 °C and 56 % relative humidity (RH) generated using a solution of K_2SO_4 [31] and the stability of the samples was checked by X-ray powder diffraction after 7, 14 and 30 days.

2.4. X-ray Powder Diffraction

X-ray powder patterns were recorded on an Inel Equinox 3000 powder diffractometer between 5 and 90° (2θ) using Cu K_α radiation (λ = 1.54178 Å, 35 kV, 25 mA).

2.5. Infra-red Spectroscopy

FT-IR spectra were recorded on a Perkin Elmer Spectrum 400 fitted with an ATR reflectance attachment. Spectra were collected in the 650 − 3600 cm^{-1} range with a resolution of 4 cm^{-1} and four integrated scans on a diamond/ZnSe window.

2.6. Differential Scanning Calorimetry

Thermal analyses were performed with a STA625 thermal analyser from Rheometric Scientific (Piscataway, New Jersey). The heating rate was 10 °C/min and the runs were performed between 20 and 300 °C. Open aluminium crucibles were used, nitrogen was purged in the ambient mode and an indium standard was used for calibration.

3. Results

3.1. Description of the Structural Motifs in the Investigated Cocrystals

The cocrystals investigated in this study are given in Table 1 and the heterosynthons observed in their crystal structures[26] are shown in Figure 2. Cocrystals with a pyridine derivative coformer have the $NH_{sulfonamide}\cdots N_{py}$ heterosynthon (motif I), the $NH_{thiadiazine}\cdots N_{py}$ heterosynthon (motif II) or the $NH_{sulfonamide}\cdots N_{py}/NH_{sulfonamide}\cdots N_{py}$ motif with the pyridine nitrogen acting as a bifurcated

H bond acceptor in the latter (motif III). Amines form $NH_{sulfonamide}\cdots N_{amine}$ (motif IV) and $NH_{thiadiazine}\cdots N_{amine}$ (motif V) H bonds with ctz, while five different motifs are found in ctz-amide cocrystals (motifs VI – X). In the benzamidinium salt of ctz charge assisted $C{=}NH_2^+\cdots{}^-N_{thiadiazine}$ (motif XI), $C{=}NH_2^+\cdots O{=}S$ (motif VIII), and $C{=}NH_2^+\cdots N(SO_2){=}C$ (motif VII) H bonds are present.

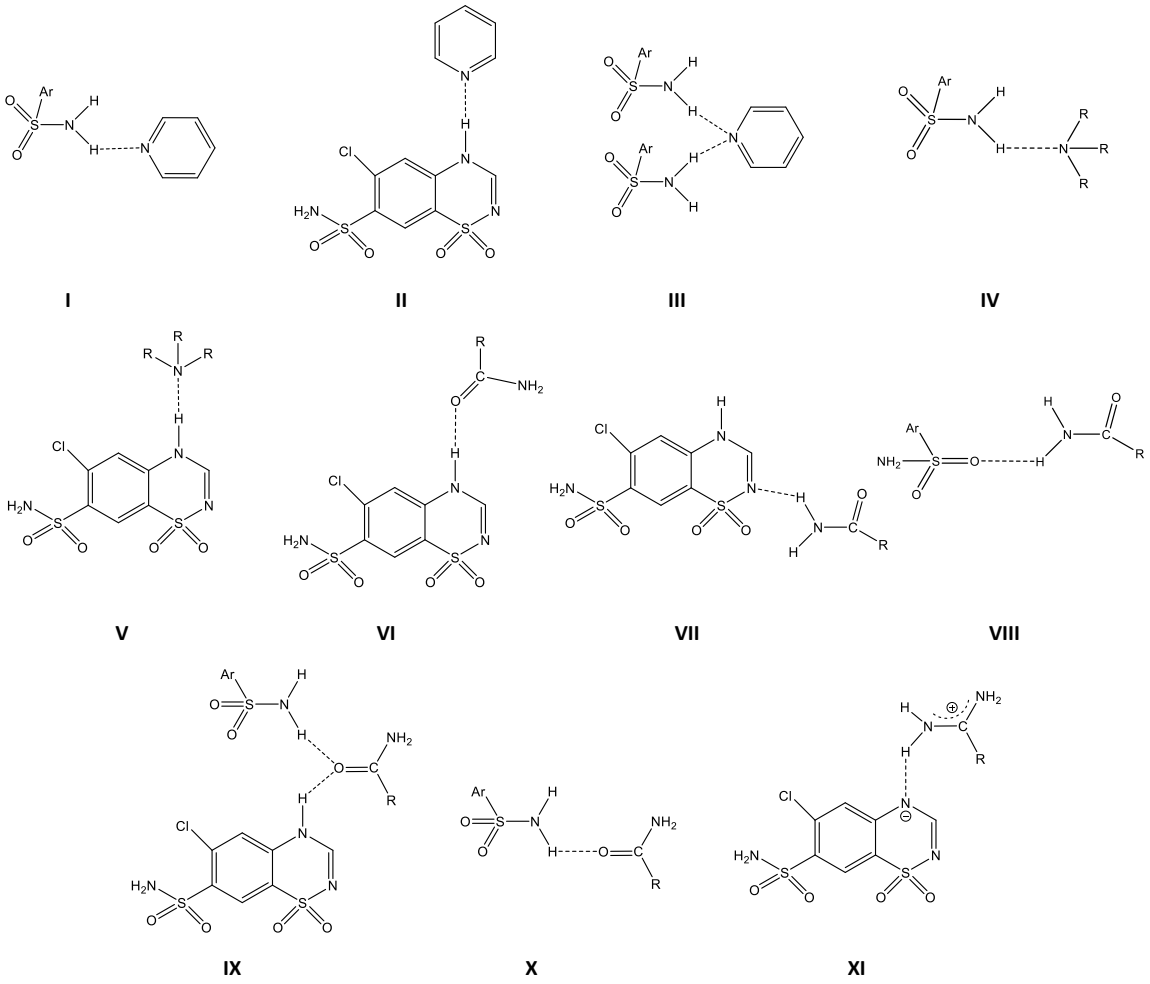


Figure 2. Heterosynthons in the cocrystals investigated in this study.

Table 1. Cocrystals investigated in this study and their structural motifs

cocrystal [a]	stoichiometry	motifs
ctz-bipy [b]	2:1	I
ctz-ebipy [b]	1:1	II, III
ctz-pbipy [b]	1:2	I, II
ctz-pyr [b]	unknown [d]	unknown [d]
ctz-hyp [b]	unknown [d]	unknown [d]
ctz-hma·CH_3CN [b]	1:1	IV, V
ctz-bza [b]	1:1	VI, VII
ctz-nia·H_2O [b]	1:1	VIII, X
ctz-ina [b]	1:1	I, VII, VIII, IX
ctz-cbz [b]	1:2	VI, VIII
ctz-aca [b]	1:1	unknown [d]
ctz-ppa [b]	1:1	unknown [d]
($bzamH^+$)(ctz^-) [b]	1:1	VII, VIII, XI
htz-nia [c]	1:1	I, X

[a] aca = acetamide, bipy = 4,4'-bipyridine, bza = benzamide, $bzamH^+$ = benzamidinium, cbz = carbamazepine, ebipy = 1,2-di(4-pyridyl)ethylene, hma = hexamethylenetetramine, htz = hydrochlorothiazide, hyp = 2-hydroxypyridine, ina = isonicotinamide, nia = nicotinamide, pbipy = 1,3-di(4-pyridyl)propane, ppa = propionamide, pyr = pyrazine. [b] ref. [26]. [c] ref [32], [d] identified by XRPD.

3.2. Interaction of Ctz and the Coformers with PVP and MCC

PVP and MCC were selected as two common excipients. MCC is an important tableting excipient due to its dry binding properties.[33-35] PVP is used as a binder in tablets and capsules[36] and is also known to enhance the dissolution rate of drugs in coprecipitates.[37] Before screening the stability of the cocrystals, the interaction of ctz and the free coformers with these two excipients was studied by IR spectroscopy. The chemical structures of PVP and MCC are shown in Figure 3. The repeating unit of PVP contains a cyclic amide group with the carbonyl oxygens presenting H bond acceptors for the $NH_{sulfonamide}$ and $NH_{thiadiazine}$ hydrogens of ctz, the NH_2 groups of the amide coformers and the amidine group in benzamidine. When ctz is milled with

PVP (1:1 weight ratio), shifts of 5 – 16 cm^{-1} of the ν(N-H) bands of the sulfonamide and of 4 cm^{-1} of the ν(C=O) band of PVP are observed indicating that H bonds are indeed formed between the API and the excipient. Likewise, on milling with PVP the ν(N-H) bands of the amides bza, nia, ina, cbz, aca and ppa shift by up to 13 cm^{-1} and the C=O stretching vibration of PVP moves to slightly higher wavenumbers ($\Delta\nu$ = 5 – 13 cm^{-1}, Table S4). The X-ray powder diffraction (XRPD) patterns of the milled ctz/PVP and amide/PVP samples show the Bragg peaks of the respective coformers with an underlying amorphous halo. For ctz, nia, cbz, bza and ina broadening of the peaks is observed which indicates a loss of crystallinity. By contrast, the peaks of aca and ppa remain sharp which suggests that in these cases the H bonding interactions are between amorphous PVP and crystalline coformer particles. After milling bzam with PVP the XRPD peaks of bzam are no longer observed and the IR spectrum features broad and poorly resolved bands in the ν(N-H) region indicating complete amorphisation.

MCC has H bond donor and H bond acceptor capability. When ctz is milled with one weight equivalent MCC, the ν(N-H), ν_{as}(S=O) and ν_{sy}(S=O) vibrations of the sulfonamide groups experience shifts of less than 3 cm^{-1}. Slightly more pronounced shifts are observed for bza as a representative example for an amide coformer. The ν(N-H) bands of bza at 3363 and 3165 cm^{-1} move to 3368 and 3170 cm^{-1} in the milled sample. The broad band of MCC at 1023 cm^{-1} with a shoulder at 1051 cm^{-1} splits into two sharp bands at 1026 and 1056 cm^{-1}. The IR spectrum of bipy/MCC as a representative example for pyridine coformer/MCC shows the MCC band at 1032/1056 cm^{-1} while changes of the bipy bands are below the resolution limit. Milling with hma results in a pronounced shift of the MCC band to 1047/1064 cm^{-1}. The strong band of hma at 1002 cm^{-1} shifts to 995 cm^{-1}. The XRPD patterns of milled bza/MCC, bipy/MCC and hma/MCC show the coformer peaks with an underlying amorphous halo. By contrast, the diffractogram of milled bzam/MCC indicates complete amorphisation and significant changes in the ν(N-H) region are observed in the IR spectrum. The bzam band at 3265 disappears on milling with MCC while the bands at 3396 and 3170 cm^{-1} shift to 3367 and 3173 cm^{-1}. The bands at 1640 and 1601 cm^{-1} are observed at 1655 and 1625 cm^{-1} after milling. Instead of the broad band of MCC around 1023, two sharp peaks appear at 1055 and 1027 cm^{-1} in the spectrum of bzam/MCC.

In summary, the IR data confirm that the components of the cocrystals can interact to a varying degree with the selected model excipients.

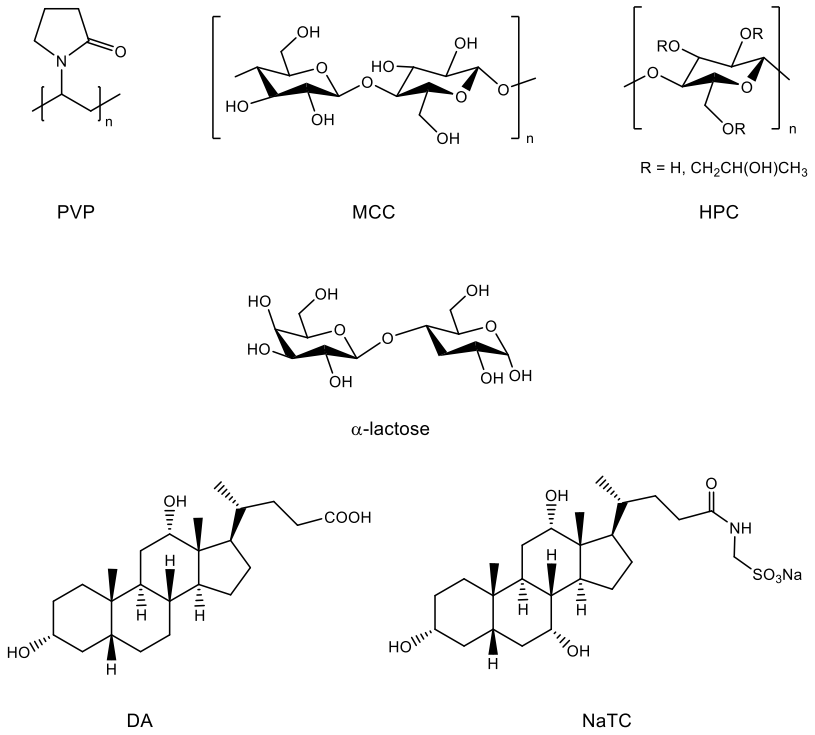


Figure 3. Chemical structures of the excipients PVP, MCC, HPC, α-lactose, NaTC and DA.

3.3. Stability and Formation of Cocrystals in the Presence of PVP and MCC

To screen the stability of the heterosynthons towards competing H bond interactions with PVP or MCC the cocrystals were mixed with the exipients (1:1 weight ratio ctz : excipient) and milled in a ball-mill for 60 min at 25 Hz. All samples containing MCC were freely flowing powders, while milling of ctz-aca, ctz-ppa, ctz-bzam, ctz-ina, ctz-nia, ctz-pyr, ctz-hyp, and ctz-hma with PVP resulted in sticky solids. The samples were analysed by XRPD immediately after milling and after storage for 30 d at 20 °C and 56 % RH (Figures 4 and S1 – S13). In the case of ctz-bipy, ctz-ebipy, ctz-pbipy, ctz-pyr, ctz-hyp, ctz-bza, ctz-nia, ctz-ina, ctz-cbz and ($bzamH^+$)(ctz^-) only the Bragg peaks of the respective cocrystal were detected and no changes occurred with time.

By contrast, the XRPD patterns showed the formation of free chlorothiazide, when ctz-ppa and ctz-aca were milled with the excipients. While ppa could be identified as well (Figure 4C), the

typically strong, characteristic peak of acetamide at 15.38 ° (2θ) is absent in the XRPD pattern of the milled ctz-aca/PVP sample (Figure 4B). It is possible that aca is formed as nanocrystalline or amorphous particles or is dispersed in the excipient. Ctz-aca was stable during milling and storage in the presence of MCC and PVP, when the amount of excipient was reduced (weight ratio MCC : ctz 1:3 and PVP : ctz 1:10). By contrast, even quantities as small as 10 wt % PVP or MCC led to the complete dissociation of ctz-ppa into ctz and amide coformer (Figure 4C). The differential scanning calorimetry thermograms of ctz-aca and ctz-ppa (in the absence of excipients) show broad endotherms at 110.5 and 58.6 °C, respectively, suggesting that the ctz-ppa cocrystal has a lower stability than ctz-aca. Ctz, aca and ppa have melting points of 342.5 - 343, 79 – 81, and 81.3 °C so that the melting point of ctz-aca is between the melting points of the two components, while ctz-ppa melts at a lower temperature.

No change in the diffractogram of ctz-hma·CH_3CN was detected immediately after milling with PVP, but on storage at 56 % RH a new XRPD pattern emerged. The same was observed in the absence of excipients and can be attributed to solvent loss or conversion of the solvate to a hydrate. The ν(C≡N) band at 2240 cm^{-1} in the IR spectrum of a freshly prepared sample of ctz-hma·CH_3CN disappears after one day while a new band is observed at 3317 cm^{-1} which may be assigned to hydrate water.

Next we investigated if the cocrystals that were stable towards milling with one weight equivalent PVP or MCC would also form by mechanochemistry, when ctz is milled with one mole equivalent coformer in the presence of one weight equivalent excipient. Traces of solvent (acetonitrile) were added to act as a catalyst for the mechanochemical reaction (liquid-assisted grinding). The XRPD patterns of the milled samples are shown in Figures 5 and S14 – S24. In all cases except for ctz-hyp the XRPD pattern of the respective cocrystal was observed after milling with MCC and no peaks for ctz or the coformers could be detected. Likewise, cocrystal formation could be confirmed in the presence of PVP, the only cocrystals that would not form in a PVP mixture being ctz-nia (Figure 5) and ctz-hyp (Figure S18). The XRPD patterns of the cocrystal formulations prepared by milling ctz, coformer and the excipient did not change during storage for one month at ambient temperature and 56 % RH except for ctz-hma·CH_3CN (see above).

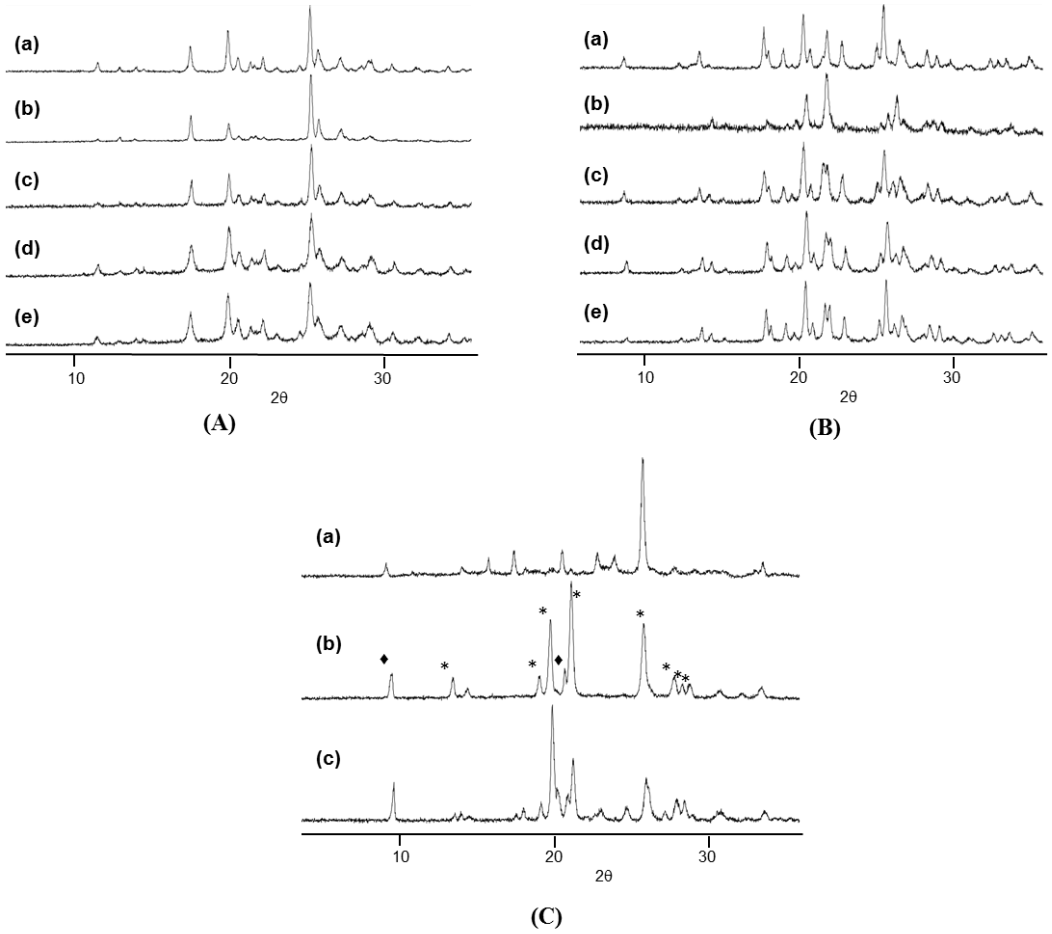


Figure 4. (**A**) XRPD pattern of (a) the ctz-ina cocrystal, (b) the ctz-ina cocrystal after milling with PVP (ctz : PVP 1:1 w/w), (c) the ctz-ina cocrystal after milling with PVP and after storage for 30 d at 20 °C, 56 % RH, (d) the ctz-ina cocrystal after milling with MCC (ctz : MCC 1:1 w/w) and (e) the ctz-ina cocrystal after milling with MCC and after storage for 30 d at 20 °C, 56 % RH. (**B**) XRPD pattern of (a) the ctz-aca cocrystal, (b) the ctz-aca cocrystal after milling with PVP (ctz : PVP 3:1 w/w), (c) the ctz-aca cocrystal after milling with PVP (ctz : PVP 10:1 w/w), (d) the ctz-aca cocrystal after milling with MCC (ctz : MCC 3:1 w/w) and (e) the ctz-aca cocrystal after milling with MCC (3:1) and after storage for 30 d at 20 °C, 56 % RH. (**C**) XRPD pattern of (a) the ctz-ppa cocrystal, (b) the ctz-ppa cocrystal after milling with PVP (ctz : PVP 10:1 w/w), (c) the ctz-ppa cocrystal after milling with MCC (ctz : MCC 10:1 w/w). ♦ ppa ∗ ctz.

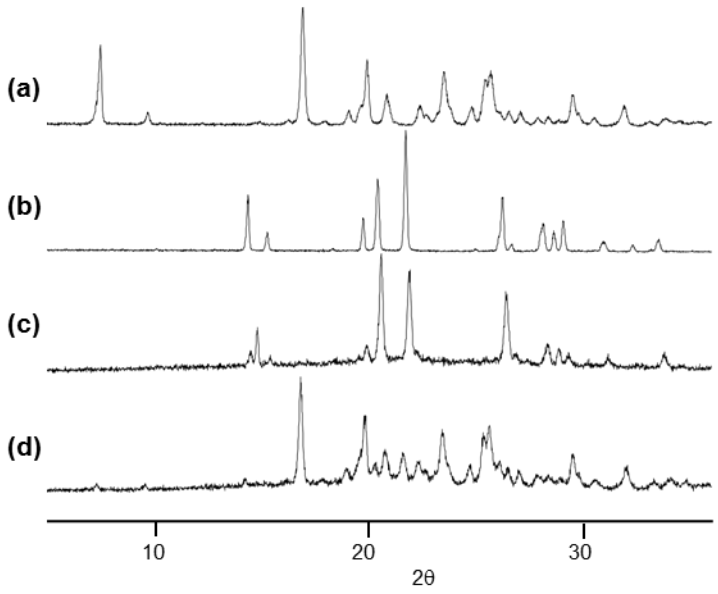


Figure 5. XRPD pattern of (a) the ctz-nia cocrystal (b) chlorothiazide, (c) a milled mixture of ctz, nia and PVP (ctz : nia = 1:1 molar ratio; ctz : PVP = 1:1 (w/w)) and (d) a milled mixture of ctz, nia and MCC (ctz : nia = 1:1 molar ratio; ctz : MCC = 1:1 (w/w)).

3.4. Stability and Formation of the ctz-nia, ctz-cbz and htz-nia Cocrystals in the Presence of HPC, α-Lactose, Sodium Taurocholate and Deoxycholic Acid

Three representative cocrystals were selected for investigating their stability towards grinding with a wider range of excipients. These included the cocrystal of ctz and the GRAS (generally recognized as safe) coformer nia, and the drug-drug cocrystal ctz-cbz. The cocrystals were chosen on the basis of their dissolution properties and their stability relative to ctz suggested by their dissolution behaviour. In our previous study we found that the dissolution rate of ctz-nia is lower than that of ctz suggesting a higher lattice energy and stability.[26] By contrast, ctz-cbz was one of the few ctz cocrystals with enhanced dissolution properties which may indicate a low stability. The nia cocrystal of the related sulfonamide htz was reported by Desiraju and coworkers to show an improved dissolution behaviour[38] and was therefore included in the present study for comparison. Hydroxypropyl cellulose (HPC), α-lactose, sodium taurocholate (NaTC) and deoxycholic acid (DA) were selected as the excipients. HPC and α-lactose are widely used as wet granulation binder and filler, respectively.[39,40] Previous work by our group

has shown that various APIs convert to the amorphous state on milling with NaTC or DA and that the two bile acids stabilise the amorphous API towards recrystallisation.[41,42]

In all of the following milling experiments the ctz : excipient weight ratio was 1:1. In the experiments on cocrystal formation in the presence of excipients traces of acetonitrile were added to the samples, while the mixtures containing the preformed cocrystals were milled neat. Ctz-nia was found to be stable towards grinding with HPC, α-lactose, NaTC and DA and no changes were observed in the XRPD patterns after storage of the samples for one month under 56 % RH (Figure S25). However, ctz-nia/HPC and ctz-nia/NaTC had transformed to sticky, rubber-like solids after grinding. Milling of ctz and nia in the presence of α-lactose or DA gave the cocrystal as a freely flowing powder, while cocrystallization did not take place in samples containing HPC or NaTC (Figure 6).

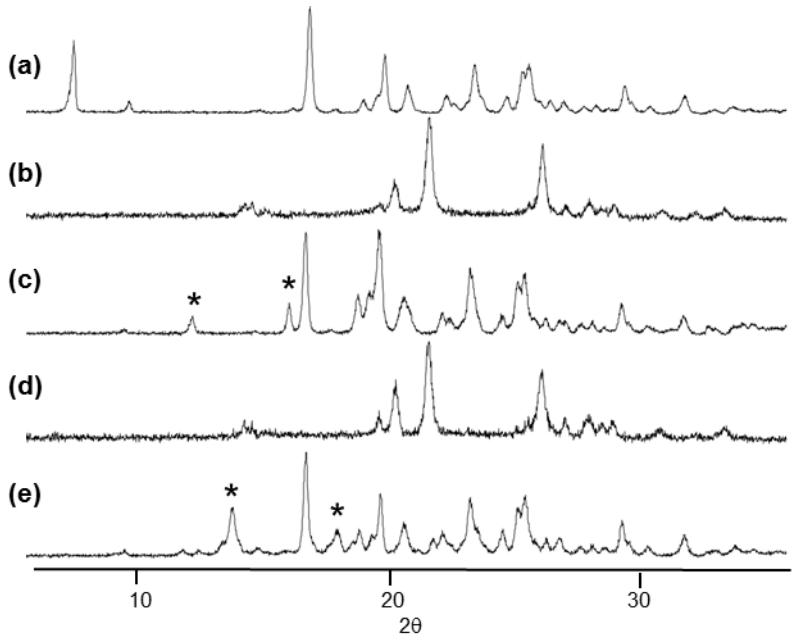


Figure 6. XRPD pattern of (a) the ctz-nia cocrystal, (b) a milled mixture of ctz, nia and HPC (ctz : nia 1:1 molar ratio; ctz : HPC 1:1 w/w), (c) a milled mixture of ctz, nia and α-lactose (ctz : nia 1:1 molar ratio; ctz : α-lactose 1:1 w/w), (d) a milled mixture of ctz, nia and NaTC (ctz : nia 1:1 molar ratio; ctz : NaTC 1:1 w/w) and (e) a milled mixture of ctz, nia and DA (ctz : nia 1:1 molar ratio; ctz : DA 1:1 w/w). * excipient peaks.

Grinding with MCC, PVP, HPC, NaTC, or α-lactose had no effect on the htz-nia cocrystal except that the htz-nia/HPC sample turned sticky. However, the XRPD pattern showed an amorphous halo, when htz-nia was milled with DA (Figure S26). The amorphous phase recrystallized to the cocrystal within 1 d under 56 % RH. The amorphous sample was analysed by IR spectroscopy to see if the $N\text{-}H_{sulfonamide}\cdots N_{py}$ and $N\text{-}H_{sulfonamide}\cdots O{=}C$ interactions of the cocrystal were present in the amorphous phase. The IR spectrum of the milled, amorphous htz-nia/DA sample shows a poorly resolved ν(N-H) region. The C=O stretching band of nia and the asymmetric and symmetric S=O stretching bands of htz appear at 1673 (ν(C=O), 1325 (ν_{as}(S=O, primary)), 1368 (ν_{as}(S=O, secondary)) and 1156 cm^{-1} (ν_{sy}(S=O)). In the IR spectrum of the cocrystal these bands are observed at 1653, 1324, 1371 and 1156 cm^{-1} in line with the literature data.[32] The ν(C=O) band of milled htz-nia/DA coincides with that of crystalline nia (1673 cm^{-1}), indicating that no interactions between nia and htz exist in the amorphous sample. However, the ν(S=O) vibrations are different from those in the spectrum of crystalline htz (1316 cm^{-1}, ν_{as}(S=O, primary), 1372 cm^{-1}, ν_{as}(S=O, secondary), 1147 cm^{-1}, ν_{sy}(S=O)) which demonstrates the absence of the catemer structure of primary sulfonamide interactions observed in the crystal structure of htz.[32]

None of the excipients hindered the cocrystal formation of htz and nia (Figure 7), including DA. In contrast to the neat-milling of pre-formed htz-nia with DA, the addition of solvent prior to the milling of htz, nia and DA resulted in an XRPD pattern with sharp peaks for the cocrystal (Figure 7).

The stability and formation of the ctz-cbz cocrystal were not affected by any of the excipients (Figures S27 and S28).

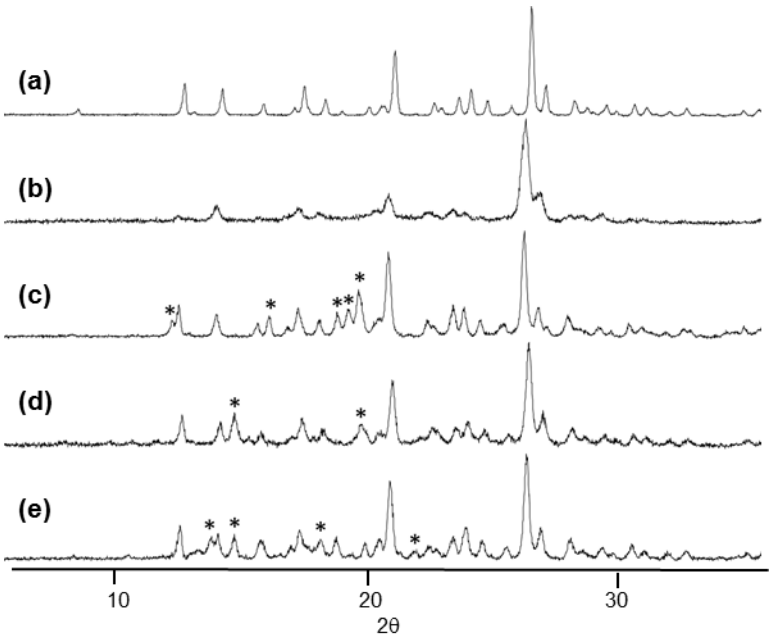


Figure 7. XRPD pattern of (a) the htz-nia cocrystal, (b) a milled mixture of htz, nia and HPC (htz : nia 1:1 molar ratio; htz : HPC 1:1 w/w), (c) a milled mixture of htz, nia and α-lactose (htz : nia 1:1 molar ratio; htz : α-lactose 1:1 w/w), (d) a milled mixture of htz, nia and NaTC (htz : nia 1:1 molar ratio; htz : NaTC 1:1 w/w) and (e) a milled mixture of htz, nia and DA (htz : nia 1:1 molar ratio; htz : DA 1:1 w/w). * excipient peaks

4. Discussion

The results of the experiments on the stability and formation of the cocrystals in the presence of the selected excipients are summarised in Table 2. For the stability of the cocrystals in formulations the excipient-coformer, excipient-ctz and ctz-coformer interactions are important. The shift of the IR band of a H bond donor or acceptor group can be taken as an indicator for the relative strength of the hydrogen bond formed by this donor or acceptor and the IR data are summarised in Tables S2 – S4.

Table 2. Results of the milling experiments.

Cocrystal	Experiment	PVP	MCC	HPC	α-lactose	DA	TC
htz-nia	stability	✓	✓	✓	✓	[a])	✓
	formation	✓	✓	✓	✓	✓	✓
ctz-nia·H_2O	stability	✓	✓	✓	✓	✓	✓
	formation	✗	✓	✗	✓	✓	✗
ctz-cbz	stability	✓	✓	✓	✓	✓	✓
	formation	✓	✓	✓	✓	✓	✓
ctz-bipy	stability	✓	✓	n.d.	n.d.	n.d.	n.d.
	formation	✓	✓	n.d.	n.d.	n.d.	n.d.
ctz-ebipy	stability	✓	✓	n.d.	n.d.	n.d.	n.d.
	formation	✓	✓	n.d.	n.d.	n.d.	n.d.
ctz-pbipy	stability	✓	✓	n.d.	n.d.	n.d.	n.d.
	formation	✓	✓	n.d.	n.d.	n.d.	n.d.
ctz-pyr	stability	✓	✓	n.d.	n.d.	n.d.	n.d.
	formation	✓	✓	n.d.	n.d.	n.d.	n.d.
ctz-hyp	stability	✓	✓	n.d.	n.d.	n.d.	n.d.
	formation	✗	✗	n.d.	n.d.	n.d.	n.d.
ctz-hma·CH_3CN	stability	[b])	[b])	n.d.	n.d.	n.d.	n.d.
	formation	✓	✓	n.d.	n.d.	n.d.	n.d.
ctz-bza	stability	✓	✓	n.d.	n.d.	n.d.	n.d.
	formation	✓	✓	n.d.	n.d.	n.d.	n.d.
ctz-ina	stability	✓	✓	n.d.	n.d.	n.d.	n.d.
	formation	✓	✓	n.d.	n.d.	n.d.	n.d.
ctz-aca	stability	✓[c])	✓[d])	n.d.	n.d.	n.d.	n.d.
	formation	✗	✗				
ctz-ppa	stability	✗	✗	n.d.	n.d.	n.d.	n.d.
	formation	✗	✗	n.d.	n.d.	n.d.	n.d.
($bzamH^+$)(ctz^-)	stability	✓	✓	n.d.	n.d.	n.d.	n.d.
	formation	✓	✓	n.d.	n.d.	n.d.	n.d.

[a]) amorphisation [b]) conversion during storage [c]) ctz : excipient = 10:1 [d]) ctz : excipient = 3:1.

The ctz-ppa cocrystal decomposes on milling in the presence of small quantities of PVP (10 %). The ppa coformer seems to interact strongly with PVP as judged by a pronounced shift of the ν(C=O) band of PVP in the IR spectrum of milled ppa/PVP which is clearly at the high end compared to the change in the carbonyl band of other coformer/PVP mixtures (Table S4). By contrast, cocrystal formation between ppa and ctz leads to moderate band shifts only.

The low stability of the ctz-aca cocrystal is more difficult to rationalize. On cocrystal formation the ν(C=O) band of aca moves by 22 cm^{-1} while the difference in the position of the PVP C=O stretching vibration between PVP and aca/PVP is only marginal. PVP is highly hygroscopic[43] and the sticky and rubber-like nature of the ctz-aca/PVP sample suggests significant water uptake which may promote the decomposition of the cocrystal as reported in the literature for theophylline-glutaric acid, theophylline-isonicotinamide and caffeine-urea.[21-24]

In the IR spectrum of milled nia/PVP strong shifts of the ν(N-H) bands are observed compared to crystalline nia which may explain why the ctz-nia cocrystal does not form in the presence of PVP. However, Δν for the C=O stretching vibration of nia in the IR spectrum of the free coformer and ctz-nia is 21 cm^{-1} suggesting also strong interactions in the cocrystal and once formed, the ctz-nia cocrystal is stable towards grinding with PVP. An alternative explanation for PVP hindrance of the cocrystallization of ctz and nia may be the ability of PVP to absorb significant amounts of water.[43] Ctz-nia crystallizes as a stoichiometric hydrate so that the cocrystal cannot form when the water in the milled mixture is taken up by the excipient.

The IR data indicate that bzam interacts strongly with MCC, yet the benzamidinium salt of ctz is stable towards grinding with MCC and readily forms in the presence of the excipient. Thus, overall, it is difficult to relate the IR data to the stability data. We have previously observed that there is apparently no correlation between the effect of cocrystal formation on specific IR bands and the relative stability of ctz cocrystals in dissolution medium.[26] It has to be kept in mind that the cocrystals generally contain more than one heterosynthon (Table 1), and while individual interactions may be weak or strong, it is the sum of all interactions that determines the stability. It is noteworthy that all cocrystals that contain the $NH_{sulfonamide}\cdots N_{py}$ or $NH_{thiadiazine}\cdots N_{py}$ synthon are stable towards all tested excipients. In contrast to ctz-nia, htz-nia and ctz-ina form in the presence of PVP and both contain the $NH_{sulfonamide}\cdots N_{py}$ motif, while ctz-nia does not. PVP also hinders the cocrystal formation between ctz and 2-hydroxypyridine. The structure of the ctz-hyp cocrystal is not known. However, 2-hydroxypyridine predominantly exists as the 2-pyridone tautomer in the solid state[44,45] and may therefore also lack the $NH_{sulfonamide}\cdots N_{py}$ motif. Bza and cbz cocrystallise with ctz during milling with added PVP. Both cocrystals contain the $NH_{thiadiazine}\cdots O{=}C$ synthon and this H bonding pattern is absent in ctz-nia. Unfortunately, we could not obtain single crystals of ctz-aca and ctz-ppa to identify the heterosynthons present in

these amide cocrystals.

Although PVP does not affect the stability of the cocrystals of ctz (except for ctz-aca and ctz-ppa), in the majority of cases the PVP formulations were sticky or rubber-like solids. MCC on the other hand is highly compatible with all the ctz cocrystals investigated.

5. Conclusions

The thiadiazine and sulfonamide groups of ctz form robust heterosynthons with pyridine, amine and amide coformers. With very few exceptions, they not only remain intact during milling with excipients presenting competing H bond donor/acceptor functionalities, but also form when ctz and the coformer are milled in the presence of excipients. Our discussion has focused on the different heterosynthons present in the cocrystals and the competition between API-coformer and coformer-excipient interactions. Whether a cocrystal is stable or dissociates during or after formulation will also depend on other factors, such as conversion kinetics, energy input or amorphization. Nevertheless, understanding the ranking in heterosynthon strength is important with a view to the rational design of viable pharmaceutical cocrystals. The formation of cocrystals in the presence of excipients is of interest with regard to co-processing a cocrystal with an excipient to reduce production costs. Out of the cocrystals and excipients investigated a number of suitable formulations in terms of stability, visual inspection of the powder properties and pharmaceutical acceptability of the coformer (GRAS or second drug) can be identified; namely ctz-nia/MCC, ctz-nia/α-lactose, ctz-nia/DA, htz-nia/MCC, htz-nia/PVP, htz-nia/NaTC, htz-nia/α-lactose, ctz-cbz/MCC, ctz-cbz/PVP, ctz-cbz/NaTC, ctz-cbz/DA, ctz-cbz/HPC, and ctz-cbz/α-lactose. For future work it will be of interest to evaluate the stabilities of these systems during downstream processing such us as compression or granulation.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org.

Sample compositions in the ball milling experiments, IR data, additional XRPD patterns.

Acknowledgement

This publication has emanated from research supported in part by a research grant from Science Foundation Ireland (SFI) and is cofunded under the European Regional Development Fund under Grant Number 12/RC/2275. M.A. acknowledges the Royal Embassy of Saudi Arabia for a Saudi Arabia Government Scholarship.

References

(1) Schultheiss, N.; Newman, A. Pharmaceutical cocrystals and their physicochemical properties. *Cryst. Growth Des*. **2009**, *9*, 2950–2967.

(2) Blagden, N.; Coles, S. J.; Berry, D. J. Pharmaceutical co-crystals – are we there yet? *CrystEngComm* **2014**, *16*, 5753–5761.

(3) Bolla, G.; Nangia, A. Pharmaceutical cocrystals: walking the talk. *Chem. Commun*. **2016**, *52*, 8342–8360.

(4) Kale, D. P.; Zode, S. S.; Bansal, A. K. Challenges in translational development of pharmaceutical cocrystals. *J. Pharm. Sci*. **2017**, *106*, 457–470.

(5) Thakuria, R.; Delori, A.; Jones, W.; Lipert, M. P.; Roy, L.; Rodriguez-Hornedo, N. Pharmaceutical cocrystals and poorly soluble drugs. *Int. J. Pharm*. **2013**, *453*, 101–125.

(6) Qiao, N.; Li, M.; Schlindwein, W.; Malek, N.; Davies, A.; Trappitt, G. Pharmaceutical cocrystals: an overview. *Int. J. Pharm*. **2011**, *419*, 1–11.

(7) Williams, H. D.; Trevaskis, N. L.; Charman, S. A.; Shanker, R. M.; Charman, W. N, Pouton, C. W.; Porter, C. J. H. Strategies to address low drug solubility in discovery and development. *Pharmacol. Rev*. **2013**, *65*, 315–499.

(8) Alsubaie, M.; Aljohani, M.; Erxleben, A.; McArdle, P. Cocrystal forms of the BCS class IV drug sulfamethoxazole. *Cryst. Growth Des*. **2018**, *18*, 3902–3912.

(9) Eddleston, M. D.; Lloyd, G. O.; Jones, W. Cocrystal dissociation and molecular demixing in the solid state. *Chem. Commun*. **2012**, *48*, 8075–8077.

(10) Arhangelskis, M.; Lloyd, G. O.; Jones, W. Mechanochemical synthesis of pyrazine: dicarboxylic acid cocrystals and a study of dissociation by quantitative phase analysis. *CrystEngComm* **2012**, *14*, 5203–5208.

(11) Eddleston, M. D.; Thakuria, R.; Aldous, B. J.; Jones, W. An investigation of the causes of cocrystal dissociation at high humidity. *J. Pharm. Sci.* **2014**, *103*, 2859–2864.

(12) Trask, A. V.; Motherwell, W. D. S.; Jones, W. Pharmaceutical cocrystallization: Engineering a remedy for caffeine hydration. *Cryst. Growth Des.* **2005**, *5*, 1013–1021.

(13) Trask, A. V.; Motherwell, W. D. S.; Jones, W. Physical stability enhancement of theophylline via cocrystallization. *Int. J. Pharm.* **2006**, *320*, 114–123.

(14) Caira, M. R.; Nassimbeni, L. R.; Wildervanck, A. F. Selective formation of hydrogen bonded cocrystals between a sulfonamide and aromatic carboxylic acids in the solid state. *J. Chem. Soc., Perkin Trans. 2* **1995**, *12*, 2213–2216.

(15) Fischer, F.; Joester, M.; Rademann, K.; Emmerling, F. Survival of the fittest: Competitive co-crystal reactions in the ball mill. *Chem. - Eur. J.* **2015**, *21*, 14969–1497.

(16) Alsirawan, M. B.; Vangala, V. R.; Kendrick, J.; Leusen, F. J.; Paradkar, A. Coformer replacement as an indicator for thermodynamic instability of cocrystals: competitive transformation of caffeine: dicarboxylic acid. *Cryst. Growth Des*. **2016**, *16*, 3072–3075.

(17) Remenar, J. F.; Peterson, M. L.; Stephens, P. W.; Zhang, Z.; Zimenkov, Y.; Hickey, M. B. Celecoxib: nicotinamide dissociation: using excipients to capture the cocrystal's potential. *Mol. Pharmaceutics* **2007**, *4*, 386–40.0

(18) Bhardwaj, S.; Lipert, M.; Bak, A. Mitigating cocrystal physical stability liabilities in preclinical formulations. *J. Pharm. Sci*. **2017**, *106*, 31–38.

(19) Arabiani, M. R.; Raju, B. K.; Bhunia, S.; Teja, P. K.; Lodagekar, A.; Chavan, R. B.; Shastri, N. R.; Reddy, C. M.; Shelat, P.; Dave, D. Brexpiprazole-catechol cocrystal: Structure elucidation, excipient compatibility and stability. *CrystEngComm* **2019**, Advance Article.

(20) Rajbhar, P.; Sahu, A. K.; Gautam, S. S.; Prasad, R. K.; Singh, V.; Nair, S. K. Formulation and evaluation of clarithomycin co-crystals tablets dosage forms to enhance the bioavailability. Pharma Innovation **2016**, *5*, 5–13.

(21) Duggirala, N. K.; Vyas,A.; Krzyzaniak, J. F.; Arora, K. K.; Suryanarayanan, R. Mechanistic insight into caffeine−oxalic cocrystal dissociation in formulations: Role of excipients. *Mol. Pharmaceutics* **2017**, *14*, 113879–3887.

(22) Koranne, S.; Sahoo, A.; Krzyzaniak, J. F.; Luthra, S.; Arora, K. K.; Suryanarayanan, R. Challenges in transitioning cocrystals from bench to bedside: Dissociation in prototype drug product environment. *Mol. Pharmaceutics* **2018**, *15*, 83297–3307.

(23) Kaur, N.; Duggirala, N. K.; Thakral, S.; Suryanarayanan, R. Role of lattice disorder in water-mediated dissociation of pharmaceutical cocrystal systems. *Mol. Pharmaceutics* **2019**, *16*, 73167–3177.

(24) Koranne, S.; Krzyzaniak, J. F.; Luthra, S.; Arora, K. K.; Suryanarayanan, R. Role of coformer and excipient properties on the solid-state stability of theophylline cocrystals. *Cryst. Growth Des*. **2019**, *19*, 868–875.

(25) Chow, P. S.; Lau, G.; Ng, W. K.; Vangala, V. R. Stability of pharmaceutical cocrystal during milling: A case study of 1:1 caffeine–glutaric acid. *Cryst. Growth Des.* **2017**, *17*, 4064–4071.

(26) Aljohani, M.; Pallipurath, A.; McArdle, P.; Erxleben, A. A comprehensive cocrystal screening study of chlorothiazide. *Cryst. Growth Des*. **2017**, *17*, 5223–5232.

(27) Walsh, D.; Serrano, D. R.; Worku, Z. A.; Norris, B. A.; Healy, A. M. Production of cocrystals in an excipient matrix by spray drying. *Int. J. Pharm*. **2018**, *536*, 467–477.

(28) Walsh, D.; Serrano, D. R.; Worku, Z. A.; Madi, A. M.; O'Connell, P.; Twamley, B.; Healy, A. M. Engineering of pharmaceutical cocrystals in an excipient matrix: Spray drying versus hot melt extrusion. *Int. J. Pharm*. **2018**, *551*, 241–256.

(29) Karimi-Jafari, M.; Ziaee, A.; Iqbal, J.; O'Reilly, E.; Croker, D.; Walker, G. Impact of polymeric excipient on cocrystal formation via hot-melt extrusion and subsequent downstream processing. *Int. J. Pharm*. **2019**, *566*, 745–755.

(30) Gajda, M.; Nartowski, K. P.; Pluta, J.; Karolewicz, B. Tuning the cocrystal yield in matrix-assisted cocrystallization via hot melt extrusion: A case of theophylline-nicotinamide cocrystal. *Int. J. Pharm.* **2019**, *569*, 118579.

(31) Lu, T.; Chen, C. Uncertainty evaluation of humidity sensors calibrated by saturated salt solutions. *Measurement*, **2007**, *40*, 591–599.

(32) Sanphui, P.; Rajput, L. Tuning solubility and stability of hydrochlorothiazide co-crystals. *Acta Cryst*. **2014**, *B70*, 81–90.

(33) Bolhuis, G. K.; Armstrong, N. A. Excipients for direct compaction—an update. *Pharm. Dev. Technol*. **2006**, *11*, 111–124.

(34) Carlin, B. Direct compression and the role of filler-binders. in Augsburger, L. L.; Augsburger, L. L.; Hoag, S. W. (Eds.), Pharmaceutical Dosage Forms: Tablets, Informa (2008), pp. 173–216.

(35) Thoorens, G.; Krier, F.; Leclercq, B.; Carlin, B.; Evrard, B. Microcrystalline cellulose, a direct compression binder in a quality by design environment—A review. *Int. J. Pharm*. **2014**, *473*, 64–72.

(36) Bühler, V. Polyvinylpyrrolidone Excipients for Pharmaceuticals: Povidone, Crospovidone and Copovidone. Berlin, Heidelberg, New York: Springer. 2005, pp. 1–254.

(37) Simonelli, A. P. Mehta, S. C.; Higuchi, W. I. Inhibition of sulfathiazole crystal growth by polyvinylpyrrolidone. *J. Pharm. Sci*. **1970**, *59*, 633–638.

(38) Sanphui, P.; Devi, V. K.; Clara, D.; Malviya, N.; Ganguly, S.; Desiraju, G. R. Cocrystals of hydrochlorothiazide: Solubility and diffusion/permeability enhancements through drug–coformer interactions. *Mol. Pharmaceutics* **2015**, *12*, 1615–1622.

(39) Dürig, T.; Karan, K. Chapter 9 - Binders in Wet Granulation. in Handbook of Pharmaceutical Wet Granulation. Theory and Practice in a Quality by Design Paradigm. Acadmic Press, 2019, 317–349.

(40) Moolchandani, V.; Augsburger, L. L.; Gupta, A.; Khan, M.; Langridge, J.; Hoag, S. W. Characterization and selection of suitable grades of lactose as functional fillers for capsule filling: part 1. *Drug Dev Ind Pharm.* **2015**, *41*,1452–1463.

(41) Gniado, K.; MacFhionnghaile, P.; McArdle, P.; Erxleben, A. The natural bile acid surfactant sodium taurocholate (NaTC) as a coformer in coamorphous systems: Enhanced physical stability and dissolution behavior of coamorphous drug-NaTc systems. *Int. J. Pharm*. **2017**, *535*, 132–139.

(42) Gniado, K.; Löbmann, K.; Rades, T.; Erxleben, A. The influence of co-formers on the dissolution rates of co-amorphous sulfamerazine/excipient systems. *Int. J. Pharm*. **2016**, *504*, 20–26.

(43) Fitzpatrick, S.; McCabe, J. F.; Petts, C. R.; Booth, S. W. Effect of moisture on polyvinylpyrrolidone in accelerated stability testing. *Int. J. Pharm*. **2002**, *246*, 143–51.

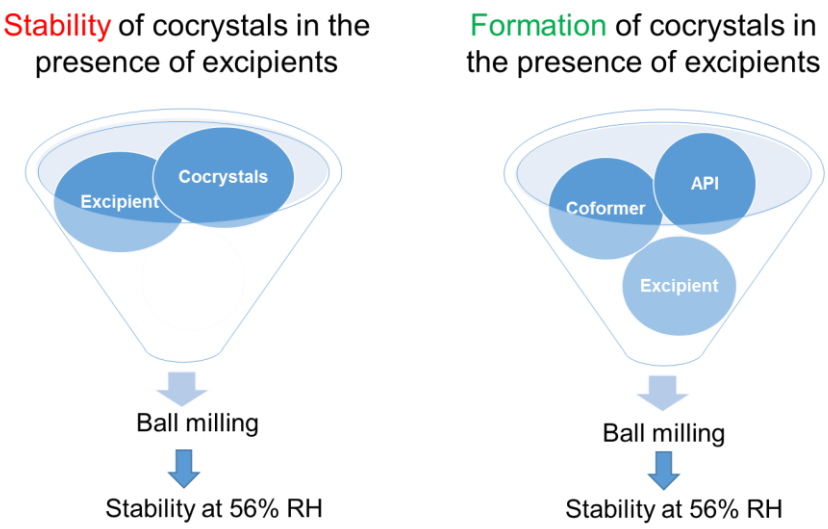
(44) Yang, H. W.; Craven, B. M. Charge density of 2-pyridone". *Acta Cryst.* **1998**, *B54*, 912–920.

(45) Ohms, U.; Guth, H.; Heller, E.; Dannöhl, H.; Schweig, A. Comparison of observed and calculated electron-density 2-pyridone, C_5H_5NO, crystal-structure refinements at 295K and 120K, experimental and theoretical deformation density studies. *Z. Kristallogr*. **1984**, *169*, 185–200.

For Table of Contents Use Only

Influence of Excipients on Cocrystal Stability and Formation

Marwah Aljohani,[1] Patrick McArdle,[1,2,*] and Andrea Erxleben[1,2,*]



Synopsis:

The stability and formation of cocrystals of chlorothiazide in the presence of excipients is investigated and discussed with regard to heterosynthons and competing H bonding interactions.