Engineering of pharmaceutical cocrystals in an excipient matrix: spray drying versus hot melt extrusion

David Walsh^{a,b}, Dolores R. Serrano^c, Zelalem Ayenew Worku^{a,b}, Atif M. Madi^{a,b}, Peter O'Connell^a, Brendan Twamley^d, Anne Marie Healy^{a,b*}

^a School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Dublin 2, Ireland.

^b SSPC, Synthesis and Solid State Pharmaceutical Centre, Ireland.

^c School of Pharmacy, Universidad Complutense de Madrid, Plaza Ramón y Cajal s/n, 28040 Madrid, Spain.

^d School of Chemistry, Trinity College Dublin, Dublin 2, Ireland.

*Corresponding author:

Anne Marie Healy

School of Pharmacy and Pharmaceutical Sciences

Trinity College Dublin

Dublin 2, Ireland.

Tel.: +353 1 896 1444

E-mail address: healyam@tcd.ie

28

29 **Abstract**

30 The comparison of spray drying versus hot melt extrusion (HME) in order to formulate
31 amorphous solid dispersions has been widely studied. However, to the best of our knowledge,
32 the use of both techniques to form cocrystals within a carrier excipient has not previously
33 been compared. The combination of ibuprofen (IBU) and isonicotinamide (INA) in a 1:1
34 molar ratio was used as a model cocrystal. A range of pharmaceutical excipients was selected
35 for processing - mannitol, xylitol, Soluplus and PVP K15. The ratio of cocrystal components
36 to excipient was altered to assess the ratios at which cocrystal formation occurs during spray
37 drying and HME. Hansen Solubility Parameter (HSP) and the difference in HSP between the
38 cocrystal and excipient (ΔHSP) was employed as a tool to predict cocrystal formation. During
39 spray drying, when the difference in HSP between the cocrystal and the excipient was large,
40 as in the case of mannitol (ΔHSP of $18.3 \text{ MPa}^{0.5}$), a large amount of excipient (up to 50%)
41 could be incorporated without altering the integrity of the cocrystal, whereas for Soluplus and
42 PVP K15, where the ΔHSP was 2.1 and $1.6 \text{ MPa}^{0.5}$ respectively, the IBU:INA cocrystal alone
43 was only formed at a very low weight ratio of excipient, i.e. cocrystal:excipient 90:10.
44 Remarkably different results were obtained in HME. In the case of Soluplus and PVP K15, a
45 mixture of cocrystal with single components (IBU and INA) was obtained even when only
46 10% excipient was included. In conclusion, in order to reduce the number of unit operations
47 required to produce a final pharmaceutical product, spray drying showed higher feasibility
48 over HME to produce cocrystals within a carrier excipient.

49

50

51

52

53 **Keywords:** cocrystal, spray drying, hot melt extrusion, ibuprofen, Hansen Solubility
54 Parameter

55

56

57

1. Introduction

Spray drying has previously been shown to be an effective method to produce cocrystals from both **congruently** and incongruently saturating solutions (Alhalaweh and Velaga, 2010). It can offer an advantage compared to other solution based methods such as cooling crystallisation, which can result in a mixture of phases (Fucke et al., 2012). Further to this, spray drying is favourable as it is a scalable, continuous one-step process often employed in the pharmaceutical industry (Broadhead et al., 1992; do Amaral et al., 2018). Spray drying parameters can also be altered to tailor the properties of particles produced by spray drying, such as particle size, shape and density (Vehring et al., 2007). However, disadvantages of spray drying include the requirement of large volumes of organic solvent (Ré, 2006), residual solvent of spray dried powders (Patel et al., 2009), the production of poorly flowable powders (Walton, 2000) **and the expense of the equipment at large scale.**

Hot melt extrusion (HME) has been explored as a method to produce cocrystals (Dhumal et al., 2010; Li et al., 2017; Moradiya et al., 2014). This process can offer a number of advantages as a formulation processing method, as it is a scalable and continuous process. Unlike spray drying, it is a solvent free method, and is therefore often regarded as a ‘greener’ method in comparison to spray drying, as large volumes of solvent are not required. As a result, the product obtained will have negligible amounts of oxygen and water, an advantage for pharmaceuticals which are susceptible to oxidation and hydrolysis (Breitenbach, 2002; Li et al., 2013). However, extrusion can also confer a number of disadvantages, as heat stress and shear force can cause chemical degradation of an active pharmaceutical ingredient (API) (Crowley et al., 2007). In the case of cocrystallisation (processing of drug and coformer) by extrusion, it has previously been demonstrated that cocrystallisation can occur when processed above the eutectic temperature (Dhumal et al., 2010).

Ibuprofen (IBU) is a Non-Steroidal Anti-Inflammatory Drug (NSAID) included in Class II of the Biopharmaceutics Classification System (BCS), demonstrating poor aqueous solubility and high permeability (Alvarez et al., 2011). Various attempts to increase the bioavailability of IBU, such as salt formation (Tung et al., 1991) and the formation of amorphous dispersions (Marsac et al., 2009; Shen et al., 2010), are abundant in the literature. Cocrystallisation of IBU can offer an alternative formulation approach to increase the bioavailability of the API without altering the chemical integrity, while maintaining the physical stability of the API. Cocrystals of ibuprofen with a number of different coformers

have been generated by methods such as solvent evaporation (Chow et al., 2012), cooling crystallisation (Friščić and Jones, 2007), liquid assisted grinding (Friščić and Jones, 2007), dry grinding (Alshahateet, 2010, 2011), HME (Dhumal et al., 2010; Kelly et al., 2012; Moradiya et al., 2014), and freeze drying (Eddleston et al., 2013). A review of the literature revealed no previous reports of an IBU cocrystal produced by spray drying.

We have previously described the production of cocrystals of another BCS Class II drug, sulfadimidine, in the presence of a third component by a one-step spray drying process in order to reduce the number of unit operations which are required to produce a final pharmaceutical product (Walsh et al., 2018). Cocrystal integrity was preserved when the cocrystal components were immiscible with the excipient, based on the difference in Hansen Solubility Parameter (HSP). However, our previous work did not consider the use of HME as an alternative continuous process to produce a cocrystal-in-excipient matrix system.

Attempts have previously been made to form the IBU:INA cocrystal by HME in the presence of xylitol, Soluplus and Eudragit EPO (Li et al., 2016). Cocrystal formation occurred only in the presence of xylitol (which has a melt temperature of 93.68 °C) at a 90:10 weight ratio of cocrystal components to xylitol, but not with Soluplus or Eudragit EPO, probably due to IBU amorphisation during the extrusion process (Li et al., 2016). Ratios of 70:30 and 50:50 (by weight) of cocrystal components to xylitol resulted in cocrystal formation, but individual crystalline IBU and INA were also detected in the extruded products. However, alteration of the processing temperature and screw configuration during extrusion led to cocrystal formation even with a higher xylitol load of 50% by weight (Li et al., 2017).

The aim of this work was to fully investigate the impact of including a carrier excipient on cocrystal formation during spray drying and to compare it to HME. Spray drying and HME techniques have previously been compared in the context of the production of amorphous solid dispersions (Tian et al., 2014) and fixed dose combinations (Kelleher et al., 2018), but the production of cocrystals in an excipient matrix by both methods has not been compared.

The combination of IBU:INA was used as model cocrystal. A range of pharmaceutical excipients was selected for processing. The ratio of cocrystal components to excipient was altered to assess the ratios at which cocrystal formation occurs. Due to the low melt temperature of xylitol and the low yield of xylitol on spray drying, mannitol (a six carbon polyol which is amenable to spray drying and has a similar HSP to xylitol, Table 2) was chosen as a model crystalline excipient for spray drying. Soluplus and PVP K15 were

122 selected as amorphous excipients for comparison purposes. Solid state characterisation was
123 performed as well as intrinsic dissolution studies from constant surface area discs to compare
124 the product characteristics of materials processed by the two different methods.

2. Materials and Methods

2.1 Materials

Racemic ibuprofen (IBU) was purchased from Kemprotec (Cumbria, U.K.). INA, mannitol and PVP K15 (average molecular weight 10,000) were obtained from Sigma-Aldrich (Wicklow, Ireland). Xylitol was purchased from Lancaster (Morecambe, England). Soluplus was a gift from BASF Corporation (Ludwigshafen, Germany). Chemical structures of the cocrystal components and excipients are illustrated in Figure 1. Ethanol was supplied by Corcoran Chemicals (Dublin, Ireland). Methanol, HPLC grade, was purchased from Sigma-Aldrich (Wicklow, Ireland). Water, analytical grade, was prepared from an Elix 3 connected to a Synergy UV system (Millipore, UK). All other chemicals used were of analytical grade.

2.2 Methods

2.2.1 Preparation of the cocrystal by solvent evaporation

IBU (2.06 g) and INA (1.22 g) were added to a beaker containing 50 ml of isopropanol as solvent. Sonication was performed to ensure complete dissolution of the API and coformer. The beaker was covered with pierced parafilm, which was placed in a fumehood and left to evaporate.

2.2.2 Preparation of the cocrystal and cocrystal-in-excipient systems by spray drying and hot melt extrusion

Nomenclature

Each formulation is named in the text with reference to the method of production (spray drying (SD) or hot melt extrusion (HME)), excipient used (M = mannitol, X = xylitol, P = PVP K15 and S = Soluplus) and excipient weight fraction. For example, the co-spray dried system with 10% mannitol is referred to as SD-M-10.

Preparation of the cocrystal by spray drying

For the cocrystal alone, a 1% w/v solution of IBU:INA (1:1 molar ratio) was prepared in ethanol or isopropanol (300 ml) and sonicated until completely dissolved. For the systems containing the cocrystal components and an excipient, a 1:1 molar ratio of IBU:INA was

dissolved in a mixture of ethanol and water at a 90:10 v/v ratio. When the two cocrystal components were fully dissolved, the carrier excipient was then added and fully dissolved. For the system containing 50 % w/w of excipient, the ratio of ethanol to water was altered to 80:20 v/v to ensure complete dissolution of the excipient. The batch size for all experiments performed by spray drying was 3 grams (300 ml of a 1 % w/v solution). Solutions were spray dried using a Büchi B-290 Mini Spray Dryer operating in the open mode (inlet temperature 90 °C, pump speed 30 % (equivalent to 9-10 ml/min), aspirator 100 % (equivalent to 35 m³/hr), nitrogen flow rate 667 Normlitres/h) (Walsh et al., 2018). The spray dried cocrystal refers to the cocrystal spray dried from ethanol, unless indicated otherwise.

For comparison purposes, physical mixtures of cocrystal and excipients were prepared using an agate pestle and mortar.

A solution of INA and Soluplus 50:50 weight ratio was dissolved in a mixture of 90:10 v/v of ethanol and water and spray dried under the same spray drying conditions.

A 1 %w/v solution of IBU was spray dried using ethanol as solvent. The inlet temperature was set at 65 °C due to the low melt temperature of IBU. All other processing conditions were kept the same.

Negative controls – Spray drying

IBU or INA was spray dried with mannitol to investigate the possible formation of a cocrystal between the API or coformer with the crystalline excipient. IBU was spray dried with mannitol at a weight ratio of 0.566: 0.1, which is the same ratio of IBU:mannitol used in the formulation comprising 90:10 (w/w) cocrystal components to excipient. INA was also spray dried with mannitol at a weight ratio of 0.334:0.1. All process parameters were unchanged. The solvent used was a mixture of 90:10 v/v ethanol and water.

Preparation of the cocrystal by hot melt extrusion

A 1:1 molar ratio of IBU and INA was premixed with either xylitol, Soluplus or PVP K15 using a mortar and pestle for 5 minutes. The ratio of cocrystal components to excipient was 90:10 (w/w). HME was performed using a co-rotating, fully intermeshing twin-screw extruder (Microlab, Rondol Technology Ltd, France). The extruder die (Rondol Technology Ltd, France) was 2 mm in diameter, and was connected via screws to the end of the barrel. Only conveying elements were assembled on the screw shafts. The extruder contained five heating zones, which were set at 70, 80, 90, 90 and 80 °C from the feeding zone to the exit

die. The batch size used was 10 grams for all extrusion studies. The cylindrical extrudate was air cooled and subsequently cryomilled.

Negative controls – Hot melt extrusion

IBU or INA was extruded with xylitol to investigate the possible formation of a cocrystal between the API or coformer with the crystalline excipient. IBU was extruded with xylitol at a weight ratio of 0.566:0.1, which is the same ratio of IBU:xylitol used in the formulation comprising 90:10 (w/w) cocrystal components to excipient. INA was hot melt extruded with xylitol at a weight ratio of 0.334:0.1. All process parameters were unchanged.

Cryomilling

HME samples were pulverised using a high-energy cryogenic ball mill (Retsch Cryomill, Haan, Germany) with circulating liquid nitrogen for 3 cycles consisting of 5 minutes of grinding followed by a 2-minute break before physicochemical analysis.

2.2.3 Solid state characterisation

Single crystal X-ray diffraction

X-ray structural analysis for crystals of IBU:INA ($C_{19}H_{24}N_2O_3$), prepared by solvent evaporation from isopropanol, was performed on a Bruker APEX Duo CCD at 100 K with an Oxford Cobra cryostat, with the sample mounted on a MiTeGen microloop using Cu $K\alpha$ radiation ($\lambda = 1.54178 \text{ \AA}$). Bruker APEX (Bruker, 2014) software was used to collect and reduce data and determine the space group. Absorption corrections were applied using SADABS (Bruker, 2014/5). Structures were solved with the XT structure solution program (Sheldrick, 2015), using Intrinsic Phasing and refined with the XL refinement package (Sheldrick, 2008) using Least Squares minimisation. All non-hydrogen atoms were refined anisotropically. Hydrogen atoms were assigned to calculated positions using a riding model with appropriately fixed isotropic thermal parameters, except for amide hydrogens (N1, N25) which were located on the difference map and refined as semi-free. The sample was weakly diffracting leading to a high wR_2 and poor high angle data. Apart from the acid moiety, each ibuprofen group is fully disordered and is modelled in two positions with O10/O12 64:36% and O34/O36 53:47% occupancy, and restraints were used for convergence of the least squares refinements (DFIX, SADI, SIMU). Crystallographic data, CCDC 1862812, can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

217

218 *Powder X-ray diffraction*

219 Powder X-ray analysis (PXRD) was performed as previously described (Walsh et al., 2018)
220 using a wide-angle Miniflex II Rigaku™ diffractometer with Ni-filtered Cu K α radiation
221 (1.54 Å). The tube voltage and tube current used were 30 kV and 15 mA, respectively. The
222 PXRD patterns were recorded (n=3) for 2 theta ranging from 5° to 40° at a step scan rate of
223 0.05° per second. Rigaku Peak Integral software was used to determine peak intensity for
224 each sample using the Sonneveld-Visser background edit procedure.

225 The programme Mercury (version 3.9, Cambridge Crystallographic Data Centre, Cambridge,
226 UK) was used for calculation of X-ray powder patterns on the basis of the single crystal
227 structure.

228 *Differential scanning calorimetry (DSC)*

229 DSC was performed as previously described (Walsh et al., 2018) using a Mettler Toledo DSC
230 821e instrument under nitrogen purge. Powder samples (3-6 mg) were placed in aluminium
231 pans (40 μ l), sealed, pierced to provide three vent holes and heated at a rate of 10 °C/min in
232 the temperature range of 25 to 200 °C. Temperature and enthalpy were calibrated using
233 indium as standard. The DSC was controlled by Mettler Toledo STARE software (version
234 6.10) working on a Windows NT operating system. All temperature values refer to onset
235 temperature. Each measurement was performed in triplicate.

236 *Modulated differential scanning calorimetry (MDSC)*

237 MDSC scans were performed using a DSC Q200 (TA Instruments, United Kingdom) with
238 nitrogen as the purge gas. Samples were loaded into sealed standard aluminium pans, held at
239 105 °C for 10 minutes to remove any residual moisture and scanned over a temperature range
240 of 25-180 °C with a modulation rate of 0.53 °C every 40 seconds, with a scanning rate of 5
241 °C/min. The instrument was calibrated for temperature and cell constant using high purity
242 indium. MDSC data was analysed using TA Universal Analysis software (TA Instruments,
243 Leatherhead, UK) version 4.5 A. Each measurement was performed in triplicate.

244 *Thermogravimetric analysis (TGA)*

245 TGA was performed using a Mettler TG50 measuring module coupled to a Mettler Toledo
246 MT5 balance (Schwerzenbach, Switzerland). Approximately 8–10 mg samples were

analyzed in open aluminum pans, using nitrogen as the purge gas. Samples were heated from 25 to 300 °C at a rate of 10 °C/min.

Attenuated Total Reflectance Fourier Transform Infrared Spectroscopy (ATR-FTIR)

Infrared spectra were recorded on a PerkinElmer Spectrum 1 FT-IR Spectrometer equipped with a UATR and a ZnSe crystal accessory. Each spectrum was scanned in the range of 650-4000 cm⁻¹ with a resolution of 4 cm⁻¹. Data were evaluated using Spectrum v 5.0.1. software. Four scans of each sample were taken.

Dynamic vapour sorption (DVS)

Vapour sorption experiments were carried out on a DVS Advantage-1 automated gravimetric sorption analyser (Surface Measurement Systems, Alpertown, UK) at 25.0 ± 0.1 °C. Ethanol was used as the probe vapour. A mass of 15-20 mg of powder was loaded on to the sample basket. Samples were dried for 1 hour at 0% relative humidity and then subjected to step changes of 10% RH up to 90% RH, and the reverse for desorption. The sample mass was allowed to reach equilibrium, defined as $dm/dt \leq 0.002$ mg/min over 10 min, before the RH was changed (Grossjohann et al., 2015). Two cycles of sorption and desorption were performed for each sample. Samples were recovered and analysed by PXRD and DSC.

Particle size analysis (PSA)

The geometric particle size distributions (PSD) were determined by laser diffraction using a Malvern Mastersizer 2000 (Malvern Instruments Ltd., Worcestershire, UK). Particles were dispersed using a Scirocco dry feeder instrument with 3 bar pressure. An obscuration of 0.5-3% was obtained under a vibration feed rate of 75%. Values reported are D₅₀ (median particle size) results. Mastersizer 2000 software (Version 5.61) was used for the analysis of the particle size. Results reported are the average of three analyses for each sample.

2.2.4. Scanning electron microscopy (SEM)

The surface images of the samples were captured at various magnifications by SEM using a Zeiss Supra Variable Pressure Field Emission Scanning Electron Microscope (Germany) equipped with a secondary electron detector at 5 kV. Samples were glued on to carbon tabs, mounted onto aluminium pin stubs and sputter-coated with gold/palladium under vacuum prior to analysis.

2.2.5. Intrinsic/constant surface area dissolution studies

The intrinsic dissolution studies of solid materials were performed using a Wood's intrinsic dissolution apparatus (Elementec, Ireland). This allowed the dissolution to be measured from constant surface area discs. Discs were prepared by compressing the powder (200 mg) into compacts using a PerkinElmer hydraulic press with an 8 mm (diameter) punch and die set at a pressure of 3 tonnes for a 1 min dwell time. The dissolution studies were carried out in phosphate buffer (pH: 7.2, volume: 900 mL, temperature: 37 °C) at a rotation speed of 100 rpm as indicated in the USP Pharmacopeia 38/NF 33. All dissolution studies were performed under sink conditions. Aliquots (5 ml) were withdrawn with volume replacement at appropriate time intervals. Samples were filtered through 0.45 µm PTFE filters and analysed for IBU content by HPLC. The study was performed in triplicate. Samples were taken at 2, 4, 6, 8, 10, 15, 20, 25, 30, 40, 50 and 60 minutes. The dissolution rate was determined from the slope of the dissolution time profiles over the first 10 minutes. At the end of the experiments, the discs were recovered, dried at ambient temperature and analysed by PXRD for process induced phase transformation.

For some samples, additional intrinsic dissolution studies were carried out at 20 °C, with all other conditions being kept the same.

Statistical analysis of dissolution profiles was performed using DDSolver (Zhang et al., 2010). Univariate ANOVA analysis was performed to compare drug dissolution profiles considering a p-value < 0.05 as significant (Yuksel et al., 2000).

2.2.6. High performance liquid chromatography (HPLC)

The concentration of IBU in solution was determined using an Alliance HPLC with a Waters 2695 Separations module system and Waters 2996 photodiode array detector. The mobile phase consisted of 85% HPLC grade methanol and 15% HPLC grade water containing 0.2% trifluoroacetic acid (Li et al., 2016). The mobile phase was degassed by sonicating for 10 minutes. Separation was performed on a Waters XBridge C18 column with a length of 150 mm, an internal diameter of 3 mm and a particle size of 3.5 µm. Samples were analysed at a UV detection wavelength of 220 nm. An injection volume of 20 µL was used. The elution was carried out isocratically with a flow rate of 0.5 mL/min. The temperature of the column chamber was maintained at 40 °C for the entire analytical process. Elution times for IBU and INA were 2.2 and 1.5 minutes respectively. With the systems containing Soluplus, the ratio

of aqueous to organic phase was altered to 70:30 v/v due to peak interference. The elution time for IBU was 5.7 minutes. Empower software was used for peak evaluation.

2.2.7. Hansen solubility parameter calculation

Hansen solubility parameters were calculated from the chemical structures using the Van Krevelen method (Van Krevelen and Te Nijenhuis, 2009). The weight average molecular weights were used to determine solubility parameters for polymeric excipients (Scott, 1992). The total HSP contribution was divided into three partial solubility parameters: dispersion (δ_d), polar (δ_p) and hydrogen bonding (δ_h). The total solubility parameter was calculated as indicated in Equations 1-4:

$$\delta_t = (\delta_d^2 + \delta_p^2 + \delta_h^2)^{0.5} \quad (\text{Eq. 1})$$

$$\delta_d = \frac{\sum_{i=1}^n F_{di}}{\sum_{i=1}^n v_i} \quad (\text{Eq. 2})$$

$$\delta_p = \frac{(\sum_{i=1}^n F_{pi}^2)^{0.5}}{\sum_{i=1}^n v_i} \quad (\text{Eq. 3})$$

$$\delta_h = \left(\frac{\sum_{i=1}^n F_{hi}}{\sum_{i=1}^n v_i} \right)^{0.5} \quad (\text{Eq. 4})$$

where i is the structural group within the molecule, F_{di} is the group contribution of the dispersion forces, F_{pi} is the group contribution of the polar forces, F_{hi} is the group contribution of the hydrogen bonding forces, and V_i is the group contribution of the molar volume (Mohammad et al., 2011).

3. Results

3.1 Single crystal X-ray diffraction characterisation of solvent evaporated cocrystal

Using an equimolar ratio of IBU:INA, the solvent evaporation method produced a colourless crystalline sample of the cocrystal. A suitable crystal was analysed via single crystal X-ray diffraction yielding a formula of $C_{13}H_{18}O_2 \cdot C_6H_6N_2O$, a 1:1 cocrystal. The asymmetric unit

consists of two independent IBU and two INA molecules, linked via hydrogen bonding, almost as predicted (Li et al., 2016). Each IBU is disordered over two positions and Figure 2A only shows the majority occupied moiety (see Supplementary material, Figure S1 and S2 for further figures). The hydrogen bonding between the INA moieties are formed via the amide NH and the opposite carbonyl group ($N1...O27 = 2.963(4)$, $N25...O3 = 2.926(4)$ Å). IBU also forms a hydrogen bond with the INA ($O...N$ 2.575(4), 2.607(4) Å with angles $> 157^\circ$) tying the four molecules into a linear array. One IBU is pointing up and the other pointing down. Each linear array is hydrogen bonded to a neighbouring array through the free INA amine NH to the IBU carbonyl ($N1...O36^{ii}$, 3.113(4) Å; symmetry transformations used to generate equivalent atoms: ii -x,-y+2,-z+1) forming a sheet (Figure 2B). Each successive layer packs on the nearest layer by slotting the IBU between each other (Supplementary material, Figure S3). There are several heterosynthron IBU cocrystals known in the literature (Alshahateet, 2010, 2011; Berry et al., 2008; Chen et al., 2010; Stone et al., 2009; Walsh et al., 2003). Many are trimers e.g. IBU:X:IBU. Only a few display the same packing motif seen here where a tetramer is formed IBU:INA:INA:IBU (Alshahateet, 2011; Berry et al., 2008). Crystallographic data of the cocrystal are presented in Table 1.

3.2 Solid state characterisation of processed spray dried and hot melt extruded materials

3.2.1 Powder X-ray diffraction

3.2.1.1 Spray drying

Spray drying the solution of IBU:INA at a 1:1 molar ratio resulted in cocrystal formation. Similar Bragg peak intensity was seen for the cocrystal produced by spray drying from ethanol and the cocrystal produced by spray drying from isopropanol. Bragg peaks attributable to IBU and INA were not present. Characteristic peaks of IBU raw material may be observed at 6.15° , 12.25° , 16.7° and 24.6° 2θ , and peaks of INA raw material at 17.85° , 18.9° , 20.85° and 23.5° 2θ (Figure 3A). Similarly to Li et al. who prepared the cocrystal by coextrusion (Li et al., 2016), Bragg peaks attributed to the IBU:INA cocrystal were observed at 6.4° , 17.45° , 18.95° and 20.1° 2θ (Figure 3A), indicating that the same form of the cocrystal was obtained by both hot melt extrusion and spray drying. Spray drying can produce a different polymorphic form of a cocrystal than other methods of cocrystal

formation, as previously seen with the sulfadimidine:4-aminosalicylic acid cocrystal (Grossjohann et al., 2015; Walsh et al., 2018). However, polymorphism of the IBU:INA cocrystal has not been reported to date. The cocrystal produced by solvent evaporation from isopropanol resulted in more intense Bragg peaks compared to the cocrystals produced by spray drying. Rapid drying processes such as spray drying can result in crystal lattice imperfections such as point defects, line defects and plane defects (Corrigan, 1995), which in turn can result in phenomena such as small peak shifts and a reduction in peak intensity on the PXRD diffractogram (Ungár, 2004). Spray dried IBU resulted in crystalline IBU, with the same polymorph obtained as the raw material (Figure 3A).

Cocrystal formation was observed for the spray dried formulations with mannitol, i.e. SD-M-10, SD-M-30 and SD-M-50 formulations (Figure 3B). Bragg peaks attributable to the individual cocrystal components were not observed. However, Bragg peaks attributable to both the cocrystal and to different polymorphic forms of mannitol were seen. Both beta and delta mannitol peaks were present in the PXRD diffractogram for all ratios of cocrystal components to excipient (Figure S4, Supplementary material). Co-spray drying mannitol with lysozyme has previously been shown to produce a mix of mannitol polymorphs (Hulse et al., 2009). The API and coformer have similar HSP values, 19.4 MPa^{0.5} and 24.4 MPa^{0.5} respectively, whereas mannitol HSP is 39.1 MPa^{0.5} (Table 2). It has previously been determined that cocrystallisation can occur when the difference in HSP between the API and coformer is less than 7 MPa^{0.5} (Mohammad et al., 2011), while cocrystal formation in the presence of a third component occurred when the difference in HSP between the cocrystal and excipient (i.e. third component) was above 9.6 MPa^{0.5} (Walsh et al., 2018).

Cocrystal formation by spray drying with different ratios of cocrystal components to Soluplus was also assessed. The SD-S-10 formulation resulted in cocrystal formation (Figure 3D). The ratio of Soluplus to cocrystal components was increased and cocrystal formation at these ratios was assessed. Bragg peaks attributable to the cocrystal were also observed for the SD-S-15, SD-S-20 and SD-S-30 formulations, as well as crystalline INA and what was taken to be an amorphous phase comprising IBU and Soluplus, given the observed shift in the T_g of Soluplus when loads of ≥ 15% Soluplus were incorporated into the feed solution. The PXRD patterns of the polymorphic forms of INA were obtained from single crystal data obtained from the Cambridge Crystal Database (Figure S5, Supplementary material). Form I (CSD ref code: EHOWIH01) is the unprocessed raw material polymorph used in these experiments (Groom et al., 2016).

A peak attributable to a polymorph of INA (form IV, CSD ref code: EHOWIH04) can be seen at 23° 2 θ when Soluplus loads $\geq$ 15% were incorporated into the process. Attempts were made to co-spray dry the cocrystal components with Soluplus at a ratio of 60:40 (w/w). However, when this ratio was used, the yield was significantly affected, with negligible amounts of product reaching the collection vessel of the spray dryer. Cocrystal formation, without other separated coformer or API components, was only seen when 10% Soluplus was used. Above this excipient loading, a mixture of cocrystal, a glass solution of IBU and Soluplus, and crystalline INA was formed, which can be explained by the fact that the difference in HSP between Soluplus and cocrystal is 2.1 MPa^{0.5}. It was previously observed that when the HSP values of cocrystal and excipient are very close, cocrystal formation only occurs when low excipient loads are used (Walsh et al., 2018).

Cocrystal formation in the presence of PVP K15 by spray drying and HME was also assessed. PVP K15 was chosen as, unlike Soluplus, its glass transition temperature was above the extrusion processing temperature (section 2.2.2). It was hypothesised that this could prevent the formation of a glass solution being formed as a side reaction. A shorter chain PVP was chosen as higher chain length polymers can be more viscous in solution, which can result in kinetic trapping of the API/coformer during the fast solvent evaporation when spray drying, resulting in the formation of an amorphous dispersion (Paudel et al., 2013).

Cocrystal formation was assessed by spray drying in the presence of PVP K15 at a ratio of 90:10 (w/w) cocrystal components to excipient. Bragg peaks attributable only to the cocrystal were seen for the SD-P-10 formulation (Figure 3C). When the SD-P-20 formulation was processed (w/w), again peaks attributable only to the cocrystal were observed.

Due to the abundance of potential hydrogen bonding sites in mannitol, negative controls were prepared to investigate the potential for cocrystal formation between the crystalline excipient (mannitol) and the API or the coformer. PXRD analyses of the control powders showed no new peaks which could be attributed to a 'cocrystal cocktail'. Results of PXRD analyses are presented in Figure S6-8, Supplementary material.

3.2.1.2 Hot melt extrusion

When the cocrystal components were processed with xylitol, HME-X-10, the hot melt extruded product showed characteristic diffraction peaks of the cocrystal, as well as peaks

attributable to crystalline xylitol, which are indicated by arrows (Figure 4A). Altering the extrusion temperature and screw configuration has been previously shown to result in cocrystal formation when higher xylitol loads are incorporated into the extrusion process (Li et al., 2017).

Hot melt extrusion was also performed using Soluplus and PVP K15, HME-S-10 and HME-P-10 respectively, as amorphous excipients. The processing temperature was above the T_g of Soluplus, and below the T_g of PVP K15. In both cases, the presence of cocrystal as well as amorphous and crystalline API/coformer was observed by PXRD (Figure 4B). Peaks attributable to INA are highlighted by arrows. However, a cocrystal was obtained with both PVP K15 and Soluplus by spray drying at the same ratio, suggesting that spray drying may offer a processing advantage over hot melt extrusion.

Negative controls were also prepared with xylitol and the API or coformer to investigate the potential for cocrystal formation between the excipient and the API or coformer. No new peaks attributable to a cocrystal between the excipient and API/coformer were observed. Results of PXRD analyses are presented in Figure S9-11, Supplementary material.

3.2.2 Differential scanning calorimetry

3.2.2.1 Spray drying

At a heating rate of 10 °C/min, IBU displayed a characteristic melting point at 75.26 ± 0.13 °C (130.96 ± 0.16 J/g), with INA displaying a polymorphic transformation at 120.08 ± 0.63 °C (13.34 ± 0.06 J/g) and a melting point at 156.40 ± 0.13 °C (196.14 ± 0.57 J/g) (Figure 5A and Table 3). For the physical mixture of IBU and INA, two endothermic events were present, one of which was below the IBU melt temperature, which may be attributed to a eutectic melt. In systems forming eutectics, cocrystal formation can occur by heating in the DSC past the eutectic temperature (Lu et al., 2008). The second endotherm can be attributed to the cocrystal. No thermal event attributable to INA was observed.

Xylitol displayed a characteristic melting point at 93.68 ± 0.16 °C (249.56 ± 9.15 J/g) (Figure 6A), while mannitol had one endothermic event characteristic of melting at 165.59 ± 0.21 °C (307.14 ± 5.87 J/g) (Figure 5B). The spray dried product of IBU and INA from ethanol at a 1:1 molar ratio displayed one endothermic peak at 119.33 ± 0.14 °C (139.10 ± 0.98 J/g) and

no exothermic peaks, indicating that cocrystal formation had occurred. The spray dried cocrystal from isopropanol displayed an endothermic peak at 119.31 ± 0.16 °C (138.64 ± 0.25 J/g), similar to that of the cocrystal produced by spray drying from ethanol with a slight reduction in the melt enthalpy. Solvent evaporation from isopropanol resulted in a material that displayed one single endothermic peak in the DSC at 119.72 ± 0.09 °C (139.43 ± 0.56 J/g) (Table 4).

Co-spray dried IBU:INA with mannitol at all three ratios, SD-M-10, SD-M-30 and SD-M-50, displayed two melting peaks, one attributable to the melting of the cocrystal and one attributable to the melting of crystalline mannitol (Figure 5B). No melting peaks attributable to the individual cocrystal components were observed, even when high mannitol loads (50 %w/w) were incorporated into the feed solution prior to spray drying. Melting point depression of the cocrystal was observed with increasing mannitol loads, as well as broad melting peaks. This was observed for both the co-spray dried systems and the physical mixtures of cocrystal and mannitol. Melting point depression and broad melting peaks were also seen for mannitol. The melting enthalpy of the co-spray dried systems and the physical mixtures were compared and the relative crystallinity of the co-spray dried systems compared to a physical mixture of cocrystal and excipient was calculated. A relative crystallinity of 98.36%, 97.43% and 91.79% was calculated for the SD-M-10, SD-M-30 and SD-M-50 formulations respectively, showing a small loss in crystallinity for the co-spray dried formulations compared to the physical mixtures.

The SD-S-10 formulation resulted in cocrystal formation, with one endothermic peak present on the DSC curve, which can be attributed to cocrystal melting (Figure 5C). When the ratio of Soluplus in the feed solution was increased, a second endothermic event was observed directly after cocrystal melting. However, this shoulder peak was not present in physical mixtures of spray dried cocrystal and Soluplus at the same ratios (Figure S12, Supplementary material). This double melting peak could be attributed to two different crystal morphologies (Blundell, 1987). Nevertheless, as this peak occurred after cocrystal melting, it is unlikely to be morphology related. This peak can probably be attributed to a significantly depressed INA melting event which can be observed when 15%, 20% and 30% Soluplus was incorporated into the feed solution prior to spray drying.

A polymorphic form of INA (form IV, CSD ref code: EHOWIH04) was generated, as well as the cocrystal, when Soluplus loads $\geq 15\%$ were used. This polymorph was also generated

when INA was spray dried with Soluplus (50:50 weight ratio), resulting in one endothermic event at 140 °C (Figure S13, Supplementary material). This polymorph has been shown to demonstrate one endothermic event on DSC analysis. No phase change is seen during DSC analysis, as only a melting event is observed (Eccles et al., 2011). At Soluplus loads $\geq 15\%$, a mixture of an amorphous phase, cocrystal and crystalline INA can be observed. When $\geq 15\%$ Soluplus is incorporated into the feed solution, a shift in the Tg of Soluplus is seen, indicating a glass solution of polymer and IBU is formed, as well as crystalline INA. mDSC results are presented in Figure S14, Supplementary material, which shows the shift in glass transitions of the systems with $\geq 15\%$ Soluplus. The relative crystallinities of the co-spray dried samples were obtained by comparing the melt enthalpies to the relevant physical mixtures of cocrystal and Soluplus. A relative crystallinity of 94.11%, 66.68%, 56.58% and 32.69% was calculated for the systems containing 10%, 15%, 20% and 30% of Soluplus respectively, indicating a significant amount of amorphous IBU, present as a glass solution with Soluplus, and crystalline INA are present in the formulations containing $\geq 15\%$ Soluplus.

The SD-P-10 formulation showed one endothermic peak at the cocrystal melting temperature (Figure 5D). The relative crystallinity of the co-spray dried product compared to the physical mixture of cocrystal and PVP was 98.94%. A Tg was observed at 10.66 ± 0.67 °C, indicating the presence of a glass solution between the polymer, API and/or coformer. A melting event of the individual components was not observed. It was not possible to determine if a separate phase of polymer was present, as the Tg of this was obscured by the melting of the cocrystal. The SD-P-20 formulation showed two endothermic peaks, one attributable to the cocrystal and a second peak after the cocrystal temperature. Like the systems with $\geq 15\%$ Soluplus, this can be attributed to crystalline INA, although this was not detected by PXRD. A Tg was also observed at 3.65 ± 0.28 °C, which is likely a glass solution of polymer, IBU and/or INA, Figure S15, Supplementary material.

3.2.2.2 Hot melt extrusion

The HME-X-10 formulation displayed two characteristic melting peaks, a depressed xylitol peak at 84.95 ± 0.16 °C (21.98 ± 0.82 J/g) and a cocrystal melting peak at 115.28 ± 0.07 °C (119.66 ± 2.27 J/g) (Figure 6A). The melting enthalpy of the hot melt extruded cocrystal in xylitol was slightly lower than the spray dried cocrystal in mannitol. However, this may be attributed to the cocrystal melting into liquid xylitol in the case of the hot melt extruded product, while the cocrystal melts in the presence of solid mannitol in the case of the spray

dried product. A relative crystallinity of 97.99% was measured for the hot melt extruded product compared to the physical mixture of cocrystal and xylitol.

The hot melt extruded products with Soluplus and PVP K15 were also analysed (Figure 6B). The HME-S-10 formulation showed an endothermic peak attributable to a eutectic melting, as well as a cocrystal melt. It is likely that the eutectic phase comprises IBU and INA, as Bragg peaks attributable to INA were observed in the PXRD diffractogram (Figure 4B). The HME-P-10 formulation showed a melting event attributable to the cocrystal, as well as a depressed INA melt, indicating that only crystalline INA was observed by DSC, and any excess IBU was rendered amorphous.

It should be noted that TGA experiments were performed on the raw materials prior to HME to demonstrate suitability of the processing temperatures used. All chemicals showed less than 5% mass loss at the extrusion processing temperature, with the exception of PVP K15. However, the weight loss observed for PVP K15 can mainly be attributed to water loss. Results of TGA experiments can be seen in Figure S16, Supplementary material.

3.2.3 Investigation of H-bonding interactions by Fourier transform infrared spectroscopy

The FTIR spectra of IBU, INA, cocrystal, mannitol, xylitol, Soluplus, PVP K15, the hot melt extruded system with xylitol and the spray dried formulations with mannitol, Soluplus and PVP K15 are presented in Figure 7. Cocrystal formation between an API and coformer can form between supramolecular heterosynthons or homosynthons (Desiraju, 1995). The FTIR spectrum for IBU showed a broad vibrational band from 3400-2800 cm^{-1} , characteristic of O-H stretching of the carboxylic acid group. Medium intensity peaks are observed from 3100-2900 cm^{-1} , representing C-H stretching in the C-H, C-H₂ and C-H₃ groups of IBU and the C-H bonds in the aromatic ring (Vueba et al., 2008). A strong band was present at 1708 cm^{-1} , indicative of stretching of the C=O group of the carboxylic acid (Maheshwari et al., 2003). Weak bands at 1008 cm^{-1} were representative of C-C stretching (Figure 7A). INA showed vibrational bands at 3361 cm^{-1} and 3178 cm^{-1} , representing asymmetric and symmetric stretching N-H respectively, for the H-bonded primary amide groups among closely packed INA molecules (Bakiler et al., 2007; Iogansen et al., 1977). Vibrational stretching at 1654

cm⁻¹ represented the amide carbonyl group, while 1621 cm⁻¹ represented bending of the N-H bond in the primary amide (Filho et al., 2006).

Some shifts in the IR peaks were observed for the cocrystal (prepared by spray drying) when compared to a physical mixture of IBU and INA, which can be attributed to H-bonding interactions between the two components. The IBU:INA cocrystal consists of two acid:amine interactions and an amide homodimer between the INA molecules. INA contains two competing H-bond acceptor sites, the pyridine N and the amide carbonyl. The nitrogen on the pyridine ring is considered a stronger H-bond acceptor than the amide carbonyl (Laurence and Berthelot, 2000). In crystalline INA, the pyridine N forms a hydrogen bond with the amide N-H. This bond is broken in the cocrystal, resulting in the formation of an N-H...O of the amide homodimer. The symmetric N-H stretching shifted from 3178 cm⁻¹ to 3171 cm⁻¹, indicating the formation of the N-H...O bond in the amide homodimer. The amide N-H asymmetric stretching shifted from 3361 cm⁻¹ to 3431 cm⁻¹, representing formation of an N-H...O bond between the amide of INA and the IBU carboxylic acid carbonyl on the adjacent IBU molecule (Saha and Desiraju, 2018). NH₂ bending of INA shifted from 1621 cm⁻¹ to 1630 cm⁻¹, resulting in the formation of the amide homodimer (Chow et al., 2012).

The broad peak attributable to O-H stretching in IBU is absent for the cocrystal, with the formation of a single peak at 3317 cm⁻¹, which can be attributed to H-bonding between the pyridine N and the O-H group of the carboxylic acid of IBU. The carboxylic acid carbonyl of IBU shifted from 1708 cm⁻¹ to 1698 cm⁻¹, due to H-bond formation between the carbonyl and the pyridine hydrogen. The C-H bending of the pyridine ring also shifted from 794 cm⁻¹ to 779 cm⁻¹. The same peaks were present when the API and coformer was co-spray dried with mannitol, xylitol, PVP K15 and Soluplus, and the hot melt extruded product with xylitol, as well as peaks attributable to the excipient, indicating that cocrystal formation occurred in the presence of the excipient (Figure 7A-D).

3.2.4. Moisture uptake and sorption-desorption profile

DVS analysis of the spray dried cocrystal, the spray dried formulations with mannitol and Soluplus and the hot melt extruded cocrystal with xylitol was performed using ethanol as the probe vapour. Initial experiments were performed using water as the adsorbate. However, due to the hydrophobic nature of IBU, samples showed negligible water uptake (data not shown). The sorption and desorption isotherms of the formulations are illustrated in Figure 8. The

maximum ethanol sorption of the spray dried cocrystal was 0.54% (Figure 8A and B), with most vapour uptake being between 50% and 90% RH. The desorption profile showed a hysteresis effect from 90% to 40% RH. No hysteresis effect was seen on the second cycle. The spray dried formulations with mannitol showed a maximum ethanol sorption of 0.93%, 1.63% and 2.88% for the SD-M-10, SD-M-30 and SD-M-50 formulations respectively. The increase in ethanol uptake with increasing mannitol loads may be due to the high surface area of the porous, spray dried mannitol particles (Littringer et al., 2011; Maa et al., 1997). The HME-X-10 formulation showed a maximum moisture uptake of 0.33% at 90% RH, showing a hysteresis at all points from 90% to 20% RH. A significant difference in moisture uptake between the first and second cycles was not seen for any system, indicating that the spray dried samples contained a negligible amorphous content prone to crystallisation. The samples were recovered and analysed by PXRD and DSC. No change in solid form was observed with any of the systems containing mannitol as carrier excipient post DVS analysis (Figure 8C).

The co-spray dried systems with Soluplus all showed a significantly higher moisture uptake than the co-spray dried systems with mannitol. This can be mainly attributed to the amorphous nature of Soluplus. However, no hysteresis effect was observed at any RH step. The ethanol uptake at 90% RH was 8.29, 14.01, 18.65 and 28.64 (% w/w) for the SD-S-10, SD-S-15, SD-S-20 and SD-S-30 formulations respectively. PXRD analysis of these systems after DVS showed a Bragg peak attributable to INA at $23^{\circ} 2\theta$ for systems containing $\geq 15\%$ Soluplus. This is not the case for the SD-S-10 formulation, as only peaks attributable to the cocrystal were present, suggesting that any amorphous content in this system crystallises to the cocrystal, or is stable as a glass solution at this ratio (Figure 8D).

3.2.5. Particle size distribution (PSD)

PSD analysis of the spray dried formulations and hot melt extruded formulation were evaluated (Table 5). Spray drying resulted in a particle size reduction when compared to the raw API and coformer materials. The spray dried cocrystal displayed a D_{50} of 6.92 ± 0.13 μm . A similar particle size was measured in the hot melt extruded product with xylitol after cryomilling (6.63 ± 0.36 μm). An increase in D_{50} was observed when mannitol was added compared to the cocrystal spray dried alone, with the largest particle size being the formulation containing 50% mannitol. The samples which resulted in cocrystal formation with the amorphous excipients, Soluplus and PVP K15, displayed a 1.7 and 1.6-fold higher

D₅₀ value of $11.75 \pm 0.27 \mu\text{m}$ and $10.95 \pm 0.46 \mu\text{m}$, respectively, compared to the spray dried cocrystal without excipients.

3.2.6 Morphology characterisation by SEM

The spray dried IBU:INA cocrystal presented as plate shaped particles, with a significantly smaller particle size than the raw materials (Figure 9). Co-spray drying of the cocrystal components with mannitol and Soluplus resulted in cocrystal plates, whereas more spherical particles were obtained when PVP K15 was used as the carrier excipient. The smaller particle size of the spray dried particles could result in poorly flowing and cohesive powder from a manufacturing point of view, but this could be negated by altering spray drying parameters, such as decreasing the airflow of the drying gas, and increasing the feed rate and concentration of the feed solution (Cal and Sollohub, 2009); however, this is not the main aim of this work and has not been further investigated.

3.3 Dissolution studies

Constant surface area dissolution studies of the spray dried cocrystal, HME-X-10, SD-M-10, SD-S-10 and SD-P-10 were performed (Figure 10A & B). Intrinsic dissolution studies of unprocessed IBU were also performed (Figure S17, Supplementary material).

Dissolution studies of the cocrystal, SD-M-10 and HME-X-10 all resulted in similar dissolution profiles. All three formulations showed a similar IDR and release after 60 minutes. The SD-S-10 formulation showed a lower release compared to the cocrystal, while the SD-P-10 formulation showed a higher release compared to the reference cocrystal. This formulation showed a 2.3-fold greater IDR for IBU compared to the spray dried cocrystal as well as the highest release of IBU after 60 minutes amongst all the tested formulations. The highest release was for the unprocessed raw material. However, it is important to note that the starting material is different for this system, as IBU is the starting material as opposed to the cocrystal. The dissolution studies were performed in pH 7.2 phosphate buffer, a medium in which IBU is very soluble (Dhingra et al., 2010). The pH-solubility curve for cocrystals can be significantly different to that of the API (Bethune et al., 2009), which can in turn impact dissolution of the API. Therefore, dissolution of the unprocessed API may not be directly

comparable with dissolution from the cocrystal when pH-solubility studies of the cocrystal have not been performed. These experiments have not been performed as part of this study.

Univariate ANOVA analysis was also performed to compare the dissolution profile of the spray dried cocrystal to the dissolution profiles of the co-spray dried and hot melt extruded formulations. The co-spray dried system with PVP was the only system which was statistically significantly different from the reference at each time point, indicating the IDR of this system was statistically higher than that of the cocrystal, as was the total release after 60 minutes.

Exposure of the cocrystal to the dissolution medium resulted in the transformation of the cocrystal to the individual components (Figure 10C). PXRD analysis of the surface of the disk after dissolution revealed peaks attributable mainly to IBU. No INA peaks were observed, suggesting that the more soluble INA was in solution, leaving the less soluble IBU on the surface of the disk. A cocrystal peak was also present at $17.4^{\circ} 2\theta$. It has previously been reported that when a large difference in solubility exists between the API and the coformer, the cocrystal can be unstable in solution and recrystallization to the individual components can occur. Recrystallisation to individual components is less likely to occur when the solubilities of the API and coformer are similar (Schultheiss and Newman, 2009). Transformation to the individual components was also observed when the hot melt extruded cocrystal with xylitol and the spray dried cocrystal with mannitol were analysed by PXRD after dissolution (Figure 10D & E). Bragg peaks attributable to IBU are indicated by arrows. Analysis of the disk after dissolution of the SD-S-10 formulation showed the same diffraction peaks as the cocrystal, indicating that Soluplus polymers prevented the recrystallization of the cocrystal to the individual components (Figure 11A). For the SD-P-10 formulation, PXRD analysis of the disk after dissolution showed mainly Bragg peaks attributable to the cocrystal. However, a characteristic peak of IBU at 6.15° can also be seen, suggesting some recrystallisation to the individual components, or crystallisation of trace amounts of amorphous IBU present in the system. (Figure 11B).

The lowest IDR and release after 60 minutes of IBU was for the spray dried system with Soluplus (Table 5). However, the low IDR may be due to the presence of Soluplus as this excipient exhibits a lower critical solution temperature (LCST) in water near 40°C (Hughey et al., 2013). Polymers can demonstrate good aqueous solubility at low temperature, but can demonstrate partial miscibility and separate from solution above the LCST (Feil et al., 1993).

At the LCST, Soluplus chains lose hydration and progressively associate, decreasing their solubility and forming a cloudy suspension that can precipitate. This behaviour is responsible for the gel-forming property of Soluplus (Fini, 2016). Attempts to measure the IDR of IBU and carvedilol from solid dispersions containing Soluplus have resulted in lower values than expected, which has been attributed to the gelling properties of Soluplus (Genina et al., 2017).

To test our hypothesis that the lower release of IBU from the co-spray dried system with Soluplus was due to the LCST of Soluplus, dissolution studies of both this system and the spray dried cocrystal were performed at 20 °C (Figure 10B). The dissolution rate of the cocrystal was significantly ($p<0.05$) lower than that of the co-spray dried system with Soluplus at 20 °C. Disks were also analysed by PXRD after dissolution. Similar to the results obtained at 37 °C, the diffractogram of the SD-S-10 formulation after dissolution showed the same Bragg peaks of the cocrystal after dissolution. However, the cocrystal without a carrier excipient showed Bragg peaks attributable to IBU and also multiple cocrystal peaks, which differs from results at 37 °C. This can be explained by the higher temperature, which may accelerate the dissociation of the cocrystal into its individual components.

4. Discussion

The comparison of spray drying versus HME in order to formulate amorphous solid dispersions has been widely studied. For spray drying, the solubility of the drug in the solvent is crucial in order to ensure a readily scalable and viable process whereas for HME, the solubility of the drug in the polymer is key to achieve a thermodynamically stable formulation. From an industrial point of view, the phase of development is also important in process selection. Bearing in mind that API availability is often limited at early-stages, spray drying is preferable because its feasibility can be determined with amounts as low as 50-100 mg (Dobry et al., 2009), whereas at least several grams of API are required for HME (Guns et al., 2012). In spite of the use of solvents, spray drying is often preferred over HME for several reasons such as thermally induced degradation of the drug (Hengsawas Surasarang et al., 2017), phase separation (Lenz et al., 2017) and high shear forces during the HME process (Guns et al., 2010).

To the best of our knowledge, the feasibility of employing both techniques to form of cocrystals within a carrier excipient has not been compared. In order to ensure cocrystal formation, the H-bonding interaction between API and coformer has to be stronger than the interaction of the individual components with the carrier excipient. Otherwise, cocrystal integrity will not be preserved.

HSP differences have been previously employed as a useful, reliable tool to predict cocrystal formation in the presence of a carrier excipient. It was previously reported that, for immiscible systems (with a difference in HSP between the cocrystal and excipient $> 9.6 \text{ MPa}^{0.5}$), cocrystal formation occurred even when the proportion of excipient was high (up to 80% w/w) when processed by spray drying. However, HSP differences should not be used as the only indicator for cocrystal formation, as the ratio of carrier excipient: cocrystal also has a major impact as well as the miscibility among the three components (drug, coformer and carrier). When the difference in HSP between the cocrystal and the excipient is very small, the cocrystal integrity can still be preserved at low excipient ratios (Walsh et al, 2018).

The impact of HSP differences has been demonstrated again in the current study for the IBU:INA cocrystal: excipient systems produced by spray drying. When the difference in HSP between the cocrystal and the excipient was greater than $9.6 \text{ MPa}^{0.5}$, as in the case of mannitol (ΔHSP of $18.3 \text{ MPa}^{0.5}$), larger amounts of excipient, up to 50%, could be incorporated during the spray drying process without altering the integrity of the cocrystal. For the other two tested excipients, Soluplus and PVP K15 where the difference in HSP (between the cocrystal and excipient) was much lower, at 2.1 and $1.6 \text{ MPa}^{0.5}$ respectively, the IBU:INA cocrystal was only formed when very low amounts of excipient (10%) were used. Remarkably different results were obtained when HME was employed for processing. In the case where xylitol was used as the excipient carrier, with a difference in HSP (between the cocrystal and excipient) of $20.7 \text{ MPa}^{0.5}$, a similar order of magnitude as that for mannitol, pure cocrystal (devoid of API or conformer contaminants) resulted on co-processing by HME. While it has been reported that cocrystal formation can occur even with high xylitol loads (50 %w/w), this required alteration of the extrusion elements and processing temperature (Li et al., 2017). Spray drying may be seen as a more robust process as alteration of spray drying parameters was not required to produce a cocrystal with high mannitol loads. In the case of Soluplus and PVP K15, a mixture of cocrystal with single components was obtained with only 10% excipient, while the equivalent spray dried systems showed cocrystal

with no contaminating API or coformer starting materials could be prepared at the equivalent weight ratios.

The different results obtained between spray drying and HME are probably related to the speed of the processes and the energy (mechanical and thermal) imparted during mixing of the cocrystal components and the excipient. The evaporation of the solvent during the spray drying process takes place in milliseconds and hence, there is less chance for the cocrystal to interact within the excipient molecules, whereas the mixing of the components in HME is a more energetic and longer process, potentially facilitating interactions between the cocrystal components and the excipients. For this reason, highly immiscible systems (cocrystal: excipient) are required to guarantee selective H-bond interactions between the drug and the coformer molecules and probably larger differences in HSP are necessary to ensure cocrystal formation in HME processes.

5. Conclusions

Cocrystallisation of an API and coformer in the presence of an excipient can be achieved through both spray drying and hot melt extrusion. However, the results obtained with the IBU:INA cocrystal suggest greater feasibility of spray drying over HME as a process for producing cocrystals within a carrier excipient, intended to reduce the number of unit operations required to produce a final pharmaceutical product. The use of HSP differences can be useful to predict cocrystal formation within a carrier excipient. However, Δ HSP values should not be used as the only indicator, as the manufacturing process, the ratio of carrier excipient:cocrystal and the overall miscibility among drug, coformer and carrier have also a major impact.

Acknowledgements

Research leading to these results was supported by the Synthesis and Solid State Pharmaceutical Centre (SSPC), financed by a research grant from Science Foundation Ireland (SFI) and co-funded under the European Regional Development Fund (Grant Number 12/RC/2275).

772 References

- 773 Alhalaweh, A., Velaga, S.P., 2010. Formation of Cocrystals from Stoichiometric Solutions of
774 Incongruently Saturating Systems by Spray Drying. *Crystal Growth & Design* 10, 3302-3305.
- 775 Alshahateet, S.F., 2010. Synthesis and supramolecularity of hydrogen-bonded cocrystals of
776 pharmaceutical model rac-ibuprofen with pyridine derivatives. *Molecular Crystals and Liquid Crystals*
777 533, 152-161.
- 778 Alshahateet, S.F., 2011. Synthesis and X-ray Crystallographic Analysis of Pharmaceutical Model Rac-
779 Ibuprofen Cocrystal. *Journal of Chemical Crystallography* 41, 276-279.
- 780 Alvarez, C., Nunez, I., Torrado, J.J., Gordon, J., Potthast, H., Garcia-Arieta, A., 2011. Investigation on
781 the possibility of biowaivers for ibuprofen. *Journal of pharmaceutical sciences* 100, 2343-2349.
- 782 Bakiler, M., Bolukbasi, O., Yilmaz, A., 2007. An experimental and theoretical study of vibrational
783 spectra of picolinamide, nicotinamide, and isonicotinamide. *Journal of Molecular Structure* 826, 6-
784 16.
- 785 Berry, D.J., Seaton, C.C., Clegg, W., Harrington, R.W., Coles, S.J., Horton, P.N., Hursthouse, M.B.,
786 Storey, R., Jones, W., Friscic, T., 2008. Applying hot-stage microscopy to co-crystal screening: a study
787 of nicotinamide with seven active pharmaceutical ingredients. *Crystal Growth and Design* 8, 1697-
788 1712.
- 789 Bethune, S.J., Huang, N., Jayasankar, A., Rodríguez-Hornedo, N.r., 2009. Understanding and
790 predicting the effect of cocrystal components and pH on cocrystal solubility. *Crystal Growth &*
791 *Design* 9, 3976-3988.
- 792 Blundell, D.J., 1987. On the interpretation of multiple melting peaks in poly(ether ether ketone).
793 *Polymer* 28, 2248-2251.
- 794 Breitenbach, J., 2002. Melt extrusion: from process to drug delivery technology. *European Journal of*
795 *Pharmaceutics and Biopharmaceutics* 54, 107-117.
- 796 Broadhead, J., Edmond Rouan, S.K., Rhodes, C.T., 1992. The spray drying of pharmaceuticals. *Drug*
797 *Development and Industrial Pharmacy* 18, 1169-1206.
- 798 Bruker, 2014. APEX v2014.11-0, Bruker AXS Inc., Madison, Wisconsin, USA.
- 799 Bruker, 2014/5. SADABS, Bruker AXS Inc., Madison, Wisconsin, USA.
- 800 Cal, K., Sollohub, K., 2009. Spray Drying Technique. I: Hardware and Process Parameters. *Journal of*
801 *Pharmaceutical Sciences* 99, 575-586.
- 802 Chen, S., Xi, H., Henry, R.F., Marsden, I., Zhang, G.G.Z., 2010. Chiral co-crystal solid solution:
803 structures, melting point phase diagram, and chiral enrichment of (ibuprofen) 2 (4, 4-dipyridyl).
804 *CrystEngComm* 12, 1485-1493.
- 805 Chow, S.F., Chen, M., Shi, L., Chow, A.H.L., Sun, C.C., 2012. Simultaneously Improving the Mechanical
806 Properties, Dissolution Performance, and Hygroscopicity of Ibuprofen and Flurbiprofen by
807 Cocrystallization with Nicotinamide. *Pharmaceutical Research* 29, 1854-1865.
- 808 Corrigan, O.I., 1995. Thermal analysis of spray dried products. *Thermochimica Acta* 248, 245-258.
- 809 Crowley, M.M., Zhang, F., Repka, M.A., Thumma, S., Upadhye, S.B., Kumar Battu, S., McGinity, J.W.,
810 Martin, C., 2007. Pharmaceutical applications of hot-melt extrusion: part I. Drug development and
811 industrial pharmacy 33, 909-926.
- 812 Desiraju, G.R., 1995. Supramolecular synthons in crystal engineering—a new organic synthesis.
813 *Angewandte Chemie International Edition in English* 34, 2311-2327.
- 814 Dhingra, G., Sreelesh, B., Nagpal, M., Rakha, P., Nagori, B.P., 2010. In Vitro Dissolution Testing of
815 Ibuprofen Using Compendial and Biorelevant Dissolution Media. *Research Journal of Pharmacy and*
816 *Technology* 3, 931-933.
- 817 Dhumal, R.S., Kelly, A.L., York, P., Coates, P.D., Paradkar, A., 2010. Cocrystalization and simultaneous
818 agglomeration using hot melt extrusion. *Pharmaceutical research* 27, 2725-2733.
- 819 do Amaral, L.H., do Carmo, F.A., Amaro, M.I., de Sousa, V.P., da Silva, L.C.R.P., de Almeida, G.S.,
820 Rodrigues, C.R., Healy, A.M., Cabral, L.M., 2018. Development and Characterization of Dapsone
821 Cocrystal Prepared by Scalable Production Methods. *AAPS PharmSciTech* 19, 2687-2699.

822 Dobry, D.E., Settell, D.M., Baumann, J.M., Ray, R.J., Graham, L.J., Beyerinck, R.A., 2009. A Model-
823 Based Methodology for Spray-Drying Process Development. *Journal of Pharmaceutical Innovation* 4,
824 133-142.

825 Eccles, K.S., Deasy, R.E., Fabian, L., Braun, D.E., Maguire, A.R., Lawrence, S.E., 2011. Expanding the
826 crystal landscape of isonicotinamide: concomitant polymorphism and co-crystallisation.
827 *CrystEngComm* 13, 6923-6925.

828 Eddleston, M.D., Patel, B., Day, G.M., Jones, W., 2013. Cocrystallization by freeze-drying: preparation
829 of novel multicomponent crystal forms. *Crystal Growth & Design* 13, 4599-4606.

830 Feil, H., Bae, Y.H., Feijen, J., Kim, S.W., 1993. Effect of comonomer hydrophilicity and ionization on
831 the lower critical solution temperature of N-isopropylacrylamide copolymers. *Macromolecules* 26,
832 2496-2500.

833 Filho, O.T., Pinheiro, J.C., Costa, E.B.d., Kondo, R.T., Souza, R.A.d., Nogueira, V.M., Mauro, A.E., 2006.
834 Theoretical and experimental study of the infrared spectrum of isonicotinamide. *Journal of*
835 *Molecular Structure: THEOCHEM* 763, 175-179.

836 Fini, A., 2016. Release Problems for Nifedipine in the Presence of Soluplus. *Ommega Internationals*
837 3, 1-8.

838 Friščić, T., Jones, W., 2007. Cocrystal architecture and properties: design and building of chiral and
839 racemic structures by solid–solid reactions. *Faraday discussions* 136, 167-178.

840 Fucke, K., Myz, S.A., Shakhtshneider, T.P., Boldyreva, E.V., Griesser, U.J., 2012. How good are the
841 crystallisation methods for co-crystals? A comparative study of piroxicam. *New Journal of Chemistry*
842 36, 1969-1977.

843 Genina, N., Hadi, B., Löbmann, K., 2017. Hot melt extrusion (HME) as solvent-free technique for a
844 continuous manufacturing of drug-loaded mesoporous silica. *Journal of Pharmaceutical Sciences*.

845 Groom, C.R., Bruno, I.J., Lightfoot, M.P., Ward, S.C., 2016. The Cambridge Structural Database. *Acta*
846 *Crystallographica Section B* 72, 171-179.

847 Grossjohann, C., Serrano, D.R., Paluch, K.J., O'Connell, P., Vella-Zarb, L., Manesiotis, P., McCabe, T.,
848 Tajber, L., Corrigan, O.I., Healy, A.M., 2015. Polymorphism in Sulfadimidine/4-Aminosalicylic Acid
849 Cocrystals: Solid-State Characterization and Physicochemical Properties. *Journal of Pharmaceutical*
850 *Sciences* 104, 1385-1398.

851 Guns, S., Dereymaker, A., Kayaert, P., Mathot, V., Martens, J.A., Van den Mooter, G., 2010.
852 Comparison Between Hot-Melt Extrusion and Spray-Drying for Manufacturing Solid Dispersions of
853 the Graft Copolymer of Ethylene Glycol and Vinylalcohol. *Pharm Res* 28, 673-682.

854 Guns, S., Mathot, V., Martens, J.A., Van den Mooter, G., 2012. Upscaling of the hot-melt extrusion
855 process: Comparison between laboratory scale and pilot scale production of solid dispersions with
856 miconazole and Kollicoat® IR. *European Journal of Pharmaceutics and Biopharmaceutics* 81, 674-
857 682.

858 Hengsawas Surasarang, S., Keen, J.M., Huang, S., Zhang, F., McGinity, J.W., Williams, R.O., 3rd, 2017.
859 Hot melt extrusion versus spray drying: hot melt extrusion degrades albendazole. *Drug development*
860 *and industrial pharmacy* 43, 797-811.

861 Hughey, J.R., Keen, J.M., Miller, D.A., Kolter, K., Langley, N., McGinity, J.W., 2013. The use of
862 inorganic salts to improve the dissolution characteristics of tablets containing Soluplus®-based solid
863 dispersions. *European Journal of Pharmaceutical Sciences* 48, 758-766.

864 Hulse, W.L., Forbes, R.T., Bonner, M.C., Getrost, M., 2009. Influence of protein on mannitol
865 polymorphic form produced during co-spray drying. *International Journal of Pharmaceutics* 382, 67-
866 72.

867 logansen, A.V., Kurkchi, G.A., Dement'eva, L.A., 1977. Infrared spectra of primary amides in thevNH
868 range. *Journal of Structural Chemistry* 18, 589-595.

869 Kelleher, J.F., Gilvary, G.C., Madi, A.M., Jones, D.S., Li, S., Tian, Y., Almajaan, A., Senta-Loys, Z.,
870 Andrews, G.P., Healy, A.M., 2018. A comparative study between hot-melt extrusion and spray-drying
871 for the manufacture of anti-hypertension compatible monolithic fixed-dose combination products.
872 *International Journal of Pharmaceutics* 545, 183-196.

873 Kelly, A.L., Gough, T., Dhumal, R.S., Halsey, S.A., Paradkar, A., 2012. Monitoring ibuprofen–
874 nicotinamide cocrystal formation during solvent free continuous cocrystallization (SFCC) using near
875 infrared spectroscopy as a PAT tool. *International Journal of Pharmaceutics* 426, 15-20.

876 Laurence, C., Berthelot, M., 2000. Observations on the strength of hydrogen bonding. *Perspectives in*
877 *Drug Discovery and Design* 18, 39-60.

878 Lenz, E., Lobmann, K., Rades, T., Knop, K., Kleinebudde, P., 2017. Hot Melt Extrusion and Spray
879 Drying of Co-amorphous Indomethacin-Arginine With Polymers. *Journal of pharmaceutical sciences*
880 106, 302-312.

881 Li, S., Jones David, S., Andrews Gavin, P., 2013. Hot Melt Extrusion: A Process Overview and Use in
882 Manufacturing Solid Dispersions of Poorly Water-Soluble Drugs. *Drug Delivery Strategies for Poorly*
883 *Water-Soluble Drugs*.

884 Li, S., Yu, T., Tian, Y., Lagan, C., Jones, D.S., Andrews, G.P., 2017. Mechanochemical Synthesis of
885 Pharmaceutical Cocrystal Suspensions via Hot Melt Extrusion: Enhancing Cocrystal Yield. *Molecular*
886 *Pharmaceutics*.

887 Li, S., Yu, T., Tian, Y., McCoy, C.P., Jones, D.S., Andrews, G.P., 2016. Mechanochemical Synthesis of
888 Pharmaceutical Cocrystal Suspensions via Hot Melt Extrusion: Feasibility Studies and
889 Physicochemical Characterization. *Molecular Pharmaceutics* 13, 3054-3068.

890 Littringer, E.M., Mescher, A., Maas, S.G., Walzel, P., Urbanetz, N.A., 2011. Influence of droplet size
891 on the crystallization behaviour of aqueous D-mannitol solutions during spray drying. *na*.

892 Lu, E., Rodríguez-Hornedo, N., Suryanarayanan, R., 2008. A rapid thermal method for cocrystal
893 screening. *CrystEngComm* 10, 665-668.

894 Maa, Y.-F., Costantino, H.R., Nguyen, P.-A., Hsu, C.C., 1997. The Effect of Operating and Formulation
895 Variables on the Morphology of Spray-Dried Protein Particles. *Pharmaceutical Development and*
896 *Technology* 2, 213-223.

897 Maheshwari, M., Ketkar, A.R., Chauhan, B., Patil, V.B., Paradkar, A.R., 2003. Preparation and
898 characterization of ibuprofen–cetyl alcohol beads by melt solidification technique: effect of
899 variables. *International Journal of Pharmaceutics* 261, 57-67.

900 Marsac, P.J., Li, T., Taylor, L.S., 2009. Estimation of drug–polymer miscibility and solubility in
901 amorphous solid dispersions using experimentally determined interaction parameters.
902 *Pharmaceutical research* 26, 139-151.

903 Mohammad, M.A., Alhalaweh, A., Velaga, S.P., 2011. Hansen solubility parameter as a tool to predict
904 cocrystal formation. *International journal of pharmaceutics* 407, 63-71.

905 Moradiya, H.G., Islam, M.T., Halsey, S., Maniruzzaman, M., Chowdhry, B.Z., Snowden, M.J.,
906 Douroumis, D., 2014. Continuous cocrystallisation of carbamazepine and trans-cinnamic acid via
907 melt extrusion processing. *CrystEngComm* 16, 3573-3583.

908 Patel, R.P., Patel, M.P., Suthar, A.M., 2009. Spray drying technology: an overview. *Indian Journal of*
909 *Science and Technology* 2, 44-47.

910 Paudel, A., Worku, Z.A., Meeus, J., Guns, S., Van den Mooter, G., 2013. Manufacturing of solid
911 dispersions of poorly water soluble drugs by spray drying: Formulation and process considerations.
912 *International Journal of Pharmaceutics* 453, 253-284.

913 Ré, M.-I., 2006. Formulating drug delivery systems by spray drying. *Drying Technology* 24, 433-446.

914 Saha, S., Desiraju, G.R., 2018. Acid–Amide Supramolecular Synthons in Cocrystals: From
915 Spectroscopic Detection to Property Engineering. *Journal of the American Chemical Society* 140,
916 6361-6373.

917 Schultheiss, N., Newman, A., 2009. Pharmaceutical cocrystals and their physicochemical properties.
918 *Crystal growth and design* 9, 2950-2967.

919 Scott, G., 1992. Properties of polymers. Their correlation with chemical structure; their numerical
920 estimation and prediction from additive group contributions. *Endeavour* 16, 97-98.

921 Sheldrick, G.M., 2008. A short history of SHELX. *Acta Crystallographica Section A: Foundations of*
922 *Crystallography* 64, 112-122.

923 Sheldrick, G.M., 2015. SHELXT—Integrated space-group and crystal-structure determination. *Acta*
 924 *Crystallographica Section A: Foundations and Advances* 71, 3-8.
 925 Shen, S.C., Ng, W.K., Chia, L., Dong, Y.C., Tan, R.B.H., 2010. Stabilized amorphous state of ibuprofen
 926 by co-spray drying with mesoporous SBA-15 to enhance dissolution properties. *Journal of*
 927 *pharmaceutical sciences* 99, 1997-2007.
 928 Stone, K.H., Lapidus, S.H., Stephens, P.W., 2009. Implementation and use of robust refinement in
 929 powder diffraction in the presence of impurities. *Journal of Applied Crystallography* 42, 385-391.
 930 Tian, Y., Caron, V., Jones, D.S., Healy, A.M., Andrews, G.P., 2014. Using Flory–Huggins phase
 931 diagrams as a pre-formulation tool for the production of amorphous solid dispersions: a comparison
 932 between hot-melt extrusion and spray drying. *Journal of Pharmacy and Pharmacology* 66, 256-274.
 933 Tung, H.-H., Waterson, S., Reynolds, S.D., 1991. Formation and resolution of ibuprofen lysinate.
 934 Google Patents.
 935 Ungár, T., 2004. Microstructural parameters from X-ray diffraction peak broadening. *Scripta*
 936 *Materialia* 51, 777-781.
 937 Van Krevelen, D.W., Te Nijenhuis, K., 2009. Chapter 7 - Cohesive Properties and Solubility, Properties
 938 of Polymers (Fourth Edition). Elsevier, Amsterdam, pp. 189-227.
 939 Vehring, R., Foss, W.R., Lechuga-Ballesteros, D., 2007. Particle formation in spray drying. *Journal of*
 940 *Aerosol Science* 38, 728-746.
 941 Vueba, M.L., Pina, M.E., Batista de Carvalho, L.A.E., 2008. Conformational stability of ibuprofen:
 942 assessed by DFT calculations and optical vibrational spectroscopy. *Journal of pharmaceutical*
 943 *sciences* 97, 845-859.
 944 Walsh, D., Serrano, D.R., Worku, Z.A., Norris, B.A., Healy, A.M., 2018. Production of cocrystals in an
 945 excipient matrix by spray drying. *International Journal of Pharmaceutics* 536, 467-477.
 946 Walsh, R.D.B., Bradner, M.W., Fleischman, S., Morales, L.A., Moulton, B., Rodriguez-Hornedo, N.,
 947 Zaworotko, M.J., 2003. Crystal engineering of the composition of pharmaceutical phases. *Chemical*
 948 *Communications*, 186-187.
 949 Walton, D.E., 2000. The morphology of spray-dried particles a qualitative view. *Drying Technology*
 950 18, 1943-1986.
 951 Yuksel, N., Kanik, A.E., Baykara, T., 2000. Comparison of in vitro dissolution profiles by ANOVA-based,
 952 model-dependent and -independent methods. *Int J Pharm* 209, 57-67.
 953 Zhang, Y., Huo, M., Zhou, J., Zou, A., Li, W., Yao, C., Xie, S., 2010. DDSolver: an add-in program for
 954 modeling and comparison of drug dissolution profiles. *AAPS J* 12, 263-271.

955

956

957

Table 1. Crystal data and structure refinement for IBU:INA cocrystal.

Empirical formula	C ₁₉ H ₂₄ N ₂ O ₃
Formula weight	328.40
Temperature/K	100(2)
Crystal system	Triclinic
Space group	P-1
a/Å	5.7025(3)
b/Å	11.5514(6)
c/Å	27.6754(13)
α/°	95.551(3)
β/°	93.326(4)
γ/°	102.210(3)
Volume/Å ³	1767.65(16)
Z	4
ρ _{calc} /g/cm ³	1.234
μ/mm ⁻¹	0.675
F(000)	704.0
Crystal size/mm ³	0.27 × 0.17 × 0.16
Radiation	CuKα (λ = 1.54178)
2θ range for data collection/°	3.218 to 138.392
Index ranges	-6 ≤ h ≤ 6, -13 ≤ k ≤ 13, -33 ≤ l ≤ 33
Reflections collected	24654
Independent reflections	6444 [R _{int} = 0.0600, R _{sigma} = 0.0759]
Data/restraints/parameters	6444/669/669
Goodness-of-fit on F ²	1.069
Final R indexes [I ≥ 2σ (I)]	R ₁ = 0.0985, wR ₂ = 0.2875
Final R indexes [all data]	R ₁ = 0.1223, wR ₂ = 0.3155
Largest diff. peak/hole / e Å ⁻³	0.40/-0.41

Table 2. Calculated HSP values of cocrystal components and carrier excipients.

Molecule	HSP value (MPa^{0.5})	ΔHSP(MPa^{0.5})
IBU	19.4	1.4
INA	24.4	3.6
Cocrystal 1:1 molar ratio	20.8	-
Mannitol	39.1	18.3
Xylitol	41.5	20.7
Soluplus	22.9	2.1
PVP K15	22.4	1.6

Table 3. Melting temperatures and heat of fusion of raw materials and physical mixture of IBU and INA (1:1 molar ratio). *Denotes glass transition temperature. **Denotes polymorphic transformation. N/A, non-applicable.

System	T _{m1} or T _g (°C)	ΔH _f (J/g)	T _{m2} (°C)	ΔH _f (J/g)
IBU	75.26 ± 0.13	130.96 ± 0.16	N/A	N/A
INA	120.08 ± 0.64**	13.14 ± 0.06	156.40 ± 0.13	196.14 ± 0.57
Physical mixture	73.67 ± 0.29	85.01 ± 1.82	117.72 ± 0.12	50.75 ± 4.84
Mannitol	165.59 ± 0.21	307.14 ± 5.87	N/A	N/A
Xylitol	93.68 ± 0.16	249.56 ± 9.15	N/A	N/A
Soluplus*	61.98 ± 0.22	N/A	N/A	N/A
PVP K15*	127.53 ± 0.23	N/A	N/A	N/A

Table 4. Summary table including thermal events of all spray dried and hot melt extruded systems. The ratio of IBU:INA cocrystal was 1:1 molar ratio for all systems.

Cocrystal: excipient (ratio, w:w)	Method of production	Result	Cocrystal melting temperature (°C)	ΔH_f (J/g)	Excipient/ other melting temperature (°C)	ΔH_f (J/g)
IBU:INA	Spray drying (from ethanol)	Cocrystal	119.33 $\pm$ 0.14	139.10 $\pm$ 0.98	N/A	N/A
IBU:INA	Spray drying (from isopropanol)	Cocrystal	119.31 $\pm$ 0.16	138.64 $\pm$ 0.25	N/A	N/A
IBU:INA	Solvent evaporation from isopropanol	Cocrystal	119.72 $\pm$ 0.09	139.43 $\pm$ 0.56	N/A	N/A
IBU:INA, mannitol (90:10 %w/w) (SD-M-10)	Spray drying	Cocrystal	118.48 $\pm$ 0.16	123.45 $\pm$ 1.75	150.37 $\pm$ 0.21	4.04 $\pm$ 0.56
IBU:INA, mannitol (70:30 %w/w) (SD-M-30)	Spray drying	Cocrystal	117.90 $\pm$ 0.06	91.30 $\pm$ 2.16	150.07 $\pm$ 0.11	70.43 $\pm$ 2.74
IBU:INA, mannitol (50:50 %w/w) (SD-M-50)	Spray drying	Cocrystal	117.09 $\pm$ 0.18	59.55 $\pm$ 0.50	151.94 $\pm$ 0.54	135.12 $\pm$ 1.78
IBU:INA, xylitol (90:10 %w/w) (HME-X-10)	HME	Cocrystal	115.28 $\pm$ 0.07	119.66 $\pm$ 2.27	84.95 $\pm$ 0.16	21.98 $\pm$ 0.82
IBU:INA, Soluplus (90:10 %w/w) (SD-S-10)	Spray drying	Cocrystal	118.35 $\pm$ 0.01	103.01 $\pm$ 1.48	N/A	N/A
IBU:INA, Soluplus (85:15 %w/w) (SD-S-15)	Spray drying	Cocrystal, amorphous API and crystalline coformer	117.78 $\pm$ 0.13	67.34 $\pm$ 1.04	123.17 $\pm$ 0.47	0.15 $\pm$ 0.06
IBU:INA, Soluplus (80:20 %w/w) (SD-S-20)	Spray drying	Cocrystal, amorphous API and crystalline coformer	115.57 $\pm$ 0.53	48.69 $\pm$ 1.19	122.39 $\pm$ 0.57	1.03 $\pm$ 0.29
IBU:INA, Soluplus (70:30 %w/w) (SD-S-30)	Spray drying	Cocrystal, amorphous API and crystalline coformer	108.82 $\pm$ 0.42	26.98 $\pm$ 0.76	118.77 $\pm$ 0.34	4.29 $\pm$ 0.23
IBU:INA, Soluplus (90:10 %w/w) (HME-S-10)	HME	Cocrystal, crystalline coformer and crystalline and amorphous API	118.30 $\pm$ 0.40	77.06 $\pm$ 1.54	65.81 $\pm$ 1.03	2.35 $\pm$ 0.49
IBU:INA, PVP K15 (90:10 %w/w) (SD-P-10)	Spray drying	Cocrystal, amorphous API/coformer	117.58 $\pm$ 0.16	90.30 $\pm$ 1.24	N/A	N/A
IBU:INA, PVP K15 (80:20 %w/w) (SD-P-20)	Spray drying	Cocrystal, amorphous API and crystalline coformer	111.67 $\pm$ 0.30	43.49 $\pm$ 1.35	119.31 $\pm$ 0.48	4.73 $\pm$ 0.34
IBU:INA, PVP K15 (90:10 %w/w) (HME-P-10)	HME	Cocrystal, amorphous API and crystalline coformer	114.31 $\pm$ 0.11	61.11 $\pm$ 2.60	139.22 $\pm$ 0.46	3.98 $\pm$ 0.77

Table 5. Particle size distribution of raw materials and spray dried and hot melt extruded IBU and INA cocrystal (1:1 molar ratio). Intrinsic dissolution rates (of IBU) were calculated at 37°C for the spray dried cocrystal and those systems containing 90% cocrystal: 10% carrier excipient. Intrinsic dissolution rates were calculated over the first 10 minutes at 37 °C.

System	D ₅₀ (µm)	Intrinsic Dissolution Rate (mg/cm ² /min)
Ibuprofen	23.69 ± 1.73	0.513 ± 0.003
Isonicotinamide	31.78 ± 1.74	-
Spray Dried Cocrystal	6.92 ± 0.13	0.199 ± 0.013
SD-M-10	9.47 ± 0.51	0.211 ± 0.006
SD-M-30	7.86 ± 0.12	-
SD-M-50	11.40 ± 0.57	-
SD-S-10	11.75 ± 0.27	0.152 ± 0.006
SD-P-10	10.95 ± 0.46	0.454 ± 0.022
HME-X-10	6.63 ± 0.36	0.207 ± 0.004

Figure 1

Figure 2

Figure 3

Figure 4

Figure 5

Figure 6

Figure 7

Figure 8

Figure 9

Figure 10

Figure 11

Engineering of pharmaceutical cocrystals in an excipient matrix: spray drying versus hot melt extrusion

David Walsh^{a,b}, Dolores R. Serrano^c, Zelalem Ayenew Worku^{a,b}, Atif M. Madi^{a,b}, Peter O'Connell^a, Brendan Twamley^d, Anne Marie Healy^{a,b*}

^a School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Dublin 2, Ireland.

^b SSPC, Synthesis and Solid State Pharmaceutical Centre, Ireland.

^c School of Pharmacy, Universidad Complutense de Madrid, Plaza Ramón y Cajal s/n, 28040 Madrid, Spain.

^d School of Chemistry, Trinity College Dublin, Dublin 2, Ireland.

*Corresponding author:

Anne Marie Healy

School of Pharmacy and Pharmaceutical Sciences

Trinity College Dublin

Dublin 2, Ireland.

Tel.: +353 1 896 1444

E-mail address: healyam@tcd.ie

Figure 1. Chemical structure of cocrystal components and selected excipients. a) IBU; b) INA; c) Xylitol, d) Mannitol; e) Soluplus and f) PVP.

Figure 2. SCXRD studies. a) Hydrogen bonded tetramer of the cocrystal $C_{13}H_{18}O_2:C_6H_6N_2O$, IBU:INA, with only the majority occupied disordered IBU moiety shown. Only heteroatoms labelled and only hydrogen atoms involved in hydrogen bonding shown. Displacement parameters shown at 50% probability, b) Hydrogen bonded sheet structure of the IBU:INA cocrystal showing the amide-ketone and hydroxide-INA donor acceptors as dotted lines as well as weak $CH...O$ interactions ($C5...O36ii = 3.316(4) \text{ \AA}$; $ii =$ symmetry equivalent transformation, $-x, -y+2, -z+1$).

Figure 3. PXRD analyses of cocrystal produced by spray drying. **A) Cocrystal formation by spray drying and solvent evaporation;** a) Cocrystal produced by spray drying from ethanol, b) Cocrystal produced by spray drying from isopropanol, c) Cocrystal produced by solvent evaporation from isopropanol, d) Spray dried IBU, e) Physical mixture of IBU and INA (1:1 molar ratio), f) INA, g) IBU. **B) Cocrystal co-spray dried with mannitol;** a) IBU:INA 50%, mannitol 50%, b) IBU:INA 70%, mannitol 30%, c) IBU:INA 90%, mannitol 10%, d) Spray dried cocrystal. **C) Cocrystal co-spray dried with PVP K15;** a) IBU:INA 80%, PVP K15 20%, b) IBU:INA 90%, PVP K15 10%, c) PVP K15, d) Spray dried cocrystal, e) INA, f) IBU. **D) Cocrystal co-spray dried with Soluplus;** a) IBU:INA 70%, Soluplus 30%, b) IBU:INA 80%, Soluplus 20%, c) IBU:INA 85%, Soluplus 15%, d) IBU:INA 90%, Soluplus 10%, e) Spray dried cocrystal.

Figure 4. PXRD analyses of cocrystal produced by hot melt extrusion. **A) Cocrystal in the presence of xylitol.** a) Extruded IBU:INA 90%, xylitol 10%, b) Spray dried cocrystal, c) Xylitol, d) INA, e) IBU. **B) Cocrystal in the presence of Soluplus and PVP K15.** a) IBU:INA 90%, PVP K15 10%, b) IBU:INA 90%, Soluplus 10%, c) Spray dried cocrystal, d) INA, e) IBU.

Figure 5. DSC curves of cocrystal produced by spray drying. **A). Cocrystal formation by spray drying and solvent evaporation;** a) IBU, b) INA, c) Cocrystal produced by slow solvent evaporation from isopropanol, d) Cocrystal produced by spray drying from ethanol, e) Cocrystal produced by spray drying from isopropanol, f) Physical mixture of IBU and INA. **B) Cocrystal co-spray dried with mannitol;** a) Mannitol, b) IBU, c) INA, d) Spray dried cocrystal, e) Spray dried IBU:INA 90%, mannitol 10%, f) Spray dried IBU:INA 70%, mannitol 30%, g) Spray dried IBU:INA 50%, mannitol 50%, h) Physical mixture of spray dried cocrystal 50% and mannitol 50%. **C) Cocrystal co-spray dried with Soluplus;** a) IBU, b) INA, c) Spray dried cocrystal, d) Physical mixture of IBU and INA (1:1 molar ratio), e) Soluplus, f) Spray dried IBU:INA 90%, Soluplus 10%, g) Spray dried IBU:INA 85%, Soluplus 15%, h) Spray Dried IBU:INA 80%, Soluplus 20%, i) Spray dried IBU:INA 70%, Soluplus 30%. **D) Cocrystal co-spray dried with PVP K15;** a) IBU, b) INA, c) Cocrystal produced by spray drying, d) Physical mixture of IBU and INA, e) PVP K15, f) Co-spray dried IBU:INA 90%, PVP K15 10%, g) IBU:INA 80%, PVP K15 20%.

Figure 6. DSC curves of cocrystal produced by HME. **A) Cocrystal in the presence of xylitol;** a) Xylitol, b) IBU, c) INA, d) Spray dried cocrystal, e) Physical mixture of IBU:INA 1:1 molar ratio, f) Physical mixture of IBU, INA 90% and Xylitol 10%, g) Hot melt extruded IBU:INA 90%, Xylitol 10%. **B) Cocrystal in the presence of Soluplus and PVP K15;** a) IBU, b) INA, c) Spray dried cocrystal, d) Physical mixture of IBU and INA at 1:1 molar ratio, e) Hot melt extruded IBU:INA 90%, Soluplus 10%, f) Hot melt extruded IBU:INA 90%, PVP K15 10%.

Figure 7. Investigation of H-bonding by FTIR. **A) Cocrystal co-spray dried with mannitol;** a) Co-spray dried IBU:INA 50%, Mannitol 50%, b) Co-spray dried IBU:INA 70%, Mannitol 30%, c) Co-spray dried IBU:INA 90%, Mannitol 10%, d) Cocrystal, e) Mannitol, f) INA, g) IBU. **B) Cocrystal co-spray dried with Soluplus;** a) Co-spray dried IBU:INA 90%, Soluplus 10%, b) Cocrystal, c) Soluplus, d) INA, e) IBU. **C) Cocrystal co-spray dried with PVP K15;** a) Co-spray dried IBU:INA 90%, PVP K15 10%, b) Cocrystal, c) PVP K15, d) INA, e) IBU. **D) Extruded cocrystal with xylitol;** a) IBU:INA 90% hot melt extruded with xylitol 10%, b) Cocrystal, c) Xylitol, d) INA, e) IBU.

Figure 8. DVS sorption (blue) and desorption (red) isotherms and PXRD analyses. **A) DVS profile of co-spray dried systems with mannitol and HME with xylitol;** a) Co-spray dried IBU:INA 50%, mannitol 50%, b) Co-spray dried IBU:INA 70%, mannitol 30%, c) Co-spray dried IBU:INA 90%, mannitol 10%, d) Spray dried cocrystal, e) Hot melt extruded IBU:INA 90%, xylitol 10%. **B) DVS profile of co-spray dried systems with Soluplus;** a) Co-spray dried IBU:INA 70%, Soluplus 30%, b) Co-spray dried IBU:INA 80%, Soluplus 20%, c) Co-spray dried IBU:INA 85%, Soluplus 15%, d) Co-spray dried IBU:INA 90%, Soluplus 10%, e) Spray dried cocrystal. **C) PXRD analyses of co-spray dried systems with mannitol after DVS;** a) IBU:INA 50%, Mannitol 50%, b) IBU:INA 70%, Mannitol 30%, c) IBU:INA 90%, Mannitol 10%, d) Spray Dried cocrystal. **D) PXRD analyses of co-spray dried systems with Soluplus after DVS;** a) IBU:INA 70%, Soluplus 30%, b) IBU:INA 80%, Soluplus 20%, c) IBU:INA 85%, Soluplus 15%, d) IBU:INA 90%, Soluplus 10%, e) Spray Dried cocrystal.

Figure 9. SEM images. Key: a) IBU, b) INA, c) Spray dried cocrystal, d) Spray dried IBU:INA 90%, mannitol 10%, e) Spray dried IBU:INA 90%, Soluplus 10%, f) Spray dried IBU:INA 90%, PVP K15 10%, g) Hot melt extruded IBU:INA 90%, xylitol 10%, h) Spray dried IBU:INA 50%, mannitol 50%.

Figure 10. Dissolution profiles of spray dried and hot melted extruded formulations and PXRD analyses after dissolution on the surface disk. **A) Dissolution studies performed at 37 °C of:** co-spray dried IBU:INA 90%, PVP K15 10% (pink ◆), co-spray dried IBU:INA 90%, mannitol 10% (blue ▲), cocrystal produced by spray drying (black ■), hot melt extruded IBU:INA 90%, xylitol 10% (red ●) and co-spray dried IBU:INA 90%, Soluplus 10% (green ▼). **B) Dissolution profiles at 20 °C of:** the cocrystal produced by spray drying (black ■) and co-spray dried IBU:INA 90%, Soluplus 10% (red ●). **C) PXRD analyses after cocrystal dissolution;** a) Cocrystal after dissolution, b) Cocrystal produced by spray drying, c) INA, d) IBU. **D) PXRD analyses after dissolution of the co-spray dried cocrystal with mannitol;** a) Co-spray dried IBU:INA 90%, mannitol 10% after dissolution, b) Co-spray dried IBU:INA 90%, mannitol 10%, c) Cocrystal produced by spray drying, d) INA, e) IBU. **E) PXRD analyses after dissolution of hot melt extruded cocrystal with xylitol;** a) Hot melt extruded IBU:INA 90%, xylitol 10% after dissolution, b) Hot melt extruded IBU:INA 90%, xylitol 10%, c) Cocrystal produced by spray drying, d) INA, e) IBU. Some peaks attributable to IBU in C), D) and E) are highlighted by arrows.

Figure 11. PXRD analyses after dissolution at 37 and 20 °C. **A) Co-spray dried cocrystal with Soluplus at 37 °C;** a) Co-spray dried IBU:INA 90%, Soluplus 10% after dissolution, b) Co-spray dried IBU:INA 90%, Soluplus 10%, c) Cocrystal produced by spray drying, d) INA, e) IBU. **B) Co-spray dried cocrystal with PVP K15 at 37 °C;** a) Co-spray dried IBU:INA 90%, PVP K15 10% after dissolution, b) Co-spray dried IBU:INA 90%, PVP K15 10%, c) Cocrystal produced by spray drying, d) INA, e) IBU. **C) Co-spray dried cocrystal with Soluplus at 20 °C;** a) Co-spray dried IBU:INA 90%, Soluplus 10% after dissolution, b)

Co-spray dried IBU:INA 90%, Soluplus 10%, c) Spray dried cocrystal, d) INA, e) IBU. **D) PXRD analyses after cocrystal dissolution studies at 20 °C;** a) Spray dried cocrystal after dissolution, b) Spray dried cocrystal, c) INA, d) IBU. Peaks of both the cocrystal and IBU can be seen after dissolution.