**Crystallo-co-spray drying as a new approach to manufacturing of drug/excipient
agglomerates: impact of processing on the properties of paracetamol and lactose mixtures**

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12 Abstract

13 The novel process of crystallo-co-spray drying of paracetamol and α -lactose monohydrate was
14 investigated by varying the spray dryer inlet temperature and inlet feed solvent composition. A
15 crystalline agglomerate was obtained with no change to the physical structure of either component
16 throughout both investigations and with possible interactions between the hydroxyl groups of the α -
17 lactose monohydrate and the amide and hydroxyl groups of the paracetamol detected. The
18 percentage soluble fraction of the components in the inlet feed had the largest influence on the
19 morphology of the final dried agglomerate. Low excipient soluble fraction resulted in an increase in
20 paracetamol surface coating and high excipient soluble fraction produced agglomerates of highly
21 mixed components. The use of crystallo-co-spray drying can serve as a method of producing an
22 agglomerated blend of crystalline co-spray dried components leading to possible opportunities for
23 process intensification with the reduction of process steps such as blending, agglomeration, drying
24 and milling into one single stage.

25 Keywords: paracetamol; α -lactose monohydrate; crystallo-co-spray drying; active pharmaceutical
26 ingredient; thermal analysis; mixing; process intensification

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28

29 Abbreviations

α -lactose monohydrate	$L\alpha \cdot H_2O$
β -lactose	$L\beta$
Active Pharmaceutical Ingredient	API
Attenuated total reflectance	ATR
Crystallo-co-agglomeration	CCA
Crystallo-co-spray drying	CCSD
Deionised water	H_2O
Differential scanning calorimetry	DSC
Dynamic vapour sorption	DVS
Ethanol	EtOH
Fourier transform infra-red spectroscopy	FTIR
Inlet temperature	T_{in}
Scanning electron microscopy	SEM
Solvent composition	Sc
Stable anhydrous α -lactose	$L\alpha_s$
Paracetamol	PAR
Powder X-ray diffraction	PXRD
Recrystallised	Rc
Unstable hygroscopic α -lactose	$L\alpha_H$

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1. Introduction

Crystallo-co-agglomeration (CCA) is an extension of the spherical crystallisation technique developed by Kawashima et al. (Kawashima et al., 1984). Kadam et al. (Kadam et al., 1997) proposed this agglomeration process in which a drug is crystallised and agglomerated with an excipient/other drug, using a bridging liquid to modify the crystal nature and obtain directly compressible agglomerates (Kawashima et al., 1982; Tapia et al., 1993b). Whereas the spherical crystallisation technique is limited only to high dose pharmaceuticals, CCA could be utilised when there is a low concentration of drug with the aid of another API or a diluent such as talc, sodium starch glycolate, and starch (Pawar et al., 2004b). CCA works by forming a homogeneous mixture of drug(s), diluent or polymers which are then stirred with a “good solvent” (high solubility) together with a bridging liquid to get a homogeneous mass in a Morishima vessel under stirring (Morishima et al., 1993; Paradkar and Pawar, 2014). A “bad solvent” (antisolvent) is then added which induces crystallisation and growth of the component in solution on the surface of the diluent/other drug and the resulting agglomerates are bound together using the bridging liquid. What follows is filtration and drying steps to obtain the dried agglomerates (Paradkar and Pawar, 2014). What is produced from this process is a spherical agglomerate that offers advantages such as excellent flow characteristics, uniform size distribution, and reproducible filling (Goskonda et al., 1994; Tapia et al., 1993a). However, what is of particular interest in this study is its capability to produce a powder with enhanced compressional properties (Jadhav, 1998; Pawar et al., 2004a, b). To do this the CCA process has been applied, with slight modification, to the co-spray drying of an active pharmaceutical ingredient (API) and an excipient, presently described, for the first time, as crystallo-co-spray drying (CCSD).

The area of co-spray drying is well established and broad. Gonnissen et al. co-spray dried various formulations with a superdisintegrant to improve the disintegration times of tablets produced by direct compression (Gonnissen et al., 2008b), and also investigated the effect of co-spray drying paracetamol with excipients on the resulting powder’s compactibility (Gonnissen et al., 2008a).

Coucke et al. co-spray dried a mixture of maize starch and a polymer with a model molecule in order to develop a powder suitable for nasal drug delivery via a one-step manufacturing process (Coucke et al., 2009), Vanhoorne et al. coated a poorly processable material with a mixture of $L\alpha\cdot H_2O$ and poly(vinylpyrrolidone) (PVP) via co-spray drying to improve the compact's tableability (Vanhoorne et al., 2014), and in a separate study, continuously manufactured the compressible σ -mannitol polymorph by co-spray drying with PVP (Vanhoorne et al., 2016). During the CCSD process an excipient in suspension is mixed with an API in solution and co-spray dried simultaneously. Within an atomised droplet, the precipitating API crystallises either heterogeneously on the surface of the excipient, or homogeneously in the bulk of the solution as the drying boundary of the droplet shrinks. Whereas in a traditional CCA process, a bridging liquid is used to promote aggregate formation, in a CCSD process it is the diffusion of the precipitated components towards the centre of each droplet as the droplet boundary shrinks that causes the material to form agglomerates.

α -lactose monohydrate ($L\alpha\cdot H_2O$, $C_{12}H_{22}O_{11}\cdot H_2O$, Figure 1) was chosen as the model excipient due to its common use as a filler/binder in tablet formulations and as its physicochemical properties, crystallisation and dehydration behaviour has been extensively studied (Brito and Giulietti, 2007; Garnier et al., 2002; Gombás et al., 2002; MacFhionnghaile et al., 2017). The crystal structure of Lactose was first described in 1971 (Beevers and Hansen, 1971; Fries et al., 1971). It is a disaccharide composed of one unit of D-glucose and one unit of D-galactose (Kou et al., 2012). It can exist in multiple forms including its α -anomer, in which it can manifest as a monohydrate, stable anhydrous or unstable anhydrous form and its β -anomer obtained via the mutarotation. β -lactose ($L\beta$) and stable anhydrous α -lactose ($L\alpha_s$) exist in a constant equilibrium of 40 α :60 β in aqueous solution at room temperature (Kirk et al., 2007). The most common form of lactose available is α -lactose monohydrate. The storage temperature, drying method, time, relative humidity and composition of the material all influence the crystal form obtained (Drapier-Beche et al., 1997; Jenness et al., 1988; Jouppila et al., 1997; Nickerson, 1962). $L\alpha\cdot H_2O$, $L\alpha_H$, and $L\beta$, crystallise in the monoclinic form whereas the crystal structure of the $L\alpha_s$ is more complex with a triclinic unit cell (Kirk et al., 2007). $L\alpha\cdot H_2O$ is readily soluble

in H₂O (18.9 g/100 mL, H₂O)(Machado et al., 2000). This decreases to 1.78 g/100 mL at a solvent composition of 50/50% v/v ethanol (EtOH)/H₂O and is practically insoluble using 100% EtOH at 25 °C (Machado et al., 2000). L α -H₂O is prepared through crystallisation from supersaturated solutions below 93.5 °C using H₂O as a solvent and an anti-solvent such as acetone, whereas L β can be prepared from solutions above this temperature via mutarotation (Buma and Wiegers, 1967; Kirk et al., 2007; Larhrib et al., 2003b). An amorphous or glassy form of lactose can be produced through spray drying from solution (Kibbe, 2000), however as the inlet temperature increases and/or the percentage soluble fraction of L α -H₂O decreases, there is a higher tendency for a crystalline material to be produced (Chiou et al., 2008; Harjunen et al., 2002).

Paracetamol (acetaminophen, PAR, C₈H₉NO₂, Figure 1) is a common API having analgesic and antipyretic properties and used in a wide range of pharmaceutical roles. It was chosen as the model drug in this study as it has been suggested that the many hydroxyl groups such as those on sugar molecules like L α -H₂O show functional group complementarity to the hydroxyl and amide functional groups of PAR (Chadwick et al., 2012). PAR has two hydrogen bond accepting functional groups (-OH, =O) and two hydrogen bond donating functional groups (-NH, -OH). It forms N-H $\cdots$ O and O-H $\cdots$ O hydrogen bonds by -NH, -OH, and -C=O groups. To date, three polymorphic forms of PAR have been reported. The crystalline structure of the commercially available and most stable form I (monoclinic) was first described by Haisa et al. (Haisa et al., 1976) and Welton et al. (Welton and McCarthy, 1988), the metastable form II (orthorhombic) was first observed by Haisa et al. (Haisa et al., 1974) in a recrystallisation study using EtOH as a solvent and the unstable form III was observed under fusion experiments (Burger, 1982). PAR form I is readily soluble in EtOH (13.39 g/100 mL) and slightly soluble in H₂O (1.53 g/100 mL) at 25 °C (Jiménez and Martínez, 2006). At a composition of 50/50% v/v EtOH/H₂O this increases to 16.4 g/100 mL (Jiménez and Martínez, 2006). Its solubility increases with an increase in EtOH concentration up to a maximum of 80% v/v EtOH/H₂O before the solubility of PAR decreases (Jiménez and Martínez, 2006). The morphology of PAR is greatly influenced by the method of crystallisation, solvent used, temperature, pressure and supersaturation rate (Sudha and

Srinivasan, 2014). We have recently demonstrated that the size and morphology of spray dried paracetamol can be controlled through the selection of spray dryer inlet temperature, solvent composition and corresponding atomised droplet characteristics (McDonagh and Tajber, 2019). Such particle engineering to tailor the crystallisation behaviour of spray dried paracetamol will be utilised in this work.

To the best of our knowledge, this work is novel in investigating the CCSD process in general and in particular studying the role of the spray dryer inlet temperature and solvent composition on the solid-state characteristics and soluble fraction of the excipient in a CCSD system, with both parameters being the largest influencers in an evaporative crystallisation process. The purpose of this research was to obtain, and characterise, mixtures of an API and an excipient of varying degrees of constituent mixing through the process of CCSD. Such a variation was possible through the selection of the soluble fraction of the excipient in the inlet feed and allowed for the investigation of the role of API-excipient interaction in the CCSD material. As well as this, the spray drying behaviour of the excipient spray dried on its own under the same conditions of the CCSD process was also investigated. The co-processing of API-excipient mixtures through CCA offers the opportunity of process intensification with individual laborious steps such as blending and agglomeration being combined into one continuous process. With the addition of spray drying, this one step process then implements drying whilst simultaneously eliminating the need for a bridging liquid. The successful implementation of this process will be capable of producing a powder blend of increased constituent mixing, decreased segregation and improved compaction behaviour capable of direct compression.

2. Materials and methods

2.1. Materials

Materials used in experiments were: paracetamol (PAR) (Sigma-Aldrich, Ireland), α -lactose monohydrate ($L\alpha\cdot H_2O$) (Sigma-Aldrich, Ireland) and Carbopol (polyacrylic acid, molecular weight of 3,000,000, Sigma-Aldrich, Ireland). Ethanol (EtOH) (technical grade) was purchased from T.E

Laboratories (Ireland), and deionised water (H₂O) was produced using a Millipore Elix 3 system (Millipore, France) and anhydrous ethanol (< 0.003% H₂O) was purchased from VWR Chemicals (Ireland).

2.2. Methods

2.2.1. Spray drying

All materials were spray dried using a Büchi B-290 mini spray dryer (Switzerland) operated in the open mode. The suspensions were stirred using a magnetic stirrer at a rate sufficient enough to maintain homogeneity before being fed into a 2-fluid atomising spray nozzle with a 0.7 mm cap. The inlet feed was kept at room temperature and fed into the spray dryer through an incorporated peristaltic pump at approximately 9 mL/min (setting: 30%), with an aspirator drying air flow rate of 38 m³/h (setting: 100%) and flow meter spraying flow rate of 475 L/h (height: 40 mm) (Büchi-Labortechnik, 2006; McDonagh and Tajber, 2019). The drying gas used was air and the atomising gas was nitrogen. The dried materials were collected from the collection vessel only and were thoroughly mixed using a spatula prior to refrigerated storage (4 ± 1 °C) in 15 mL amber powder bottles.

2.2.1.1. Effect of spray dryer inlet temperature and solvent composition on α -lactose monohydrate

A series of 5% w/v L α -H₂O suspensions were made up and spray dried (n = 3) at varying inlet temperatures (T_{in}): L#1, L#2, L#3, L#4, L#5, L#6, L#7 and solvent compositions (Sc): L#8, L#9, L#10, L#11, L#12 and L#13. A summary of spray drying parameters used can be seen in Table 1 below.

2.2.1.2. Effect of spray dryer inlet temperature and solvent composition on paracetamol + α -lactose monohydrate crystallo-co-spray dried agglomerates

A series of 10% w/v PAR + L α -H₂O suspensions in equal weight ratios were made up and spray dried (n = 3) at varying inlet temperatures (T_{in}): PL#1, PL#2, PL#3, PL#4, PL#5, PL#6, PL#7 and solvent compositions (Sc): PL#8, PL#9, PL#10, PL#11, PL#12 and PL#13. A summary of spray drying parameters used can be seen in Table 2 below.

2.2.2. Recrystallisation of α -lactose monohydrate

α -lactose monohydrate was recrystallised using a cooling crystallisation technique from deionised H₂O (n = 3) modified from a procedure proposed by Larhrib et al. (Larhrib et al., 2003a). A 250 mL crystallising vessel (Radley's Reactor-Ready, UK) was charged with 100 mL of deionised H₂O and heated to 60 °C using a Huber pilot 1 temperature control unit (Huber, Offenburg, Germany). It was stirred using a PTFE 4 pitched blade stirrer powered by a Heidolph Hei-torque overhead stirrer (Germany) at a rate of 500 rpm. Once thermally stable, 0.2 g of Carbopol was added in small additions until a uniform viscous media was produced. 50 g of L α -H₂O was then added and constantly stirred until a translucent yellow gel was produced with a pH of approximately 3. The rate of stirring was increased to 800 rpm and 1M NaOH was added dropwise until a pH of 7 was achieved, increasing the solution's viscosity. Once achieved, this was extracted into a beaker, completely covered in tin foil and allowed to cool in the dark for 48 hours. After this time the pH of the solution was increased to between 2.8 – 3.5 using 1M HCl reducing the solutions viscosity and allowing the suspended crystals to settle to the bottom of the beaker. The mother liquor remaining was then decanted and the remaining crystals were washed 4 times, first with a 60 % v/v EtOH/H₂O mixture to remove any remaining mother liquor, then with 100% EtOH 3 times before leaving the crystals to dry overnight at 70 °C. The dried crystals were then placed in a 106 μ m sieve, gently bushed to prevent chipping and the size fraction obtained between 53 μ m and 106 μ m was then placed in a sealed desiccator for storage.

2.2.3. Recrystallisation of paracetamol

Recrystallised samples of paracetamol were produced using a solvent evaporation technique (n=3) (McDonagh and Tajber, 2019). 100 mL of EtOH was filtered using a Fisherbrand 0.45 μ m PTFE hydrophilic membrane syringe filter (Ireland) and added to 10 g of PAR to form a solution. This was then added to a glass specimen tube and sealed using parafilm. Holes were punctured in the film to allow the evaporated EtOH to be removed and the time required for supersaturation to be induced

was around 2 weeks. After this time, the evaporated crystals were removed and allowed to dry in air before being crushed using a mortar and pestle. The crushed powder was then placed in an oven at 60 °C overnight to remove any residual solvent.

2.2.4. Thermal analysis

Thermal analysis was done using differential scanning calorimetry (DSC) using a Mettler Toledo DSC 821e (Switzerland). Samples were heated using a range of 25 – 250 °C at a rate of 10 °C/min. Nitrogen was used as the purging gas and had a flowrate of 10 mL/min. A microbalance was used to accurately weigh the samples between 5 – 7 mg (Mettler Toledo MT5, Switzerland) in 40 µL aluminium crucibles. Gases produced during the analysis were removed through three holes punched in the lid of the crucible. All measurements were carried out in triplicate. In this work, the characteristic temperatures of thermal events are represented as onset temperatures (McDonagh and Tajber, 2019).

2.2.5. Powder X-Ray diffraction (PXRD)

An X-ray diffractometer (Rigaku Miniflex II, Japan) was used to obtain PXRD profiles of the samples investigated. It was operated in the Bragg–Brentano reflection mode using Cu K α (1.54 Å) as a radiation source. Samples were placed on a zero-background silicon sample holder using a spatula and gently pressed using a glass slide to obtain a uniform depth. The samples were then scanned over a range of 5–40° (2 θ). All measurements were carried out in triplicate (McDonagh and Tajber, 2019).

2.2.6. Attenuated total reflectance Fourier transformation infra-red spectroscopy (ATR-FTIR)

FTIR absorbance spectra were obtained from a PerkinElmer Spectrum 1 FT-IR (USA) with an ATR and ZnSe crystal accessory. The scanning range was 4000 – 650 cm⁻¹ using a resolution of 4 cm⁻¹ and the reported results are presented as an average of 10 scans per each sample. All measurements were carried out in triplicate (McDonagh and Tajber, 2019).

2.2.7. Dynamic vapour sorption (DVS)

Gravimetric DVS (DVS Advantage–1, Surface Measurement Systems, UK) was used to measure the vapour sorption capabilities of the spray dried samples. Samples were tested isothermally (25.0 ± 0.1 °C) using water and ethanol separately as the adsorbing vapour. A steady state weight change of 0.0002 mg/min was used and the initial mass of material was between 15 and 20 mg. The required time for the first measurement to be read was between 1 – 2 hours at 0% relative humidity (RH) (for water) and 0 partial pressure (p/p_0) (for ethanol). Once stable, the samples were exposed to changes in RH/ p/p_0 from 10% RH/0.1 p/p_0 to 90% RH/0.9 p/p_0 in 10% RH/0.1 p/p_0 increments and in reverse during the desorption process. The samples were analysed using two sorption/desorption cycles and were re-tested using DSC and PXRD post-DVS analysis (McDonagh and Tajber, 2019).

2.2.8. Scanning electron microscopy (SEM)

A Carl Zeiss ultra 3 SEM (Germany) was used to obtain SEM images of the samples investigated. Double-sided adhesive pads were used to hold the samples and after gently applying the material, excess was removed using compressed air prior to coating. Gold/palladium coating was achieved using a Cressington 208HR sputter coater (UK) for 25 seconds. An accelerating voltage of 5 kV was used along with a working distance of 8 mm (McDonagh and Tajber, 2019).

2.2.9. Soluble fraction of paracetamol and α -lactose

A range of suspensions containing 2.5 g of PAR and 2.5 g of $L\alpha$ -H₂O were made up using solvent compositions ranging from 100% EtOH to 50/50 % v/v EtOH/H₂O in 50 mL Eppendorf conical tubes. They were sealed well and shaken for one hour at a rate of 200 rpm using an orbital shaker (IKA MTS 2/4, Germany). All samples were then moved to an incubator set at 25 ± 3 °C and left for 12 hours to give the suspension adequate time to settle to the bottom of the vial. Two 20 mL aliquots were taken from the supernatant at 25 °C and filtered (25 mm syringe filter with a 0.45 μ m polyethersulfone membrane, Fischer, Ireland) labelling one vial as vial 1 and the other as vial 2. Vial 1 was used to test for the concentration of PAR dissolved in solution using a UV-Vis spectrometer (UV-1700 PharmaSpec UV-VIS, Shimadzu, Japan) and scanned at a wavelength of 248 nm (Rote et al., 2012). Vial 2 was left

for 48 hours in a fume hood at 25 °C to allow the EtOH constituent of the solvent mixture to evaporate and then left for 24 hours in an incubator (Gallenkamp Size 1, UK) set at 60 °C to evaporate the remaining H₂O constituent. This evaporation of the solvent resulted in large PAR + L α -H₂O crystals. By subtracting the known weight of PAR found in vial 1 from the weight of the crystallised mixture in vial 2, the amount of dissolved L α -H₂O in the mixture was determined.

2.2.10. Particle size analysis

Particle size analysis by laser light diffraction, in triplicate for each sample, was performed using a Malvern Mastersizer 2000 (UK) with a Scirocco dry powder accessory as previously described (McDonagh and Tajber, 2019).

2.2.11. Statistical analysis

Differences between spray dried samples were statistically tested by running a one-way ANOVA model with a two-sided confidence interval with 95% confidence. Tukey comparisons were used to check the significance of individual responses and a p-value of 0.05 was the cut off for significance. Normal probability plots, histograms of residuals and residuals vs. fitted values were also plotted to check for deviations from statistical assumptions.

3. Results and discussion

3.1. Powder X-ray diffraction

3.1.1. Spray dried α -lactose monohydrate

To understand the spray drying behaviour of L α -H₂O during the CCSD process, it was spray dried on its own at various T_{in} and Sc. L α -H₂O remained stable throughout all of the spray drying conditions tested with no structural change occurring. The α -anomer was produced at each inlet temperature and solvent composition investigated with the characteristic Bragg peak positions and corresponding hkl planes of the α -anomer at 16.4 ° (040), 20.0 ° (011) and 23.8 ° (200) obtained (Figure

2). The characteristic peaks of the β anomer: 10.6 ° (011), 19.2 ° (110), 20.7 ° (11-1) and 21.1 ° (111) and of the stable anhydrous α -lactose: 12.4 ° (1-10), 19.4 ° (130) and 23.2 ° (1-3-1) were not observed.

A crystalline material was obtained at each spray dryer inlet temperature and solvent composition investigated, with a decrease in peak area of the most intense $L\alpha\cdot H_2O$ PXRD peak (011) as the concentration of H_2O in the inlet feed decreased, corresponding to a decrease in material crystallinity.

3.1.2. Crystallo-co-spray dried α -lactose monohydrate and paracetamol

The addition of PAR and its CCSD with $L\alpha\cdot H_2O$ at both varying inlet temperatures and inlet feed solvent compositions had no effect on structural properties of the initial components (Figure 3). PAR form I was the prominent crystal structure obtained as was the monohydrated α -anomer. The crystallinity of the PAR component of the CCSD mixture remained unchanged throughout all spray dryer inlet temperatures and solvent compositions, as did the crystallinity of the $L\alpha\cdot H_2O$ component, as the inlet temperature was varied. By varying the inlet feed solvent composition and by increasing the H_2O concentration of the feed, there was a decrease in the crystallinity of the $L\alpha\cdot H_2O$ component of the CCSD mixture in comparison to the other CCSD agglomerates of varying Sc , similar to trends presented in Figure 2b. The peak area of the (011) peak of $L\alpha\cdot H_2O$ was largest for the CCSD mixture produced using 100% EtOH (PL#8) which decreased for the agglomerate produced at 80% v/v EtOH/ H_2O (PL#10) before decreasing further for the agglomerate produced at 50/50% v/v EtOH/ H_2O (PL#13), similar to the work previously published by Islam et al. (Islam and Langrish, 2010) and Harjunen et al. (Harjunen et al., 2002). Experiments were also conducted in which $L\alpha\cdot H_2O$ was spray dried at higher H_2O concentrations (Figure S1 and Figure S2) and it was found that $L\alpha\cdot H_2O$ crystallinity decreased as the concentration of H_2O increased in the feed with a simultaneous increase in amorphous content similar to previously published data (Gombás et al., 2002).

3.2. Dynamic vapour sorption (DVS)

3.2.1. Spray dried α -lactose monohydrate

DVS analysis of $L\alpha\cdot H_2O$ spray dried from 100% EtOH sample using water as the probe vapor showed no significant change in the maximum % weight increase as the T_{in} increased with both Figure 4b and 4d showing a maximum % change in mass of ca. 0.08%. This confirmed that there was no change in material crystallinity as the spray dryer inlet temperature was varied, for the constant EtOH content in the feed, similar to trends presented in PXRD data (Figure 2a). By increasing the H_2O concentration in the inlet feed (L#13, Figure 4e, Figure 4f), a larger % change in mass was observed. This trend is due to the increased disorder in the samples spray dried at higher H_2O concentrations, evident from PXRD results (Figure 2b). Between 40-60% RH there was a slight change in sample mass for samples spray dried at 120 °C (Figure 4d and Figure 4f). This is attributed to a possible crystallisation event as the event did not appear in the second DVS cycle. The high degree of sample crystallinity indicated from PXRD analysis was evident in the small % change in mass for both the water, and ethanol sorbing vapour in the DVS analysis.

Using EtOH as the probe vapour showed a slight increase in maximum % mass change as the inlet temperature of the spray dryer increased (0.03% - 0.06%, Figure 4a - Figure 4c) and as the concentration of EtOH in the feed decreased (0.06% - 1.4%, Figure 4c – Figure 4e). The larger sorption seen in Figure 4e is a result of the increased accessibility of the sorbing ethanol vapour for the crystalline water of the $L\alpha\cdot H_2O$. $L\alpha\cdot H_2O$ spray dried at higher H_2O concentrations had a higher degree of disorder. With this increased accessibility and ethanol's affinity for water, there is an increase in sorbing vapour uptake. During the desorption portion of the first cycle, this crystalline water (mixed together with the sorbed ethanol) is then liberated from the crystal structure leading to a decrease in sample mass with the sample being around 2% lighter compared to at the start of the first cycle.

3.2.2. Crystallo-co-spray dried α -lactose monohydrate and paracetamol

DVS kinetic plots of the CCSD agglomerates can be seen in Figure 5. Increasing the spray dryer inlet temperature had the effect of producing a more hygroscopic material with powders spray dried

at the PL#8 temperature having a higher maximum % change in mass for both the EtOH (0.20%, Figure 5c) and water vapour (0.17%, Figure 5d) compared to the PL#7 agglomerate. As no difference in % mass change was observed for $\text{L}\alpha\text{-H}_2\text{O}$ spray dried on its own, this increase was attributed to the PAR component of the mixture.

As discussed previously, with an increase in material disorder present in CCSD agglomerates using higher H_2O concentrations (50/50% v/v EtOH/ H_2O , PL#13, Figure 3b), there was a larger uptake of sorbing vapor (Figure 5e). However, during the desorption process of the first cycle there is only a 0.5% change in mass relative to the starting weight. In theory, with the agglomerate containing 50% $\text{L}\alpha\text{-H}_2\text{O}$, and the sorbing vapour is unobstructed, then it should lose 1% of its weight at the end of the first cycle as presented in Figure 4e ($\text{L}\alpha\text{-H}_2\text{O}$ spray dried on its own lost ca. 2% wt.). However, PAR coating the surface of the $\text{L}\alpha\text{-H}_2\text{O}$ is hindering the vapour uptake and crystalline water removal resulting in a smaller % weight loss.

3.3. Fourier transformation infra-red spectroscopy (FTIR)

To investigate the possible interactions that could take place between the two components of a CCSD mixture, FTIR spectroscopy was performed. It was also used to confirm the physical structure of the spray dried and CCSD materials presented in the PXRD data.

3.3.1. Spray dried α -lactose monohydrate

FTIR analysis showed no changes between the $\text{L}\alpha\text{-H}_2\text{O}$ spray dried samples both using different spray dryer inlet temperatures and solvent compositions. Figure 6 shows the FTIR spectra of $\text{L}\alpha\text{-H}_2\text{O}$ spray dried for both these investigations. All spectra showed the stretching vibrations of the crystalline water ($3450 - 3442 \text{ cm}^{-1}$), the stretching vibrations of the hydroxyl group ($3400\text{-}3200 \text{ cm}^{-1}$), the asymmetric stretching of the C – H bonds ($2936 - 2916 \text{ cm}^{-1}$), the bending vibration of the hydroxyl groups of the crystalline water (1650 cm^{-1}), the deformation of the hydroxyl group ($1480\text{-}1410 \text{ cm}^{-1}$), the asymmetric stretching vibration of the C-O-C bond between the glucose and galactose units (1200

– 1070 cm^{-1}) and the stretching vibration of the C–O bond (1075 – 1000 cm^{-1}). The peaks distinguishing the different forms of lactose can be seen highlighted in Figure 6.

The main differences between the IR spectra of the various lactose structures can be seen between 1000 – 800 cm^{-1} . The monohydrated α -anomer had a specific peak ca. 920 cm^{-1} , the β -anomer has a peak ca. 950 cm^{-1} (Listiohadi et al., 2009) and the stable anhydrous α -lactose structure can be identified with its spectrum missing a peak corresponding to the free –OH vibrations of the crystalline water molecules ca. 3500 cm^{-1} . All peaks corresponded to the hydrated α -anomer of lactose and confirmed PXRD results that no structural change occurred to the $\text{L}\alpha\cdot\text{H}_2\text{O}$ during the spray drying process of both investigations.

3.3.2. Crystallo-co-spray dried α -lactose monohydrate and paracetamol

The FTIR spectra of PAR + $\text{L}\alpha\cdot\text{H}_2\text{O}$ CCSD agglomerates processed at various T_{in} and Sc can be seen in Figure S3. The characteristic bond vibrations of PAR form I; N-H stretching vibration (3161 cm^{-1}), C-H stretching vibration of the phenyl ring (1610 cm^{-1}), deformation of the C-NH bond mixed with the stretching vibration of the phenyl ring (1565 cm^{-1} and 1516 cm^{-1}), deformation of the methyl group mixed with the stretching vibration of the phenyl ring (1442 cm^{-1}) and the deformation of the Ph-H bond mixed with the stretching of the C-N bond, all match to those of the spray dried agglomerates (T_{in} and Sc) (Burgina et al., 2004). The same absorption peaks as stated above corresponding to the α -anomer of lactose were also present, confirming the PXRD results that no structural changes occurred to the CCSD mixtures during both investigations.

To investigate further into the possible interactions between the PAR and $\text{L}\alpha\cdot\text{H}_2\text{O}$ when CCSD together, the second order derivative of the FTIR spectra were calculated. The differences between the 2nd order spectra of the CCSD agglomerates (Figure 7) to that of the physically mixed sample correspond to the combination of C-N stretching and N-H deformation of PAR (1550 cm^{-1}), the deformation of the hydroxyl group bonded to the phenol ring of the $\text{L}\alpha\cdot\text{H}_2\text{O}$ (1360 cm^{-1}), the stretching of the C-O bond of the PAR (1165 cm^{-1}), the stretching of the C-N bond of PAR (1120 cm^{-1}) and the out

of plane deformation of the C-H bond of $L\alpha\cdot H_2O$ (925 cm^{-1}). Chadwick et al. suggested that the many hydroxyl groups such as those on sugar molecules like $L\alpha\cdot H_2O$ show functional group complementarity to the hydroxyl and amide functional groups of PAR (Chadwick et al., 2012). FTIR analysis shows these possible interactions between the hydroxyl groups of the aromatic rings of the $L\alpha\cdot H_2O$ and the amide and hydroxyl groups of the PAR evident in subtle changes in their 2nd derivative spectra. To investigate the interaction of the API and the excipient further, DSC analysis was performed on the spray dried and CCSD samples.

3.4. Differential scanning calorimetry (DSC)

The temperatures and enthalpy values of all thermal events are presented in Table S1a-c. DSC thermograms for $L\alpha\cdot H_2O$ spray dried on its own and $L\alpha\cdot H_2O$ + PAR CCSD mixtures at various T_{in} and Sc were investigated to obtain greater understanding of the effect of spray drying on the excipient and the possible interactions between the drug and excipient when CCSD. All temperature values for thermal events are presented as the onset temperature (T_o).

3.4.1. Spray dried α -lactose monohydrate

DSC thermograms of $L\alpha\cdot H_2O$ spray dried at various T_{in} ranging from $120\text{ }^\circ\text{C}$ (L#1) to $60\text{ }^\circ\text{C}$ (L#7) can be seen in Figure 8a and from various Sc ranging from 100% EtOH (L#8) to 50/50% v/v EtOH/ H_2O (L#13) EtOH in Figure 8b. The recrystallised lactose ($L\alpha\cdot H_2O$ Rc) had an endotherm of crystalline water vaporisation followed by an exothermic peak at $162.64 \pm 0.30\text{ }^\circ\text{C}$ corresponding to a lattice rearrangement event as a result of the loss of the lattice bound crystalline water of the α -lactose monohydrate (Garnier et al., 2002). This then lead to another two endotherms that corresponded to the melting of the $L\alpha$ at $210.34 \pm 0.21\text{ }^\circ\text{C}$ and melting of the $L\beta$ anomer at $226.10 \pm 0.22\text{ }^\circ\text{C}$ in agreement with previously published data (Gombás et al., 2002). There was good agreement between the thermogram of the $L\alpha\cdot H_2O$ Rc sample and those of the samples spray dried at various T_{in} except for the temperature of crystalline water vaporisation, which was lower in the spray dried samples, shifted to between $140.7 - 142.4\text{ }^\circ\text{C}$ and is referred to as the depressed onset temperature of $L\alpha\cdot H_2O$

crystalline water vaporisation. When spray drying $L\alpha$ -H₂O from suspension using high EtOH concentrations, the EtOH may affect the water bound in the crystal lattice. This was evident in DVS analysis presented in Figure 4e. Because of this, during the vaporisation of crystalline water thermal event, this crystalline water is then liberated at a lower temperature.

As the spray drying inlet temperature increased, the onset temperature of lattice rearrangement for the spray dried samples also increased to a maximum of 172.05 ± 1.02 °C for the L#4 sample before decreasing to a minimum of 161.89 ± 1.82 °C for the L#1 sample. The values of enthalpy of lattice rearrangement followed a similar trend to that of the onset temperature of lattice rearrangement. The enthalpy of $L\alpha$ melting did not change with a change in spray dryer inlet temperature and there was no difference to the melting of the $L\alpha$ -H₂O Rc sample ($p = 0.161$). Amongst all the spray dried samples as well as the Rc sample, a small melting endotherm was seen ca. 226 °C attributed to the melting of $L\beta$. As the spray dryer inlet temperature decreased there was a slight decrease in the onset temperature of $L\beta$ melting. This trend was also seen in the enthalpy of melting values of the $L\beta$ indicating to the presence of larger quantities of this anomer at higher spray dryer T_{in} , consistent with the previous work by Islam et al. (Islam and Langrish, 2010).

For the $L\alpha$ -H₂O samples spray dried at various inlet feed solvent compositions, there was a difference between the onset temperature of crystalline water vaporisation of the $L\alpha$ -H₂O Rc sample and the spray dried samples ($p = 0.01$), with all spray dried samples having a significantly lower temperature of this event in comparison to the $L\alpha$ -H₂O Rc sample. Similar to spray drying $L\alpha$ -H₂O from various T_{in} , EtOH has the effect of depressing the temperature of crystalline water vaporisation. However, when the concentration of H₂O in the inlet feed increased, the crystallinity of the material then applied a combinational effect on this thermal event depressing it further. $L\alpha$ -H₂O is dehydrated through channels parallel to the c-axis (Garnier et al., 2002). With a decrease in crystallinity these channels are not as tightly packed resulting in the easier loss of crystalline water and would also lead to a depression in this thermal event. Such a reduction in crystallinity between the Rc $L\alpha$ -H₂O and the

$\text{L}\alpha\text{-H}_2\text{O}$ samples spray dried at varying S_c can be seen in PXRD results given above (Figure 2b). With an increase in EtOH concentration in the liquid feed from 50/50% v/v EtOH/ H_2O (L#13) to 100% EtOH (L#8) there was also an increase in the enthalpy of the depressed crystalline water vaporisation event ($p = 0.003$) however, the only samples statistically different to the $\text{L}\alpha\text{-H}_2\text{O}$ Rc sample were those spray dried using condition L#13.

Looking at the lattice rearrangement event there was no change in the onset temperature as the concentration of EtOH increased in the inlet feed ($p = 0.205$) as was there no difference between the onset temperature of lattice rearrangement of the spray dried samples to that of the $\text{L}\alpha\text{-H}_2\text{O}$ Rc sample ($p = 0.113$). However, as the solvent composition was varied there was a difference in the enthalpy of lattice rearrangement between the samples with larger values associated with solvent compositions of higher H_2O concentrations (L#13). To explain the difference in material crystallinity as the composition of the inlet feed was varied, the soluble fraction of each component in each solvent used was determined. With an increase in H_2O concentration there was a larger % $\text{L}\alpha\text{-H}_2\text{O}$ soluble fraction in the inlet feed (Figure 9).

PXRD (Figure 2b) and DVS results (Figure 4e) show that $\text{L}\alpha\text{-H}_2\text{O}$ spray dried from higher H_2O concentrations resulted in a reduction in crystallinity, and with a reduction in crystallinity came a larger heat liberation during the lattice rearrangement event. This reduction in crystallinity is due to the greater quantity of $\text{L}\alpha\text{-H}_2\text{O}$ crystallising rapidly from solution at spray dryer solvent compositions of higher H_2O concentrations. This effect is also seen in Figure 8b in which the temperature of crystalline water vaporisation depresses as the concentration of H_2O in the spray dryer inlet feed increases up to 80/20% v/v EtOH/ H_2O (L#10) before it reaches a steady temperature value, which follows with the slope of the $\text{L}\alpha\text{-H}_2\text{O}$ % soluble fraction in Figure 9.

3.4.2. Crystallo-co-spray dried α -lactose monohydrate and paracetamol

Figure 10 shows the thermal events present for the CCSD agglomerates at various spray dryer inlet temperatures (Figure 10a) and inlet feed solvent compositions (Figure 10b).

With a decrease in T_{in} there was a decrease in the onset temperature of the crystalline water vaporisation event for the CCSD agglomerates (PL#1 – PL#7). Similar to spray drying $L\alpha\cdot H_2O$ on its own at varying T_{in} (Figure 8a), EtOH caused the crystalline water to be liberated at a lower temperature. What was different when PAR was CCSD together with the $L\alpha\cdot H_2O$ was that the depressed onset temperature of crystalline water vaporisation peak was further shifted to lower temperatures with a decrease in inlet temperature. As this thermal event was also at a lower temperature for the physically mixed sample in comparison to the Rc sample, PAR also influenced the position of the crystalline water vaporisation peak. The PL#1 agglomerate lost the lattice bound water at 134.29 ± 0.27 °C and this shifted to 123.40 ± 0.22 °C for the PL#7 agglomerate. For the CCSD agglomerates dried at varying inlet temperatures, a shoulder appeared (ca. 145 °C) after the depressed crystalline water vaporisation event not seen in any of the $L\alpha\cdot H_2O$ samples spray dried on their own. This shoulder only occurred in the CCSD agglomerates and the physically mixed sample indicating that PAR was the source of its presence. PAR on the surface of the $L\alpha\cdot H_2O$ could be inhibiting the removal of the lattice bound water thus requiring higher temperatures for its liberation.

There was a statistically significant decrease in the onset of melting and enthalpy of melting for the PAR component of the CCSD agglomerates dried at varying inlet temperatures in comparison to the PAR Rc sample, with all spray dried agglomerates having lower onset temperature and enthalpy values in comparison to the sample Rc. With the addition of PAR, a new melting endotherm also appeared for the $L\alpha\cdot H_2O$ component of the agglomerates. This depressed melting endotherm appeared between 181.77 °C and 186.58 °C. Within a mixture of two or more components, either component can act as an impurity upon the other resulting in a depression of the onset temperature of melting. As the T_{in} decreased so did the onset temperature of this event, however this trend did not apply to the enthalpy of melting with no statistically significant change being seen between the agglomerates with a change in temperature. This was also true for the original onset of melting thermal event with no change seen between the spray dried agglomerates at varying inlet temperatures or between the spray dried agglomerates and the $L\alpha\cdot H_2O$ Rc sample. All CCSD

agglomerates processed at various inlet temperatures had enthalpy of melting endotherms lower than those of the $L\alpha$ -H₂O Rc sample ($p < 0.001$) and as the spray dryer inlet temperature decreased so did the enthalpy of melting. The difference between the enthalpy of $L\beta$ melting of the spray dried agglomerates and the $L\alpha$ -H₂O Rc sample were statistically significant ($p < 0.001$) with all spray dried agglomerates having a $L\beta$ melting enthalpy less than the $L\beta$ melting endotherm of the $L\alpha$ -H₂O Rc sample.

DSC thermograms for PAR + $L\alpha$ -H₂O CCSD at various solvent compositions can be seen in Figure 10b. As the concentration of EtOH increased in the inlet feed, so did the enthalpy of the crystalline water vaporisation event attributed to the change in solvent composition as there was also a change in $L\alpha$ -H₂O samples spray dried on their own. As seen in Figure S2, this thermal event disappears as the concentration of water in the inlet feed increases past 40/60% v/v EtOH/H₂O as a result of the decrease in sample crystallinity (Chidavaenzi et al., 1997), as presented earlier in PXRD and DVS analysis. Similar to above, a shoulder appeared when PAR was CCSD with the $L\alpha$ -H₂O (ca. 145 °C) with no statistically significant difference in the enthalpy of this event seen as the solvent composition changed. Unlike the co-spray drying of PAR and $L\alpha$ -H₂O at various T_{in} , when the concentration of H₂O in the solvent feed increased the lattice rearrangement event become more pronounced evident in a larger enthalpy value. No exothermic peak was seen when 100% EtOH (PL#8) was used as the inlet feed solvent composition but appeared at a composition of 90/10% v/v EtOH/H₂O (PL#9) and increased as the concentration of H₂O increased to a maximum of 11.66 ± 0.85 J/g for the 50/50% v/v EtOH/H₂O (PL#13) CCSD agglomerate. The difference between the onset temperatures of PAR melting between the CCSD agglomerates of varying solvent compositions was not statistically different to each other however, the values were all statistically different to that of the PAR Rc sample with all CCSD agglomerates melting at a lower temperature. As the concentration of H₂O increased in the solvent feed the enthalpy of melting for the $L\alpha$ -H₂O constituent of the CCSD mixture decreased (34.69 ± 3.90 J/g to 0.08 ± 0.02 J/g), while simultaneously the enthalpy of the depressed melting point increased (11.79 ± 2.22 J/g to 40.00 ± 1.86 J/g) along with a slight increase in

the onset temperature. Melting point depression occurs when an impurity acts upon a melting crystal lattice. The phenomenon is primarily seen in polymer blends (Dangseeyun et al., 2004), however the same process can apply to pharmaceutical compounds (Charoenchaitrakool et al., 2000). The enthalpy trends of the original $\text{L}\alpha$ melting point, new depressed $\text{L}\alpha$ melting point and $\text{L}\alpha$ lattice rearrangement event as the spray dryer inlet temperature and concentration of H_2O in the spray dryer inlet feed increased can be seen in Figure 11.

In order to explain these trends, one must look at the soluble fraction of $\text{L}\alpha\text{-H}_2\text{O}$ and PAR in the solvent mixtures (Figure 9). On average across all the spray drying conditions between 100% EtOH and 50/50% v/v EtOH/ H_2O (PL#8 – PL#13), 97.13 ± 1.07 % of the PAR solubilised. In contrast, for $\text{L}\alpha\text{-H}_2\text{O}$ component, 45.89 ± 1.34 % was in solution using 50/50% v/v EtOH/ H_2O (PL#13) as a solvent composition and decreased to a minimum of 0.18 ± 0.13 % for the 100% EtOH (PL#8) solvent composition, the rest of the material was in suspension. With an increase in H_2O concentration there was a greater quantity of $\text{L}\alpha\text{-H}_2\text{O}$ in solution together with the PAR. During the spray drying process, both components in solution precipitated simultaneously as the atomised droplet dried which resulted in a larger degree of constituent mixing in the final dried agglomerate. Using a solvent composition of 100% EtOH (PL#8), in which the $\text{L}\alpha\text{-H}_2\text{O}$ was almost exclusively in suspension, PAR can either crystallise homogeneously in the bulk of the solution, or heterogeneously on the surface of these suspended particles.

Melting point depression is an indication of a decrease in crystallinity within a crystal lattice. The more “imperfect” or disordered a crystalline material becomes, the lower its melting point. An increase in disorder can be the result of the presence of an impurity acting upon the melting crystal lattice. The constituents of a crystal lattice are held together by various intermolecular forces. These forces become disrupted as the lattice melts as a result of the addition of energy. The stronger the lattice is held together the more energy is required to break these forces to allow the lattice to melt. Any impurity within a crystal lattice will disrupt these repeating intermolecular forces weakening the

strength of the lattice and thus depressing the melting temperature. This effect of increased constituent mixing (PL#13) caused PAR to act as an impurity upon the melting crystal lattice of the $\text{L}\alpha\text{-H}_2\text{O}$ with the larger the quantity of $\text{L}\alpha\text{-H}_2\text{O}$ molecules in contact with PAR molecules in the final dried powder blend, the larger the melting endotherm of the depressed $\text{L}\alpha\text{-H}_2\text{O}$ melting point and the smaller the enthalpy of the original melting point.

3.5. Particle morphology

Spray dried $\text{L}\alpha\text{-H}_2\text{O}$ formed irregularly shaped particles at all spray dryer inlet temperatures with defined crystal faces indicating a degree of crystallinity (Figure 12). $\text{L}\alpha\text{-H}_2\text{O}$ spray dried at a composition of 50/50% v/v EtOH/ H_2O (L#13) produced visually smaller particles in comparison to the other compositions of higher EtOH concentrations. The results of particle size analysis are presented in Table S2.

By crystallo-co-spray drying $\text{L}\alpha\text{-H}_2\text{O}$ with PAR a material of heterogenous morphology was produced. The $\text{L}\alpha\text{-H}_2\text{O}$ with varying quantities in suspension was coated with the PAR precipitating from solution. The PAR formed semi-spherical crystallites that agglomerated together onto the surface of the previously suspended $\text{L}\alpha\text{-H}_2\text{O}$ (Figure 13c) (McDonagh and Tajber, 2019). As the concentration of EtOH in the inlet feed increased this became more apparent with a greater degree of surface coating seen (Figure 13f). This surface coating inhibited crystalline water removal which was evident in DVS data (Figure 5e).

4. Conclusions

Crystallo-co-spray dried agglomerates of paracetamol and α -lactose monohydrate were obtained through the selection of spray dryer inlet temperature and inlet feed solvent composition. The robustness of the process was demonstrated with no change to the physical structure of either component throughout the crystallo-co-spray drying process. The percentage soluble fraction of both components in the inlet feed was determined to have the largest influence on the physical morphology

528 of the processed agglomerates with an increase in soluble fraction resulting in an increase in
529 constituent mixing. Through the careful selection of solvent properties, and spray drying parameters,
530 an agglomerated blend of crystallo-co-spray dried components can be obtained leading to possible
531 opportunities for process intensification with the reduction of process steps such as blending,
532 agglomeration, drying and milling into one single stage, with increased constituent mixing, decreased
533 segregation and improved compaction behaviour capable of direct compression.

534 Declaration of Competing Interest

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

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Figure captions

Figure 1. Chemical structures of paracetamol (left) and α -lactose monohydrate (right).

Figure 2. Powder X-ray diffraction diffractograms of spray dried $\text{L}\alpha\text{-H}_2\text{O}$ at a) L#1, L#2, L#3, L#4, L#5, L#6, L#7 and b) L#8, L#9, L#10, L#11, L#12 and L#13 as well as $\text{L}\alpha\text{-H}_2\text{O}$ recrystallised by cooling crystallisation from H_2O ($\text{L}\alpha\text{-H}_2\text{O}$ Rc). Lactose diffractograms of α -lactose monohydrate ($\text{L}\alpha\text{-H}_2\text{O}$), stable anhydrous α -lactose ($\text{L}\alpha_s$) and β -lactose ($\text{L}\beta$) were calculated from crystal structures obtained from CCDC: LACTOS03, EYOCUQ01 and BLACTO02, respectively.

Figure 3. Powder X-ray diffraction diffractograms of CCSD PAR + $\text{L}\alpha\text{-H}_2\text{O}$ at a) PL#1, PL#2, PL#3, PL#4, PL#5, PL#6 and PL#7 and b) PL#8, PL#9, PL#10, PL#11, PL#12 and PL#13 as well as $\text{L}\alpha\text{-H}_2\text{O}$ recrystallised by cooling crystallisation from H_2O ($\text{L}\alpha\text{-H}_2\text{O}$ Rc) and PAR recrystallised from the slow evaporation of EtOH (PAR Rc). Lactose diffractogram of α -lactose monohydrate ($\text{L}\alpha\text{-H}_2\text{O}$) was calculated from crystal structures obtained from CCDC: LACTOS03 and PAR diffractogram of form I was calculated from crystal structures obtained from CCDC: HXACAN01.

Figure 4. Dynamic vapour sorption kinetic plots of $\text{L}\alpha\text{-H}_2\text{O}$ samples spray dried at conditions L#7 using a) ethanol and b) water as the probe vapour; L#8 using c) ethanol and d) water as the probe vapour and L#13 using e) ethanol and f) water as the probe vapour.

Figure 5. Dynamic vapour sorption kinetic plots of PAR + $\text{L}\alpha\text{-H}_2\text{O}$ CCSD agglomerates spray dried at conditions: PL#7 using a) ethanol and b) water as the probe vapour; PL#8 using c) ethanol and d) water as the probe vapour and PL#13 using e) ethanol and f) water as the probe vapour.

Figure 6. Attenuated total reflectance Fourier transform infra-red spectroscopy of $\text{L}\alpha\text{-H}_2\text{O}$ at a) T_{in} : L#1, L#2, L#3, L#4, L#5, L#6 and L#7 and b) L#8, L#9, L#10, L#11, L#12 and L#13 as well as $\text{L}\alpha\text{-H}_2\text{O}$ recrystallised by cooling crystallisation from H_2O . ν are stretching vibrations, δ are deformation vibrations.

Figure 7. Attenuated total reflectance Fourier transform infrared second order derivative spectra of

686 PAR + $\text{L}\alpha\text{-H}_2\text{O}$ CCSD agglomerates processed at a) PL#1, PL#2, PL#3, PL#4, PL#5, PL#6, PL#7 and b) PL#8,
687 PL#9, PL#10, PL#11, PL#12 and PL#13 spray drying conditions as well as $\text{L}\alpha\text{-H}_2\text{O}$ recrystallised from
688 cooling crystallisation ($\text{L}\alpha\text{-H}_2\text{O}$ Rc), paracetamol recrystallised by slow evaporation from EtOH (PAR Rc)
689 and their physical mixture (PAR Rc + $\text{L}\alpha\text{-H}_2\text{O}$ Rc PM). Arrows indicate parts of spectra where slight
690 changes were detected.

691 Figure 8. Differential scanning calorimetry thermograms of $\text{L}\alpha\text{-H}_2\text{O}$ at a) L#1, L#2, L#3, L#4, L#5, L#6
692 and L#7 and b) L#8, L#9, L#10, L#11, L#12 and L#13 as well as $\text{L}\alpha\text{-H}_2\text{O}$ recrystallised by cooling
693 crystallisation from H_2O ($\text{L}\alpha\text{-H}_2\text{O}$ Rc). Broken lines represent general trends in thermal events.

694 Figure 9. Percentage soluble fraction of PAR and $\text{L}\alpha\text{-H}_2\text{O}$ using various EtOH/ H_2O solvent compositions.

695 Figure 10. Differential scanning calorimetry thermograms of CCSD PAR + $\text{L}\alpha\text{-H}_2\text{O}$ at a) PL#1, PL#2, PL#3,
696 PL#4, PL#5, PL#6 and PL#7 and b) PL#8, PL#9, PL#10, PL#11, PL#12 and PL#13 as well as $\text{L}\alpha\text{-H}_2\text{O}$
697 recrystallised by the cooling crystallisation from H_2O ($\text{L}\alpha\text{-H}_2\text{O}$ Rc), PAR recrystallised from the slow
698 evaporation from EtOH (PAR Rc) and a physical mixture of $\text{L}\alpha\text{-H}_2\text{O}$ Rc and PAR Rc (PAR + $\text{L}\alpha\text{-H}_2\text{O}$ Rc
699 PM). Broken lines represent general trends in thermal events.

700 Figure 11. Comparison of enthalpy of melting and lattice rearrangement for the $\text{L}\alpha\text{-H}_2\text{O}$ constituent of
701 the CCSD mixtures at various spray dryer inlet temperatures (a) and inlet feed solvent compositions
702 (b). $H_{\text{L}\alpha\text{-H}_2\text{O m-de}}$ is the enthalpy of depressed $\text{L}\alpha\text{-H}_2\text{O}$ melting point, $H_{\text{L}\alpha\text{-H}_2\text{O m}}$ is the enthalpy of the $\text{L}\alpha\text{-H}_2\text{O}$
703 melting point and H_{re} is the enthalpy of the $\text{L}\alpha\text{-H}_2\text{O}$ lattice rearrangement event.

704 Figure 12. Scanning electron microscopy images of α -lactose monohydrate spray dried at varying inlet
705 temperatures: a) L#7, b) L#4 and c) L#1, and inlet feed solvent compositions: d) L#13, e) L#10 and f)
706 L#8.

707 Figure 13. Scanning electron microscopy images of paracetamol and α -lactose monohydrate co-spray
708 dried at varying inlet temperatures: a) L#7, b) L#4 and c) L#1, and inlet feed solvent compositions: d)
709 L#13, e) L#10 and f) L#8.