

Journal Pre-proof

The impact of the degree of intimate mixing on the compaction properties of materials produced by crystallo-co-spray drying

Alan F. McDonagh , Bronagh Duff , Lorna Brennan , Lidia Tajber

PII: S0928-0987(20)30294-3
DOI: <https://doi.org/10.1016/j.ejps.2020.105505>
Reference: PHASCI 105505



To appear in: *European Journal of Pharmaceutical Sciences*

Received date: 31 March 2020
Revised date: 28 July 2020
Accepted date: 4 August 2020

Please cite this article as: Alan F. McDonagh , Bronagh Duff , Lorna Brennan , Lidia Tajber , The impact of the degree of intimate mixing on the compaction properties of materials produced by crystallo-co-spray drying, *European Journal of Pharmaceutical Sciences* (2020), doi: <https://doi.org/10.1016/j.ejps.2020.105505>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2020 Published by Elsevier B.V.

The impact of the degree of intimate mixing on the compaction properties of materials produced by crystallo-co-spray drying

Alan F. McDonagh ^{a,b)}, Bronagh Duff ^{a)}, Lorna Brennan ^{a)}, Lidia Tajber ^{a,b)*}

^{a)} School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, Dublin 2, Ireland

^{b)} Synthesis and Solid State Pharmaceutical Centre, Ireland

* corresponding author: Dr. Lidia Tajber, School of Pharmacy and Pharmaceutical Sciences, Trinity College Dublin, College Green, Dublin 2, Ireland. Tel: +35318962787. Email: ltajber@tcd.ie

Journal Pre-proof

Abstract

Direct compression remains one of the most favourable methods available to produce tablet compacts due to its simplicity, efficiency and cost effectiveness however, the technique still remains unsuitable for the majority of formulations due to materials exhibiting poor physical properties such as inadequate compressibility and deformation mechanisms. Whereas crystallo-co-spray drying of various blends has shown to improve the tableting properties of poorly processable materials, the role of the solvent feed composition in altering the soluble fraction ratio of the excipient to the drug in a crystallo-co-spray dried agglomerate is not well understood. The aim of this work was to investigate the role of the soluble fraction of a drug (paracetamol) and an excipient (α -lactose monohydrate) on the tableting properties of their crystallo-co-spray dried agglomerates produced via co-spray drying using various inlet feed solvent compositions in order to vary the soluble fraction of the excipient in the feed. It was found that an increase in excipient soluble fraction in the inlet feed resulted in a greater degree of intimate mixing in the final spray dried powder blend, which in turn led to an improvement in tableting properties of the poorly processable drug.

Keywords: paracetamol; lactose; crystallo-co-spray drying; compressibility; compactibility; properties of tablets.

1. Introduction

Direct compression is regarded as one of the most promising approaches to tablet manufacture due to its lack of laborious steps such as those involved in wet and dry granulation [1]. It is a process in which tablets are compressed directly from powder blends without any prior pre-treatment meaning that it is simple, quick and cost-effective [2, 3]. It is the most preferred method for tablet manufacture, however only a small number of pharmaceutical blends can utilise this method due to unfavourable characteristics such as poor compaction behaviour [4]. In recent years the area of crystallo-co-agglomeration has gained increased interest as a method of improving the tableting properties of materials [5, 6]. Through the use of a “good solvent” into which the drug is soluble, and a “bad solvent” to act as an antisolvent to induce nucleation and growth, a spherical agglomerate of the drug and diluents such as talc, sodium starch glycolate, and starch will be produced using a bridging liquid [6, 7]. The concept of crystallo-co-agglomeration has successfully been translated to spray drying to produce crystalline agglomerates of a drug and an excipient with the exception that instead of a bridging liquid being required for agglomerate formation, the diffusion of the components of an atomised droplet towards the centre of the droplet was instead utilised [8].

Continuous processing has become more and more popular in the pharmaceutical industry in recent years due to the promise of lower running costs, such as reduced capital investment, reduction in labour cost, less required floor space and minimal material wastage as well as faster product output [9, 10]. It is advantageous over traditional batch processes due to the reduction in time-to-market as a result of scale up benefits and better quality [9, 11, 12]. Spray drying is one such process. It is a fast, versatile technique with a one step process capable of producing a range of particles based on the nature of the material to be dried and spray dryer parameters chosen [13]. The technique is scalable with the ability to modify the physical form of excipients and drugs, capable of improving the material's physicochemical properties such as compressibility and compactibility [14]. However, as the flowability of a powder material is subject to the material's density, size and shape [15], it is common for spray dried materials to exhibit poor flowability. As previously demonstrated, the morphology and size of spray dried paracetamol (PAR) can be controlled through the careful selection of spray dryer operating parameters based on the atomised droplet's characteristics [16], and in another study, the degree of component mixing in a crystallo-co spray dried agglomerated powder blend was tailored through the selection of the excipients soluble fraction in the inlet feed [8].

The compression of commercial PAR and molecules of similar tableting characteristics is a significant issue that the pharmaceutical industry faces. PAR crystals can exist in three polymorphic forms; form I (monoclinic), form II (orthorhombic) and form III (triclinic). Form I is the commercial form of PAR and is the most thermodynamically stable at room temperature but has poor tableting properties and is prone to capping due to its rigid crystal lattice structure and high elastic deformation tendency as a result of the 'zig zag' layered arrangement of the PAR molecules held together by strong hydrogen bonds [17, 18]. In order to improve this, poorly processable drugs are processed with a range of excipients to mask the material's unfavourable characteristics [19, 20]. The choice of excipients is therefore critical in the formulation of directly compressed tablets, most notably the filler-binder. The roles of the filler-binder include improving compactibility, and to bulk up the formulation to produce a conveniently sized tablet [21]. α -lactose monohydrate (α -L α -H $_2$ O) is widely used in pharmaceutical formulations due to its high stability, non-hygroscopic nature and low cost [2]. It is the crystalline α -L α -H $_2$ O that is usually used in direct compression processes due to its favourable flowability [22]. α -L α -H $_2$ O deforms by a combination of particle fracture and plastic deformation [23]. Gonsel and Lachman found that spray dried α -L α -H $_2$ O produces harder, less friable tablets when compacted [24], this improvement in tableting makes spray dried α -L α -H $_2$ O an ideal candidate for direct compression.

The area of co-spray drying to improve the physical properties of tablets of various excipient mixtures is well established [2, 25]. For example StarLac, a co-processed excipient by Meggle Excipients & Technology consisting of α -L α -H $_2$ O and maize starch which is produced by co-spray drying shows improved compressibility and disintegration times [26]. This is also true for drug-excipient blends. Gonnissen et al. studied the co-spray drying of PAR with a range of excipients and investigated the blend's flowability, yield and disintegration time [27]. In a separate study Gonnissen et al. co-spray dried PAR with a range of carbohydrates and investigated the blend's hygroscopicity, flowability, and compactibility [28]. Al-Zoubi et al. co-spray dried metformin hydrochloride with various polymers leading to improvements in compactibility and tableting [29].

We have shown recently that in crystallo-co spray drying the inlet feed composition had the most pronounced impact on the morphology of the agglomerates [8]. However, this effect of excipient to drug soluble fraction in the feed and the resulting variability in the degree of intimate mixing on the physical properties of their respective tablets has not been studied. The aim of this study was therefore to investigate the compaction properties of PAR/ α -L α -H $_2$ O agglomerates produced through the new process of crystallo-co-spray drying with particular focus on the role of the soluble fraction of the excipient in the spray dryer inlet feed, to produce a material with improved physicochemical characteristics to allow for direct compression to be utilised.

2. Materials and methods

2.1 Materials

Paracetamol (PAR, batch number 078K0032), α -lactose monohydrate ($L\alpha\cdot H_2O$, lot number SLBX2254), magnesium stearate (powder), sodium hydroxide and monobasic potassium phosphate were obtained from Sigma-Aldrich (Ireland). Ethanol (EtOH, technical grade) was purchased from T.E Laboratories (Ireland), and deionised water was produced using a Millipore Elix 3 system (Millipore, Saint-Quentin, France).

2.2 Methods

2.2.1 Preparation of powders

2.2.1.1 Crystallo-co spray drying of PAR + $L\alpha\cdot H_2O$

Crystallo-co spray dried (CC-SD) samples were prepared as described previously [8]. A series of 10% w/v PAR + $L\alpha\cdot H_2O$ suspensions in equal weight ratios were made up at different solvent compositions (S_c): 100% EtOH (#1), 90/10% v/v EtOH/ H_2O (#2), 80/20% v/v EtOH/ H_2O (#3), 70/30% v/v EtOH/ H_2O (#4), 60/30% v/v EtOH/ H_2O (#5) and 50/50% v/v EtOH/ H_2O (#6) and SD using a Büchi B-290 mini spray dryer (Switzerland). The suspensions were stirred using a magnetic stirrer 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) [8, 16]. The drying gas used was air and the dispersant spraying 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. The spray dryer inlet temperature was kept constant at 120 °C and all samples were SD in triplicate.

Table 1 Summary of spray dryer experimental parameters. T_{out} – outlet temperature, $C_{s1,i}$ – concentration of EtOH used, $C_{s2,i}$ – concentration of H_2O used. N/A – not applicable.

Sample number	T_{out} (°C)	$C_{s1,i}$ (% v/v)	$C_{s2,i}$ (% v/v)	Excipient soluble fraction in mixture (%) [8]
#1	86 ± 1	100	0	0.13 ± 0.18
#2	78 ± 1	90	10	0.81 ± 1.15
#3	75 ± 1	80	20	1.63 ± 2.31
#4	73 ± 1	70	30	6.54 ± 1.46

#5	72 ± 1	60	40	16.97 ± 1.91
#6	70 ± 1	50	50	45.89 ± 1.34
PAR SD	77 ± 1	100	0	N/A
L α -H ₂ O SD	85 ± 1	100	0	N/A

2.2.1.2 Spray drying of PAR and L α -H₂O separately

PAR and L α -H₂O were SD separately (n = 3) to investigate the tableting behaviour of the two components individually. PAR solutions and L α -H₂O suspensions were SD using the same conditions as described in Table 1 and Section 2.2.1.1 with the exemption of the concentration with both materials being processed at 5% w/v.

2.2.1.3 Preparation of physical mixtures

For comparison purposes, 1:1 w/w physical mixtures of unprocessed PAR and L α -H₂O (PM non-SD) as well as PAR and L α -H₂O, which were spray dried separately using conditions as outlined in Table 1 and Section 2.2.1.2, (PM SD), were made up. The mixtures were obtained by physically mixing both components together for 10 minutes using a spatula.

2.2.2 Characterisation of powders

2.2.2.1 Quantification of PAR and L α -H₂O in spray dried deposits collected from glassware wall

PAR and L α -H₂O quantification in the material deposited on the inner walls of the spray dryer drying chamber, drying chamber-cyclone connector and cyclone was performed to test the powder's homogeneity. Random samples were taken (n = 3) of the deposited material from each region, accurately weighed using a microbalance (Mettler Toledo MT5, Switzerland), and then placed in 50 mL centrifuge conical tubes. 45 mL of EtOH was added to each tube, the vials were sealed well, and then 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. The quantification of both components was then performed as previously described [8].

2.2.2.2 Particle size analysis

Measurements of particle size and particle size distributions were obtained using a laser diffraction particle sizer (Mastersizer 3000, Malvern Instruments, U.K.) (n = 3). Particles were dispersed using a Malvern Aero S accessory equipped with a micro volume sample tray using 3 bar pressure. An obscuration of between 0.5–6% was obtained using a vibration feed rate of 75%. A

pressure titration was conducted before measurements to ensure that the pressure applied did not induce particle breakage during testing. This was performed by measuring the particle size at various air pressures to determine at what pressure particle breakage and attrition occurred. Mastersizer 3000 software (v 3.63) was used for analysis and to generate the particle size distribution data of the dry powder samples.

2.2.2.3 True and tap density

The true density of the powders ($n = 3$) was determined using an AccuPyc 1330 pycnometer (Micromeritics, Norcross, GA, USA) using helium (99.995% purity). A 1 cm^3 cell was used, the equilibration rate was 5×10^{-3} psig/min and the system was purged 10 times. Tapped density ($n = 3$) was measured by adding a known quantity of material to a 5 mL graduated glass cylinder and tapping the cylinder off the table top the required number of times for the compacted powder to reach a constant volume value [30]. Once the volume reading was constant over 100 tap periods, the weight was measured again and the density was calculated.

2.2.3 Tablet preparation

Tablets of 200 ± 2 mg weight were produced using a laboratory scale single punch NP-RD10 Manually Operated Tablet Press (Natoli Engineering Co Inc. USA). The die, lower punch and upper punch were lightly lubricated with magnesium stearate using a brush prior to compression. A minimal amount of lubrication was used as to not influence the tablet weight and/or mechanical strength. The powder was compressed at forces of 1250, 2500, 5000, 7500, 10000, 12500 and 15000 N using 8 mm flat faced punches corresponding to compression pressures of 25, 50, 100, 149, 199, 249 and 299 MPa, respectively. The dwell time of each tablet under compression was approximately 1 minute [31]. The tablets were accurately weighed using a microbalance (Mettler Toledo MT5, Switzerland) and inspected after the compression process for defects such as lamination, chipping, capping and sticking.

2.2.3.1 Heckel plots

The following model is proposed by Heckel [32].

$$\ln\left(\frac{1}{1-D}\right) = KP + A \quad \text{Eqn.6}$$

where D is the relative density of the compact, P is the applied pressure, A is a constant suggested to represent particle rearrangement and the reciprocal of K is used to calculate apparent mean yield pressure (P_y). Heckel plots were produced for each compact investigated by plotting the natural log of $1/1-D$ versus the compaction pressure (MPa) used. The slope of the plot was taken from a point qualitatively chosen to be the centre of the most linear region of the curve and a linear

regression fitting approach as described by Hooper et al. applied [33]. The linear region was extended in approximately 10 MPa steps. Once the part of the curve which contained the highest regression coefficient (specific to x coordinate) was established the step size was decreased until an accuracy of 1 MPa was reached [33].

2.2.4 Mechanical properties of tablets

Dimensional analysis, tablet breaking force and the tablet weight was measured immediately after tablet ejection to reduce variance that could arise due to the tablets hygroscopicity or elastic recovery. All tests performed are detailed below.

2.2.4.1 Dimensional measurements

Dimensional analysis of the tablets was performed using a 0 – 25 mm 1×10^{-3} mm digital micrometre (Digital Measurement Metrology, Toronto, Canada). Tablets were lightly de-dusted using a brush immediately after ejection and the compact's width and thickness were then measured carefully as to not crush or chip the tablet prior or tablet breaking force testing [31].

2.2.4.3 Tablet tensile strength and porosity

The tablet breaking force was measured with a Digital Portable Hardness Tester EH-01 94010, (Electrolab, India) from an average of 10 tablets. Tensile strength (σ) represents the resistance of the tablets to fracturing under diametric compression between two flat faces. Tensile strength values were calculated from the Breaking Force (F) values using Equation 1 assuming conditions of ideal line loading [34, 35], where d is the diameter of the tablet and h is the thickness of the tablets [36].

$$\sigma = \frac{2F}{\pi hd} \quad \text{Eqn.1}$$

Equation 1 can only be used when testing round, flat-faced tablets [37]. Solid fraction (SF), was calculated using Equation 2, where Wt is the tablet weight, v is volume of tablet and ρ_{true} is true density of the powder [17, 31, 38].

$$\text{SF} = \frac{Wt}{\rho_{\text{true}} \cdot v} \quad \text{Eqn.2}$$

The tablet porosity (ϵ) was then calculated from SF using the following equation [31,38].

$$\epsilon = 1 - \text{SF} \quad \text{Eqn.3}$$

The compaction pressure was calculated from the applied compression force and the cross-sectional area of the tablets.

2.2.5 Friability testing

Friability tests were conducted using a Friability Tester Model TA 20 (Copley Scientific, UK). 10 tablets were dusted and accurately weighed before placing in the drum apparatus. Tablets were then tested for 4 min (100 rotations) before removing the tablets, re-dusting and reweighing. This procedure was conducted for each of the compression pressures used. The criteria to pass the friability test was a weight loss of no more than 1% as per the USP [39].

2.2.6 Disintegration testing

Disintegration tests were conducted using the Erweka ZT 44 Tablet Disintegration Tester (Copley Scientific, UK). Six tablets were placed into each of the six glass tubes (one tablet per each tube) with open tops and mesh screens on the bottom. The basket racks containing the tubes with the tablets were submerged in 900 mL of deionised water at 37 ± 2 °C. These were oscillated up and down through a distance of 5 - 6 cm at 28-32 cycles per min. The time it took for all the tablets to disintegrate and for all of the particles to pass through the 10-mesh screen was recorded as the disintegration time. This procedure was conducted for each of the seven compression pressures investigated. The criteria to pass the disintegration test was a disintegration time no longer than 15 minutes as per the USP [40, 41].

2.2.7 Dissolution testing and evaluation of dissolution profiles

Dissolution tests for PAR were conducted as per the USP monograph for acetaminophen tablets using a Vanderkamp 6 Spindle Dissolution Tester VK600 (Vankel Industries, USA) configured into a paddle apparatus (apparatus 2) using sink conditions [42]. Three tablets made at each compression force were selected and each tablet was then placed into a separate dissolution vessel containing 900 mL phosphate buffer (solution of monobasic potassium phosphate adjusted to pH 5.8 with NaOH) maintained at 37 °C [42]. The rotation speed of the paddles was 50 rpm. Tablets were added after the dissolution medium had reached a steady velocity and settled to the bottom of the bath once added. An aliquot of 5 mL from each bath was withdrawn using a syringe at each time point, filtered (25 mm syringe filter with a 0.45 µm polyethersulfone membrane, Fischer, Ireland), diluted and then tested using UV-Vis spectroscopy at a wavelength of 243 nm. Samples from the vessels were withdrawn at several time intervals; 1 min, 2 min, 5 min, 10 min, 20 min, 30 min, 40 min, 50 min and 60 min, and at 10 min intervals after this up to 120 min if 100% release had not been achieved by then. This procedure was conducted for tablets made at each of the seven compression forces of the 50/50% v/v EtOH/H₂O (#6) and PM non-SD samples.

Dissolution profiles were evaluated by calculating the f_1 and f_2 fit factors for every pair of dissolution curves obtained from tablets made at a given compression pressure [43], taking that of the tablets made of the physical mixture (PAR and $\text{L}\alpha\text{-H}_2\text{O}$ 50:50 w/w, unprocessed) as the reference (R) and that of the CC-SD powder (#6) as the test sample (T). In brief, the difference factor (f_1) measures the dissimilarity between two dissolution profiles at different time points, while the similarity factor (f_2) calculated the degree of closeness between two dissolution curves. The f_1 and f_2 values were calculated using Eqn. 4 and Eqn. 5 using DDSolver, an Excel add-in for modelling and comparison of drug dissolution profiles [44]:

$$f_1 = \left\{ \frac{\sum_{t=1}^n |R_t - T_t|}{\sum_{t=1}^n R_t} \right\} \cdot 100 \quad \text{Eqn.4}$$

$$f_2 = 50 \cdot \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^n (R_t - T_t)^2 \right]^{-0.5} \cdot 100 \right\} \quad \text{Eqn.5}$$

where n is the number of timepoints, R_t and T_t are the mean percent dissolved from the reference and test products at a timepoint t , respectively. The f_1 value is equal to 0 and the f_2 factor is 100 when the R and T dissolution profiles are the same [43].

3. Results and discussion

3.1 Evaluation of powders and mechanical properties of tablets

As previously described, all CC-SD PAR and $\text{L}\alpha\text{-H}_2\text{O}$ samples were crystalline post spray drying with no polymorphic change in either the PAR or the $\text{L}\alpha\text{-H}_2\text{O}$ seen [8, 16]. Also, the PAR and $\text{L}\alpha\text{-H}_2\text{O}$ solubility in the hydroethanolic feed had a substantial influence on the morphology of the CC-SD agglomerates. A low excipient soluble fraction, when 100% ethanol was used, produced an increase in PAR surface coating and a high excipient soluble fraction, when ethanol/water 1:1 v/v mixture was used, resulted in agglomerates of highly mixed components (Figure 1) [8]. It was therefore anticipated that the variability in the degree of intimate mixing following a crystallo-co-spray drying process may affect the downstream processing, in particular tableting, of the materials obtained.

The median particle size of the CC-SD materials varied between 13.6 μm (sample #1) and 16.4 μm (sample #4) [8] and the particle size data for the other samples are presented in Table 2. Table SI.1 gives the number of tablets produced and the number tested for each material at each compression pressure. What is also given is the number of tablets produced that showed signs of lamination; these tablets were not further tested. Lamination is the splitting of a tablet into two or more distinct horizontal layers. Similar to capping, the cause of this is as a result of entrapped air during the compression process or if the material tabletted exhibits elastic recovery [45]. Most of the CC-SD materials showed a lower tendency to laminate in comparison to the physically mixed

materials with no tablet defects seen at any compression pressure for samples #3 - #6. For materials CC-SD at higher EtOH concentrations such as samples #1 and #2, defects did occur at higher compression pressures due to the effect of over compaction and increasing tendency for elastic recovery (Figure 2). The robustness of the crystallo-co-spray drying process is highlighted in the instability of the individual components and physical mixtures during the tableting process (Figure 2). The PM SD, PM non-SD, PAR SD and PAR non-SD all showed increased signs of lamination at lower compression pressures in comparison to the CC-SD samples. No tablets could be produced for both PAR materials (SD and non-SD) as well as the PM non-SD, at the highest compression pressure tested (299 MPa) due to the high lamination tendency.

Table 2 True density, particle size distribution and mean yield pressure (P_y) of the samples tested.

Sample number	True density (g/cm ³)	Tap density (g/cm ³)	Particle size distribution*			P_y (MPa)
			d(0.1) μm	d(0.5) μm	d(0.9) μm	
#1	1.38 \pm 0.02	0.654 \pm 0.017	3.24 \pm 0.44	13.60 \pm 0.73	53.39 \pm 6.34	166.6
#2	1.39 \pm 0.01	0.638 \pm 0.018	3.45 \pm 0.56	15.79 \pm 1.28	64.09 \pm 6.28	153.8
#3	1.39 \pm 0.01	0.618 \pm 0.019	3.71 \pm 0.33	16.37 \pm 1.00	68.45 \pm 6.79	151.5
#4	1.40 \pm 0.01	0.593 \pm 0.017	3.84 \pm 0.30	16.39 \pm 0.28	64.82 \pm 5.27	135.1
#5	1.39 \pm 0.01	0.564 \pm 0.024	3.79 \pm 0.55	16.01 \pm 0.84	51.70 \pm 7.56	131.6
#6	1.36 \pm 0.01	0.548 \pm 0.014	3.89 \pm 0.25	14.38 \pm 0.49	38.91 \pm 1.46	93.4
PM SD	1.46 \pm 0.01	0.598 \pm 0.009	5.42 \pm 0.25	29.50 \pm 0.61	117 \pm 5.79	294.1
PM non-SD	1.42 \pm 0.01	0.773 \pm 0.006	5.09 \pm 0.05	21.80 \pm 0.33	83.05 \pm 7.11	714.3
PAR SD	1.31 \pm 0.01	0.549 \pm 0.011	2.33 \pm 0.16	11.36 \pm 0.84	24.44 \pm 1.46	138.8
PAR non-SD	1.32 \pm 0.01	0.684 \pm 0.009	1.86 \pm 0.11	7.82 \pm 0.24	17.13 \pm 0.38	256.4
$\text{L}\alpha\text{-H}_2\text{O}$	1.50 \pm 0.01	0.726 \pm	3.88 \pm 0.17	25.21 \pm 0.21	86.81 \pm 1.42	136.9

SD		0.022				
L α -H ₂ O	1.48 \pm 0.03	0.806 \pm	4.42 \pm 0.09	25.04 \pm 0.70	88.41 \pm 2.85	212.7
non-SD		0.006				

* - data for the systems #1-#6, PM non-SD and L α -H₂O non-SD were reprinted from [8], with permission from Elsevier.

3.1.1 Compressibility

Figure 3 shows the compressibility profiles of the various tablet samples. With an increase in compression pressure, the sharpest decrease in porosity was attributed to the #6 sample. The next sharpest decrease was seen in the #5 sample with all other CC-SD samples behaving similarly with the exception to the #1 sample which reduced in porosity to the smallest extent. The largest decrease in volume was associated with the #6 sample. Under compression a powder reduces in volume until reduction is no longer possible and deformation occurs. A larger reduction in volume results in the shortening of the distance between particles and therefore an increase in interparticle bonding. With this increase in bonding area comes an increase in compact strength as seen in Figure 2.

The large reduction in material porosity for the #6 sample seen in Figure 3 was due to the material's low tap density (Table 2). At higher water concentrations more L α -H₂O was SD from solution resulting in a greater degree of intimate mixing in the final dried agglomerate [8]. With this increase in mixing came a decrease in material tap density in comparison to at higher EtOH concentrations in which L α -H₂O was predominantly SD from suspension. With the #6 agglomerate having the lowest tap density, an increase in compression pressure lead to the largest reduction in porosity (Figure 3). The largest decrease in volume on tapping of the physical mixtures and individual components of the agglomerates was attributed to the PAR SD. It was the most porous material of the physical mixtures and individual components, which could be a result of it being the only material SD from solution. In work previously described, PAR was SD from solution and characterised based on the physical characteristics of atomised droplets. It was found that spray drying from solution had the effect of forming semi-spherical particles of varying densities based on the spray drying parameters chosen [16]. This can also be seen in Table 2 with the lowest tap density value of the individual components being attributed to the PAR SD material.

All SD materials had lower tap density in comparison to their non-SD counterparts (Table 2). This resulted in larger reduction in material porosity values for the SD materials as the compression pressure increased (Figure 3). Similar to the above, with a greater reduction in material porosity and

subsequent increase in interparticle interaction, there was an increase in compact tensile strength [46]. For this reason, there was an increase in tensile strength for materials that were SD in comparison to their non-SD counterparts (Figure 2). Both $\text{L}\alpha\text{-H}_2\text{O}$ materials had the highest tablet bulk density accounting for the low porosity seen in Figure 3. This is evident in materials that undergo brittle fragmentation under compression leading to an increase in densification [47].

To help understand the densification process further, Heckel plots were derived for each compact tested (Figure 4). Figure 4a shows the Heckel plots of the CC-SD agglomerates. During the initial stages of compression, the #6 agglomerate underwent more extensive densification in comparison to the other agglomerates. This may be due to the #6 agglomerates readily undergoing more rearrangement at low compression pressures due to the low density of the particles (Table 2). Further rearrangement and densification were also facilitated by the fragmentation of the $\text{L}\alpha\text{-H}_2\text{O}$ constituent of the agglomerate in which the #6 agglomerate had the highest degree of PAR - $\text{L}\alpha\text{-H}_2\text{O}$ interaction. Towards the higher end of the compression pressures used the #6 agglomerate exhibited plastic behaviour however, its densification appeared to be hindered indicating a maximum compression had been reached. The other agglomerates exhibited a much more gradual densification process in comparison. Figure 4b gives the Heckel plots of the individual components of the CC-SD agglomerates investigated. Similar to the #6 agglomerate, the SD samples exhibited a more extensive densification process in comparison to their non-SD counterparts also in line with the trends seen in the tap density values (Table 2). The LAC SD sample underwent the largest degree of densification and the PAR non-SD sample underwent the least, in line with the material's poor compressibility evident in signs of overcompaction. The mean yield pressure values (Table 2) indicate that the #6 agglomerate, with the lowest P_y value, exhibited the most plastic behaviour in comparison to other systems.

3.1.2 Compactibility

The tabletability profiles of PAR and $\text{L}\alpha\text{-H}_2\text{O}$ CC-SD agglomerates at various inlet feed solvent compositions can be seen in Figure 2 and of the individual components of the agglomerates both SD and non-SD, together with their physical mixtures, in Figure 2. The #6 agglomerate produced tablets with the highest tensile strength at the lowest compression pressures used. As the compression pressure increased, using this sample, past a maximum tensile strength achieved at 100 MPa, the strength of the tablets decreased as a result of overcompaction. At this maximum, the #6 sample had a tensile strength 1.5 times larger than the #5 sample and 2.9 times the strength of the PM SD. The #5 sample had the highest tensile strength at a higher compression pressure reaching a maximum strength at 249 MPa with a similar trend in overcompaction seen as the compression

pressure increased past this point. The average tensile strength of the compacts decreased with an increasing concentration of EtOH in the feed with the exception of the #1 sample that showed an improved strength over the #2 and #3 samples over the compression pressures of 100 MPa, 149MPa and 199 MPa, however tablets could not consistently be produced at the maximum compression pressure used of 299 MPa for the #1 sample due to the presence of lamination.

The compactibility of a material is its ability to be transformed into tablets of required strength during densification [48, 49]. This plot is quite useful for tablet evaluation as it represents two very important parameters, the tensile strength and porosity. Both may influence the dissolution properties of the compact. The compactibility profiles for both the CC-SD agglomerates and their individual components can be seen in Figure 5.

It is favourable for a tablet to have an adequate tensile strength whilst maintaining a desired level of porosity [49]. If such a trade-off can be achieved, then a tablet can be produced with a favourable mechanical strength and dissolution profile [50]. The #6 sample had the highest tensile strength on average with respect to the porosity. With an increase in the EtOH concentration of the CC-SD feed, the compactibility of the materials decreased up to a composition of 70% v/v EtOH/H₂O (#4) after which the so-SD mixtures behaved similarly. It can be seen in Figure 5 that by spray drying the individual components of the agglomerates, an improvement can be made to the compactibility profile with all SD materials behaving more favourably in comparison to their non-SD counterparts. The PM SD sample had the best compactibility profile of the individual components and physical mixtures in terms of maximising both tensile strength and porosity. The poor tableting performance of PAR non-SD is evident in Figure 5 in which all tablets produced had a low tensile strength as well as a high solid fraction indicating how unfavourable the material's crystal packing is for compaction.

Alderborn and Frenning state that the compactibility of a material is defined as the ability of a powder to form a coherent tablet as a result of compression, with such a material having a high resistance towards fracturing without tendencies to cap or laminate [51]. As evident in Figure 2, the PM both SD and non-SD showed signs of such tablet defects at higher compression pressures. PAR SD and non-SD also showed signs of lamination and capping, which is common for the material [52], resulting in no tablets being reliably produced at the maximum compression pressure investigated (299 MPa). But these defects were also present in the CC-SD agglomerates SD using 100% EtOH (#1) and 90% v/v EtOH/H₂O (#2) in the inlet feed with no tablets able to be produced for the #1 sample at this maximum pressure (Figure 2). This is further evidence for the high compactibility of the CC-SD agglomerates processed at higher water concentrations/soluble fractions of the excipient in the spray dryer inlet feed [8].

3.1.2.1 PAR and $L\alpha\cdot H_2O$ soluble fraction in inlet feeds

PAR was taken as the model drug in this study due to its poor compaction behaviour with tablet tensile strength only ranging from 0.04 MPa to 0.31 MPa (for compaction pressures of 25 MPa to 299 MPa respectively) (Figure 2). In order to understand the improvement in tableting performance associated with the crystallo-co-spray drying of PAR and $L\alpha\cdot H_2O$ we must first look at the soluble fraction of each component in the solvent feed. As presented previously [8], by crystallo-co-spray drying PAR and $L\alpha\cdot H_2O$ from a Sc of 50/50% v/v EtOH/ H_2O (#6), 45.89 ± 1.34 % of the $L\alpha\cdot H_2O$ was in solution together with $96.95 \pm 0.22\%$ of PAR. As an atomised droplet dried, both these components in solution precipitated almost simultaneously. This produced a dried particle consisting of highly mixed components. For the #1 sample, only 0.18 ± 0.13 % of the $L\alpha\cdot H_2O$ was in solution as well as $96.72 \pm 0.93\%$ of the PAR. Due to the vast majority of $L\alpha\cdot H_2O$ now being in suspension, the only places that the precipitating PAR can form is either homogeneously in the bulk of the droplet or on the surface of the suspended $L\alpha\cdot H_2O$ particles, greatly reducing the degree of intimate mixing in the final dried powder blend. With an increase in soluble fraction of $L\alpha\cdot H_2O$ in the solvent feed also came a minor decrease in $L\alpha\cdot H_2O$ crystallinity in the final spray dried agglomerate, as evidenced by powder X-ray diffraction and dynamic vapor sorption [8]. This increase in disorder may have impacted on particle rearrangement under compression resulting in an improvement in the tableting of the material evident in Figure 2 in which $L\alpha\cdot H_2O$ that was spray dried showed an improvement over its non-SD counterpart. For these reasons, the #6 sample showed a greater improvement in tableting at low compression pressures compared to agglomerates produced by crystallo-co-spray drying from higher EtOH feed concentrations. The improvement over the PM SD shows that a stronger tablet is obtained when both components are SD simultaneously in comparison to individually and then physically mixed.

Tablet compaction increases strength through particle fracture and packing rearrangement where the bed is sheared and the particles are deformed [53]. As stated by Hoag et al, through the process of compaction, the volume between particles is reduced and rearrangement occurs into a closer packing structure. At some point, the packing characteristics of the powder and friction between the particles prevent any further reduction in volume and at this point the particles deform either elastically (reversible), plastically (irreversible) or viscoelastically [54]. Some materials fragment under compression such as $L\alpha\cdot H_2O$, which further reduces the powder volume [47]. As a result of this process, particle surfaces come into close proximity leading to the formation of interparticle bonds and therefore increasing compact strength [54]. Chadwick et al. and Telford et al. found molecular functionality between the hydroxyl groups of the $L\alpha\cdot H_2O$ molecule and the hydroxyl and amide groups of the PAR form I molecule [55, 56]. In work previously published by this research

group, second derivative Fourier transform infra-red spectroscopy analysis of CC-SD PAR and $\text{L}\alpha\text{-H}_2\text{O}$ showed subtle changes in these functional groups in both materials [8]. With an increase in soluble fraction of the excipient in the spray dryer inlet feed, there was a higher degree of intimate mixing in the final dried agglomerate [8]. During consolidation, this increase in drug-excipient mixing increased the interparticle bonding strength and therefore the tensile strength of the resulting compact (Figure 2). With a reduction in component mixing, this strength decreased, evident in materials CC-SD at higher EtOH concentrations. Also, considering similar tap density values (Table 2), the #6 sample had the largest tensile strength indicating that at the same material compaction, this sample had the strongest interparticle bonding.

At a compression pressure of 149 MPa, a third of tablets produced from the physically mixed blend of PAR + $\text{L}\alpha\text{-H}_2\text{O}$ (PM non-SD) showed signs of lamination as a result of the poor compressibility of the material further emphasising the improvement associated with spray drying. $\text{L}\alpha\text{-H}_2\text{O}$ SD showed an improvement in tabletability in comparison to its non-SD counterpart. A similar trend was seen for PAR with the PAR SD having a greater tensile strength at each compression pressure compared to PAR non-SD. At the final compression pressure used of 299 MPa, there was no data point for either the PAR SD or the PAR non-SD due to tablet capping and lamination, as evident in materials prone to elastic deformation [52, 57]. The improvement in tabletability for SD materials over non-SD materials is down to the materials density which will be discussed in the next section.

3.2. Functional properties of tablets

3.2.1 Friability and disintegration

To further emphasise the effect of component soluble fraction on the improvement in physiochemical properties associated with the crystallo-co-spray drying of PAR and $\text{L}\alpha\text{-H}_2\text{O}$, friability and disintegration studies of the tablets were also conducted (Figure 6).

The #6, #5 and #4 agglomerates all compressed into tablets that obtained the required maximum % weight loss of 1% to pass friability testing (Figure 6a). The #6 tablets produced at 100 MPa, 149 MPa and 199 MPa all passed this criterion. The effect of over compaction of the #6 sample is evident in Figure 6a with a sharp increase in % weight loss for tablets produced at the maximum compression pressure. Interestingly, the #6 sample behaved differently to the rest of the other CC-SD mixtures with respect to the disintegration tests. All tablets made of CC-SD samples disintegrated between 27 and 32 minutes however the tablets prepared at the lowest compression pressure used

of 25 MPa disintegrated as quickly as 10.6 minutes, satisfying the maximum allowable time of 15 minutes for uncoated tablets to disintegrate according to the British Pharmacopeia [41].

3.2.2 Dissolution studies

The dissolution profiles of the tablets made of CC-SD #6 sample and of the physically mixed PAR + $L\alpha$ -H₂O sample that was not spray dried (PM non-SD), at various compression pressures can be seen in Figure 7. The tablets made of the physically mixed sample released the drug quicker than the tablets made of the CC-SD sample as a result of the tablet's inferior compaction (Figure 7a). The #6 agglomerate produced much harder tablets in comparison to the PM non-SD which is evident in Figure 2.

Table 3 The f_1 and f_2 values for the dissolution profiles of tablets made of PAR and $L\alpha$ -H₂O (50:50 w/w). The dissolution curves obtained from tablets by compacting the physical mixture of unprocessed components were taken as the reference product (R), while the dissolution curves of the tablets made of the CC-SD powder were taken as the test product (T). Values in large bold italic font indicate similar profiles ($f_1 < 15$ and/or $f_2 > 50$).

Compaction pressure (MPa)	f_1	f_2
25	27.27	30.21
50	32.48	30.99
100	16.21	51.95
149	16.29	52.08
199	9.40	69.06
249	18.97	56.80
299	22.45	46.88

The f_1 and f_2 values calculated using Eqns. 4 and 5 show that the dissolution profiles of the tablets made of the CC-SD powder and of the physically mixed PAR + $L\alpha$ -H₂O were different when 25, 50 and 299 MPa compression pressure was used (Table 3). Considering both fit factors, only the tablets compacted at 199 MPa can be regarded as comparable, since the value of f_1 was below 15 and the f_2 value was above 50 [43]. However, the formulations tableted at 100, 149 and 249 MPa may also be considered as similar, based on one fit factor only, f_2 (Table 3).

What was interesting was that the tablets of the CC-SD material (#6) dissolved giving a higher PAR concentration, equivalent to around 120 mg drug loading, than expected and not consistent with the PAR to $L\alpha$ -H₂O ratio of 50/50% w/w. Analysis of wall deposition in the spray dryer for the #6 agglomerate found that around 88% w/w of material deposited on the inner wall of the drying chamber was $L\alpha$ -H₂O as was 48% of material in the drying chamber-cyclone connector and 38.5% of material deposited in the cyclone. With more $L\alpha$ -H₂O being deposited on the inner walls of the dryer than PAR, there was a greater concentration of PAR in the final dried particle blend with an average drug content of $58.5 \pm 2.6\%$ w/w in the final powder blend. This makes the results previously described even more significant in that a stronger tablet compact is produced in comparison to physical mixtures even with a higher concentration of PAR with its inherent poor tableting properties being present.

3.3 Tablet profiles summary

A summary of the CC-SD sample's tablet characterisation (tableability, compressibility and compactibility [49]) is given in Figure 8 below. The desirable characteristics of a tablet compact in which the strongest tablet possible is produced at the lowest compression pressure required while also maintaining the highest material porosity is best described in Figure 8f for the #6 sample. For this CC-SD material, a compression pressure of 100 MPa best fits the above criteria. Tableability (Figure 2), compactibility (Figure 5) and compressibility profiles (Figure 3) indicate that the #6 sample exhibits the best physical properties for direct compression in comparison to agglomerates SD using higher EtOH concentrations in the spray dryer inlet feed and compared to the individual components of the agglomerates both SD and non-SD. It was the best performing sample with a decrease in processability from here as the concentration of EtOH increased in the spray dryer inlet feed (#5 - #1).

Tableability profiles show that stronger tablets are produced with an increase in component mixing of CC-SD PAR + $L\alpha$ -H₂O agglomerates as a result of an increase in the water concentration of the spray dryer inlet feed (Figure 2 and Figure 7). Compactibility profiles showed that agglomerates CC-SD using higher soluble fraction of components in the inlet feed produced compacts with the highest tensile strength with respect to the tablet's porosity (Figure 5) and that at such soluble fractions, a material less prone to tablet defects such as lamination was produced. Compressibility profiles (Figure 3) showed that this increase in tablet tensile strength was due to the increased volume loss associated with powders of lower tap density (Table 2), and an increase in interparticulate bonding between PAR and $L\alpha$ -H₂O molecules. The process of CC-SD enhances the

masking ability of the excipient as stronger tablets are produced at lower compaction pressures even with an increase in drug concentration in the powder blend (Figure 2 and Figure 7).

4. Conclusions

The crystallo-co-spray drying of a poorly compressible drug with a compressible excipient material can improve the tableting performance of the agglomerate, through the process of crystallo-co spray drying, if the composition of the spray dryer inlet feed is properly evaluated. The increase in the degree of intimate mixing in the final spray dried agglomerate as a result of the increase in soluble fraction of the excipient in the spray dryer inlet feed as well as a slight increase in $\alpha\text{-H}_2\text{O}$ disorder, leads to improvements to the blend's tensile strength resulting in a tablet of higher mechanical strength being produced at lower compaction pressures even at higher drug ratios. Improvements to the tableting properties of the individual components was also seen after spray drying with both PAR and $\alpha\text{-H}_2\text{O}$ forming harder compacts after spray drying individually. With the increase in mechanical strength for the tableted CC-SD agglomerates, the criteria to pass friability and disintegration testing could then be met. Therefore, the crystallo-co-spray drying of a drug and an excipient to improve the degree of intimate mixing can be used as a method to improve the tableting properties of a blend to allow for direct compression to be utilised.

5. 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).

Credit Author Statement

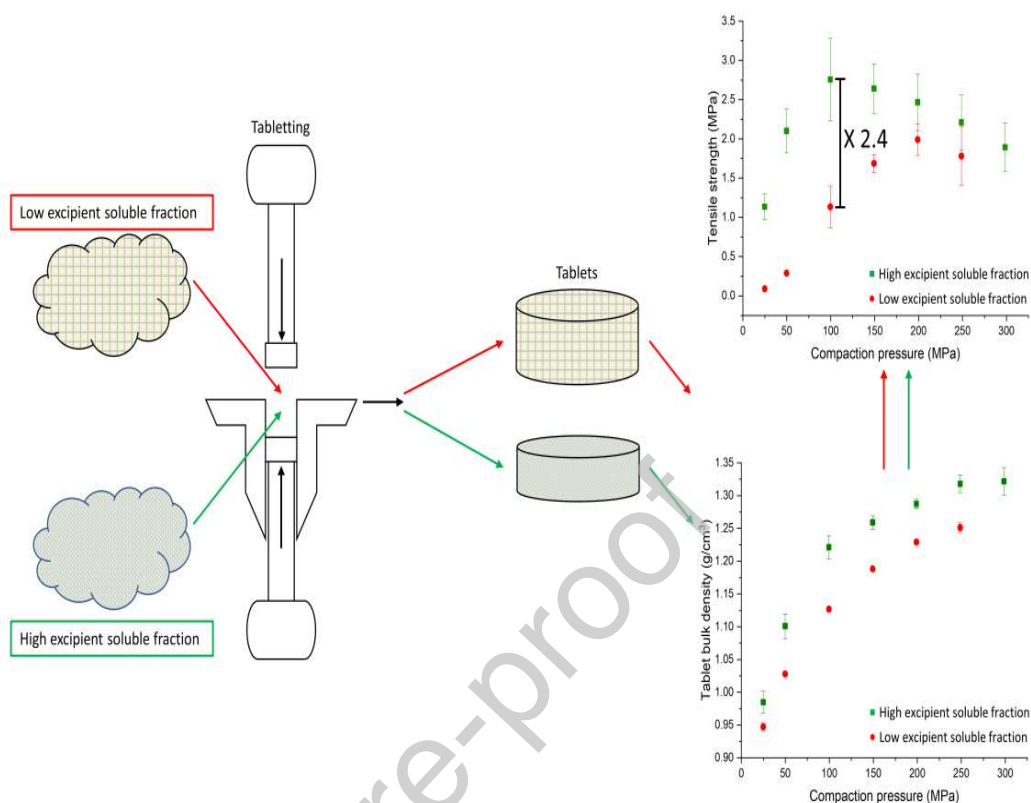
Alan F. McDonagh: Conceptualization, Methodology, Formal analysis, Investigation, Writing - Original Draft, Visualization.

Bronagh Duff: Methodology, Formal analysis, Investigation

Lorna Brennan: Formal analysis, Investigation

Lidia Tajber: Conceptualization, Writing - Review & Editing, Visualization, Supervision, Funding acquisition.

Graphical abstract



6. References

- [1] S.L. Chauhan, S.V. Nathwani, M.M. Soniwala, J.R. Chavda, Development and characterization of multifunctional directly compressible co-processed excipient by spray drying method, *AAPS PharmSciTech*, 18 (2017) 1293-1301.
- [2] M.C. Gohel, P.D. Jogani, A review of co-processed directly compressible excipients, *Journal of Pharmaceutical Sciences*, 8 (2005) 76-93.
- [3] R.F. Shangraw, A survey of current industrial practices in the formulation and manufacture of tablets and capsules, *Pharmaceutical Technology*, 32 (1993) 32-44.
- [4] R.F. Shangraw, Compressed tablets by direct compression, *Pharmaceutical dosage forms: Tablets*, 1 (1989) 195-246.
- [5] M. Maghsoodi, O. Taghizadeh, G.P. Martin, A. Nokhodchi, Particle design of naproxen-disintegrant agglomerates for direct compression by a crystallo-co-agglomeration technique, *International Journal of Pharmaceutics*, 351 (2008) 45-54.
- [6] A.R. Paradkar, A.P. Pawar, Crystallo-co-agglomeration: A novel particle engineering technique, *Asian Journal of Pharmaceutics*, 4 (2014) 4-10.

- [7] A.P. Pawar, A.R. Paradkar, S.S. Kadam, K.R. Mahadik, Crystallo-co-agglomeration: A novel technique to obtain ibuprofen-paracetamol agglomerates, *AAPS PharmSciTech*, 5 (2004) 57-64.
- [8] A.F. McDonagh, L. Tajber, 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, *International Journal of Pharmaceutics*, 577 (2020) 119051.
- [9] C. Vervaet, J.P. Remon, Continuous granulation in the pharmaceutical industry, *Chemical Engineering Science*, 60 (2005) 3949-3957.
- [10] N.-O. Lindberg, Some experience of continuous granulation, *Acta Pharmaceutica Suecica*, 25 (1988) 239-246.
- [11] H. Leuenberger, New trends in the production of pharmaceutical granules: batch versus continuous processing, *European Journal of Pharmaceutics and Biopharmaceutics*, 52 (2001) 289-296.
- [12] H. Leuenberger, New trends in the production of pharmaceutical granules: the classical batch concept and the problem of scale-up, *European Journal of Pharmaceutics and Biopharmaceutics*, 52 (2001) 279-288.
- [13] J. Broadhead, S.K. Edmond Rouan, C.T. Rhodes, The spray drying of pharmaceuticals, *Drug Development and Industrial Pharmacy*, 18 (1992) 1169-1206.
- [14] S. Mangal, F. Meiser, D. Morton, I. Larson, Particle engineering of excipients for direct compression: Understanding the role of material properties, *Current Pharmaceutical Design*, 21 (2015) 5877-5889.
- [15] J.S. Kaerger, S. Edge, R. Price, Influence of particle size and shape on flowability and compactibility of binary mixtures of paracetamol and microcrystalline cellulose, *European Journal of Pharmaceutical Sciences*, 22 (2004) 173-179.
- [16] A.F. McDonagh, L. Tajber, The control of paracetamol particle size and surface morphology through crystallisation in a spray dryer, *Advanced Powder Technology*, 31 (2019) 287-299.
- [17] B. Govedarica, R. Injac, S. Srcic, Formulation and evaluation of immediate release tablets with different types of paracetamol powders prepared by direct compression, *African Journal of Pharmacy and Pharmacology*, 5 (2009) 31-41.
- [18] H. Ahmed, M.R. Shimpi, S.P. Velaga, Relationship between mechanical properties and crystal structure in cocrystals and salt of paracetamol, *Drug Development and Industrial Pharmacy*, 43 (2017) 89-97.
- [19] Z. Huang, J.V. Scicolone, X. Han, R.N. Davé, Improved blend and tablet properties of fine pharmaceutical powders via dry particle coating, *International Journal of Pharmaceutics*, 478 (2015) 447-455.

- [20] K. Pingali, R. Mendez, D. Lewis, B. Michniak-Kohn, A. Cuitino, F. Muzzio, Mixing order of glidant and lubricant–influence on powder and tablet properties, *International Journal of Pharmaceutics*, 409 (2011) 269-277.
- [21] M.E. Aulton, K.M. Taylor, *Aulton's Pharmaceutics E-Book: The Design and Manufacture of Medicines*, Elsevier Health Sciences, 2017.
- [22] S.C. Gad, *Preclinical development handbook: ADME and biopharmaceutical properties*, John Wiley & Sons, 2008.
- [23] R.J. Roberts, R.C. Rowe, The effect of punch velocity on the compaction of a variety of materials, *Journal of Pharmacy and Pharmacology*, 37 (1985) 377-384.
- [24] W.C. Gungel, L. Lachman, Comparative evaluation of tablet formulations prepared from conventionally-processed and spray-dried lactose, *Journal of Pharmaceutical Sciences*, 52 (1963) 178-182.
- [25] J. Rojas, I. Buckner, V. Kumar, Co-processed excipients with enhanced direct compression functionality for improved tableting performance, *Drug Development and Industrial Pharmacy*, 38 (2012) 1159-1170.
- [26] G.W.B.E.T. Meggle, Technical brochure StarLac, in, 2014.
- [27] Y. Gonnissen, S.I.V. Goncalves, B.G. De Geest, J.P. Remon, C. Vervaet, Process design applied to optimise a directly compressible powder produced via a continuous manufacturing process, *European Journal of Pharmaceutics and Biopharmaceutics*, 68 (2008) 760-770.
- [28] Y. Gonnissen, J.P. Remon, C. Vervaet, Development of directly compressible powders via co-spray drying, *European Journal of Pharmaceutics and Biopharmaceutics*, 67 (2007) 220-226.
- [29] N. Al-Zoubi, F. Odeh, L. Nikoliakakis, Co-spray drying of metformin hydrochloride with polymers to improve compaction behavior, *Powder Technology*, 307 (2017) 163-174.
- [30] J.-J. Yang, C.-Y. Liu, L.-H. Quan, Y.-H. Liao, Preparation and in vitro aerosol performance of spray-dried Shuang-Huang-Lian corrugated particles in carrier-based dry powder inhalers, *AAPS PharmSciTech*, 13 (2012) 816-825.
- [31] M. Paczkowska, A.F. McDonagh, K. Bialek, L. Tajber, J. Cielecka-Piontek, Mechanochemical activation with cyclodextrins followed by compaction as an effective approach to improving dissolution of rutin, *International Journal of Pharmaceutics*, 581 (2020) 119294.
- [32] R. Heckel, Density-pressure relationships in powder compaction, *Transactions of the Metallurgical Society of AIME*, 221 (1961) 671-675.
- [33] D. Hooper, F. Clarke, J. Mitchell, M. Snowden, A modern approach to the Heckel Equation: The effect of compaction pressure on the yield pressure of ibuprofen and its sodium salt, *Journal of Nanomedicine and Nanotechnology*, 7 (2016) 2.

- [34] J. Fell, J. Newton, Determination of tablet strength by the diametral-compression test, *Journal of Pharmaceutical Sciences*, 59 (1970) 688-691.
- [35] O.F. Akande, M.H. Rubinstein, P.H. Rowe, J.L. Ford, Effect of compression speeds on the compaction properties of a 1: 1 paracetamol–microcrystalline cellulose mixture prepared by single compression and by combinations of pre-compression and main-compression, *International Journal of Pharmaceutics*, 157 (1997) 127-136.
- [36] J. Fell, J. Newton, Determination of tablet strength by the diametral-compression test, *Journal of Pharmaceutical Sciences*, 59 (1970) 688-691.
- [37] J.M. Newton, I. Haririan, F. Podczek, The influence of punch curvature on the mechanical properties of compacted powders, *Powder Technology*, 107 (2000) 79-83.
- [38] R.M. Iyer, S. Hegde, J. Dinunzio, D. Singhal, W. Malick, The impact of roller compaction and tablet compression on physicochemical properties of pharmaceutical excipients, *Pharmaceutical Development and Technology*, 19 (2014) 583-592.
- [39] U.S.Pharmacopeia, Tablet friability, in: W.E. Brown (Ed.) U.S.Pharmacopeia, United States Pharmacopeial Convention, Rockville, MD, 2019.
- [40] U.S.Pharmacopeia, Disintegration, in: W.E. Brown (Ed.) U.S.Pharmacopeia, United States Pharmacopeial Convention, Rockville, MD, 2019.
- [41] British-Pharmacopoeia, Disintegration testing, in: T.S. Office (Ed.) British-Pharmacopoeia, Stationery Office, 2019.
- [42] U.S.Pharmacopeia, Acetaminophen Tablets, in: A.M. Clydewyn (Ed.) U.S.Pharmacopeia, United States Pharmacopeial Convention, Rockville, MD, 2019.
- [43] J. Moore, H. Flanner, Mathematical comparison of dissolution profiles, *Pharmaceutical Technology*, 20 (1996) 64-74.
- [44] Y. Zhang, M. Huo, J. Zhou, A. Zou, W. Li, C. Yao, S. Xie, DDSolver: an add-in program for modeling and comparison of drug dissolution profiles, *The AAPS Journal*, 12 (2010) 263-271.
- [45] K.A. Khan, C.T. Rhodes, Production of tablets by direct compression, *Canadian Journal of Pharmaceutical Sciences*, 8 (1973) 1-5.
- [46] A. McKenna, D.F. McCafferty, Effect of particle size on the compaction mechanism and tensile strength of tablets, *Journal of Pharmacy and Pharmacology*, 34 (1982) 347-351.
- [47] H. Vromans, A.H. De Boer, G.K. Bolhuis, C.F. Lerk, K.D. Kussendrager, H. Bosch, Studies on tableting properties of lactose, *International Journal of Clinical Pharmacy*, 7 (1985) 186-193.
- [48] C.C. Sun, D.J.W. Grant, Influence of crystal structure on the tableting properties of sulfamerazine polymorphs, *Pharmaceutical Research*, 18 (2001) 274-280.

- [49] C.K. Tye, C.C. Sun, G.E. Amidon. Evaluation of the effects of tableting speed on the relationships between compaction pressure, tablet tensile strength, and tablet solid fraction. *Journal of Pharmaceutical Sciences*, 94 (2005) 465-472.
- [50] S. Bandari, R.K. Mittapalli, R. Gannu, Orodispersible tablets: An overview, *Asian Journal of Pharmaceutics*, 2 (2008) 2-11.
- [51] L.L. Augsburger, S.W. Hoag, Mechanical strength of tablets, in: G. Alderborn, G. Frenning (Eds.) *Pharmaceutical dosage forms: Tablets*, Informa healthcare USA, New York, 2008, pp. 207-236.
- [52] J.S.M. Garr, M.H. Rubinstein, An investigation into the capping of paracetamol at increasing speeds of compression, *International Journal of Pharmaceutics*, 72 (1991) 117-122.
- [53] E.N. Hiestand, Mechanical properties of compacts and particles that control tableting success, *Journal of Pharmaceutical Sciences*, 86 (1997) 985-990.
- [54] S.W. Hoag, V.S. Dave, V. Moolchandani, Compression and compaction, in: *Pharmaceutical dosage forms-tablets*, CRC Press, 2008, pp. 571-646.
- [55] K. Chadwick, J. Chen, A.S. Myerson, B.L. Trout, Toward the rational design of crystalline surfaces for heteroepitaxy: role of molecular functionality, *Crystal Growth & Design*, 12 (2012) 1159-1166.
- [56] R. Telford, C.C. Seaton, A. Clout, A. Buanz, S. Gaisford, G.R. Williams, T.J. Prior, C.H. Okoye, T. Munshi, I.J. Scowen, Stabilisation of metastable polymorphs: the case of paracetamol form III, *Chemical Communications*, 52 (2016) 12028-12031.
- [57] P. Di Martino, A.M. Guyot-Hermann, P. Conflant, M. Drache, J.C. Guyot, A new pure paracetamol for direct compression: the orthorhombic form, *International Journal of Pharmaceutics*, 128 (1996) 1-8.

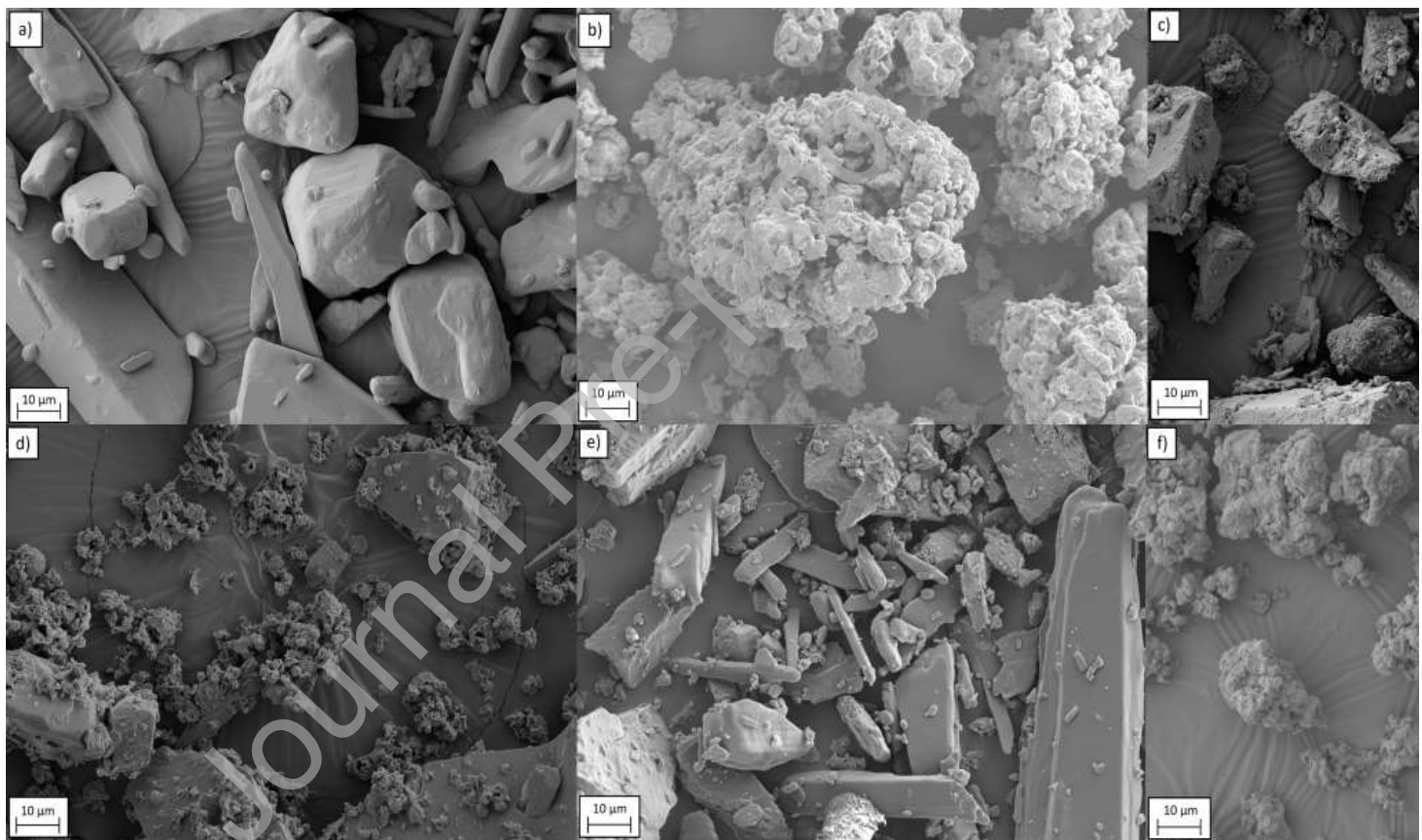


Figure 1. Scanning electron microscopy images of PAR as received from the supplier (PAR non-SD, a), PAR spray dried using 100% EtOH (PAR SD, b), $\text{L}\alpha\text{-H}_2\text{O}$ as received from the supplier (LAC non-SD, c), $\text{L}\alpha\text{-H}_2\text{O}$ spray dried using 100% EtOH ($\text{L}\alpha\text{-H}_2\text{O}$ SD, d), PAR + $\text{L}\alpha\text{-H}_2\text{O}$ physically mixed 1:1 ratio (PM non-SD, e) and PAR + $\text{L}\alpha\text{-H}_2\text{O}$ spray dried separately and then physically mixed (PM SD, f).

Journal Pre-proof

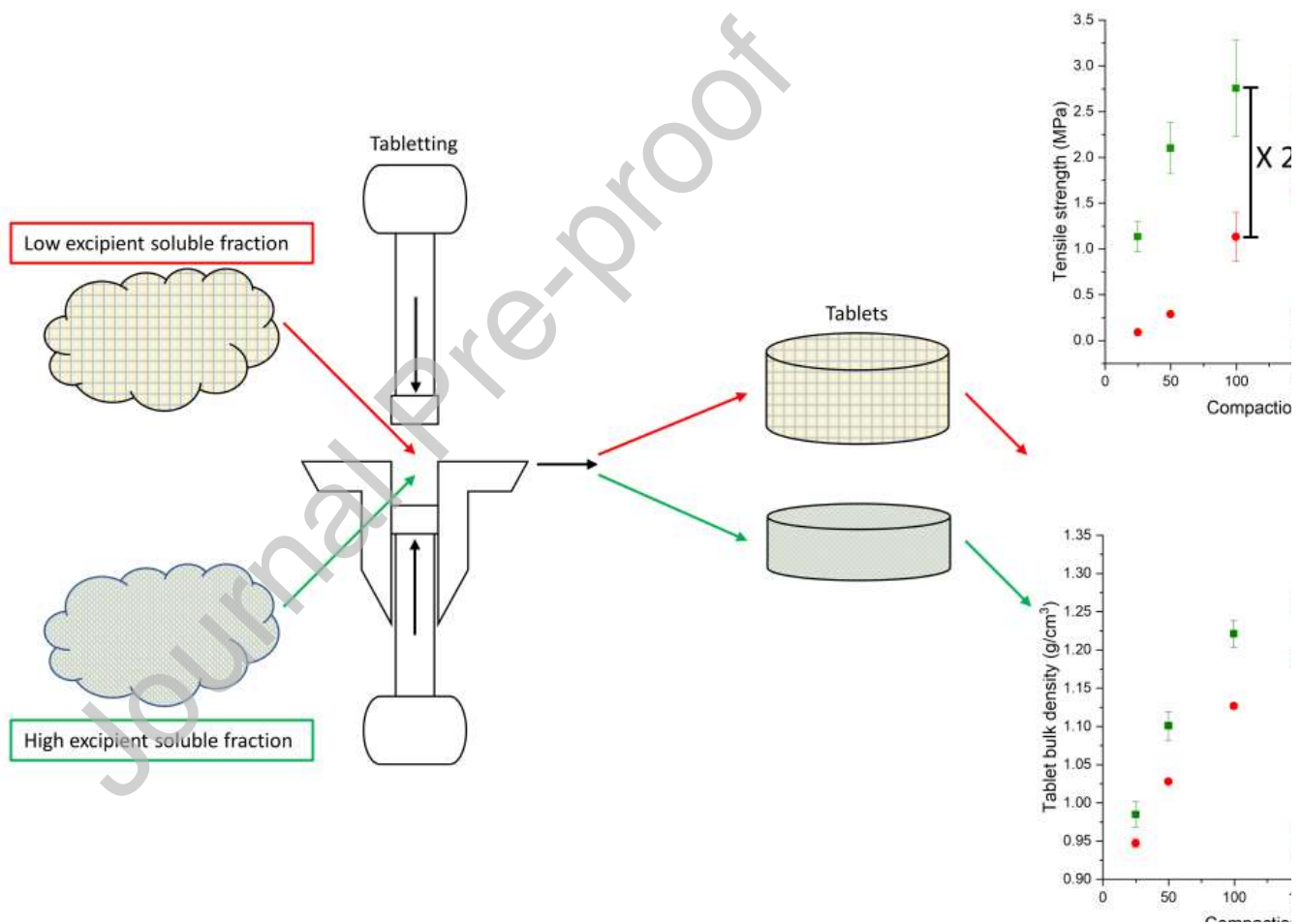


Figure 2. Tableability profiles of PAR and L α -H₂O mixtures CC-SD at various inlet feed solvent compositions and their individual components both SD and non-SD as well as their SD and non-SD physical mixtures. A solid datapoint indicates that all tablets produced were free from any defects, a hollow datapoint indicates that some tablets showed defects (Table SI.1) and if no datapoint is present then no tablets could be reliably produced at that compression pressure. Lines are to guide between datapoints only. Error bars represent standard deviation.

Journal Pre-proof

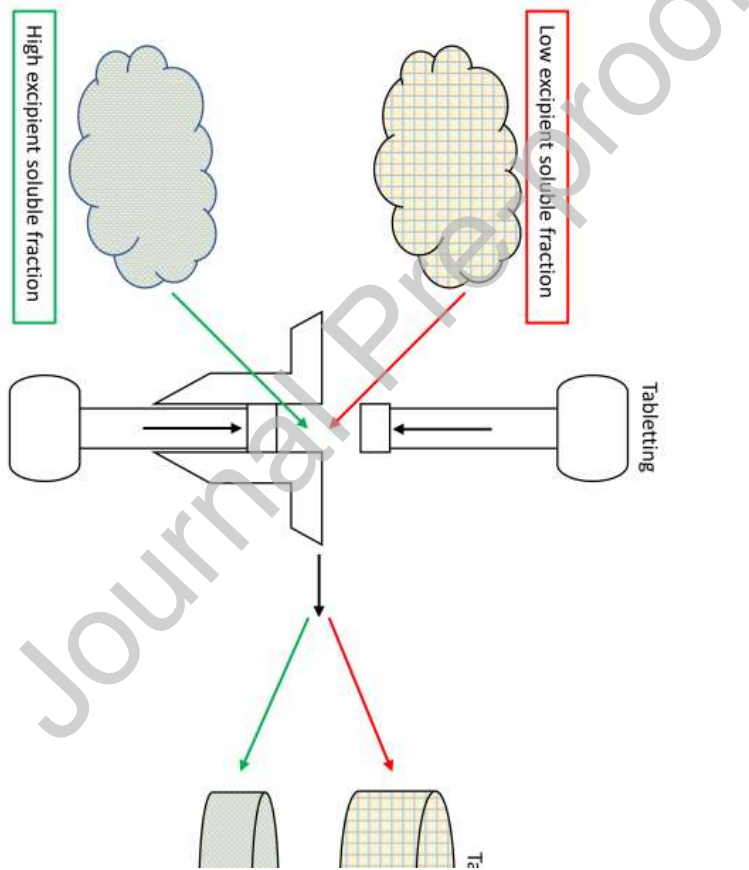


Figure 3. Compressibility profiles of PAR and L α -H₂O mixtures CC-SD at various inlet feed solvent compositions and their individual components both SD and non-SD as well as their SD and non-SD physical mixtures. A solid datapoint indicates that all tablets produced were free from any defects, a hollow datapoint indicates that some tablets showed defects (Table SI.1) and if no datapoint is present then no tablets could be reliably produced at that compression pressure. Lines are to guide between datapoints only. Error bars represent standard deviation.

Journal Pre-proof

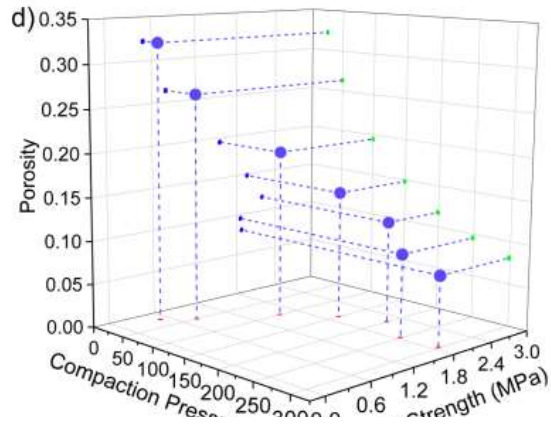
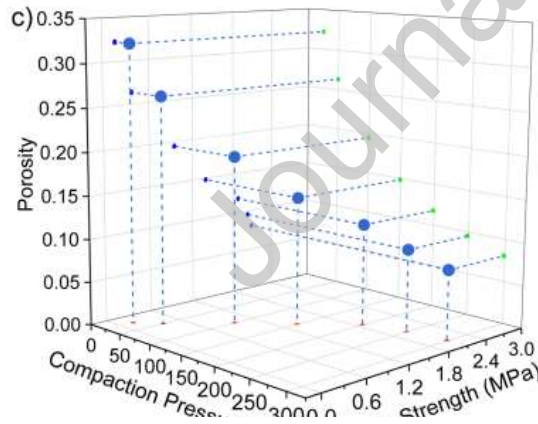
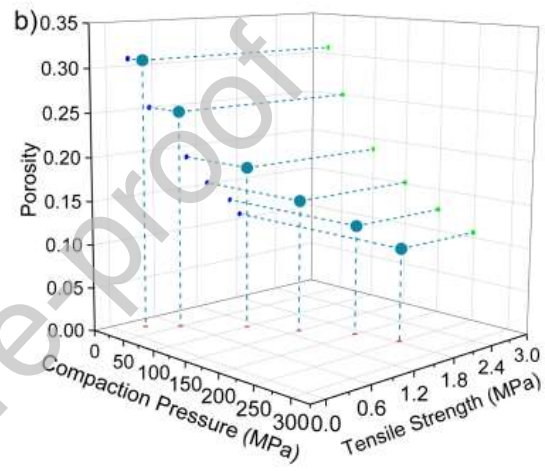
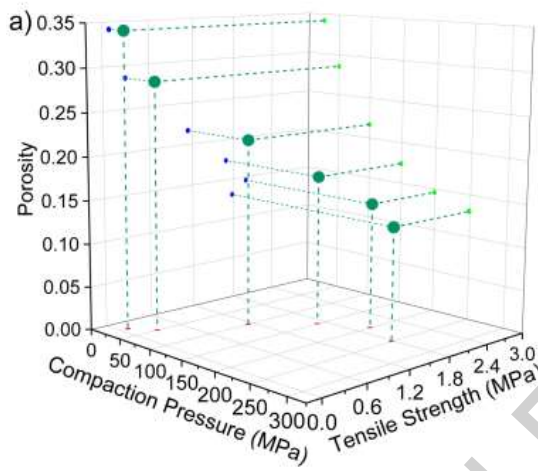


Figure 4. Heckel plots for PAR + $\text{L}\alpha\text{-H}_2\text{O}$ CC-SD mixtures (a) and the individual components (b) investigated.

Journal Pre-proof

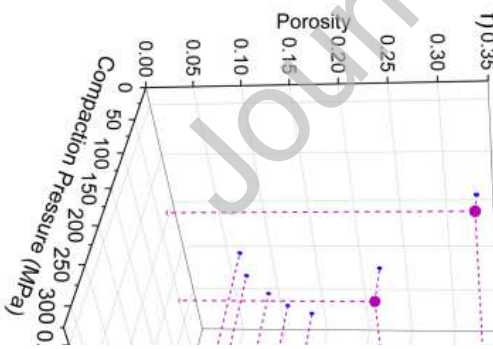
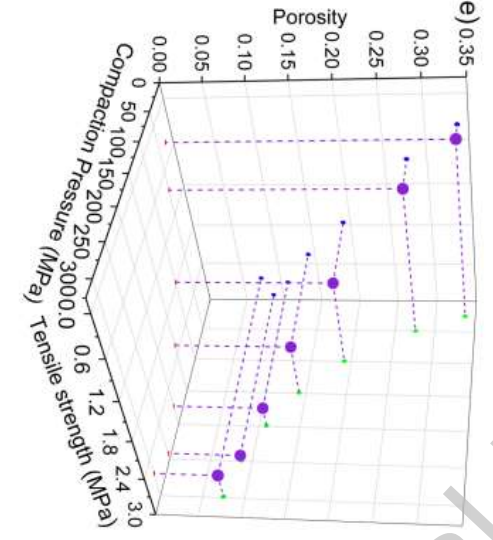
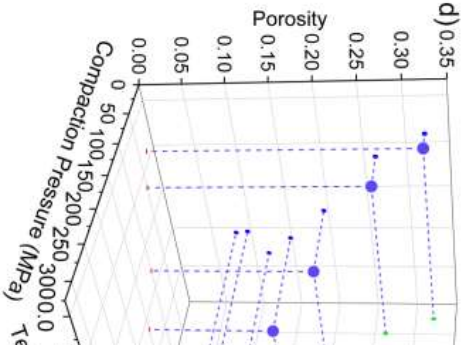
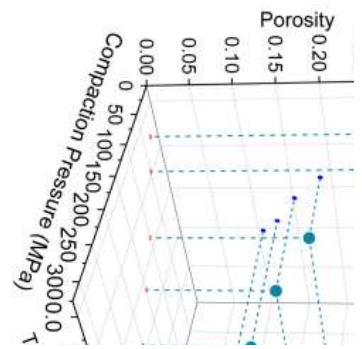
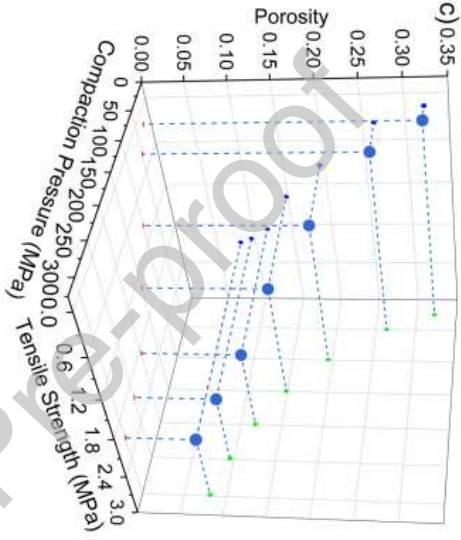
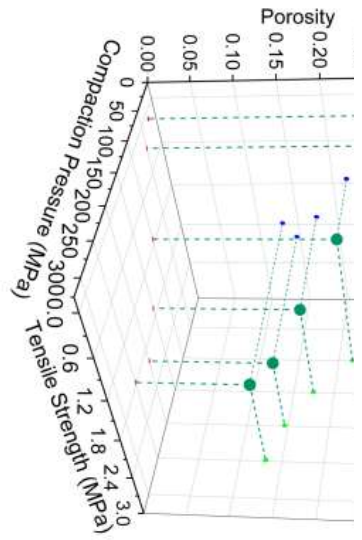


Figure 5. Compactibility profiles of PAR and L α -H₂O mixtures CC-SD at various inlet feed solvent compositions and their individual components both SD and non-SD as well as their SD and non-SD physical mixtures. A solid datapoint indicates that all tablets produced were free from any defects, a hollow datapoint indicates that some tablets showed defects (Table SI.1) and if no datapoint is present then no tablets could be reliably produced at that compression pressure. Lines are to guide between datapoints only. Error bars represent standard deviation.

Journal Pre-proof

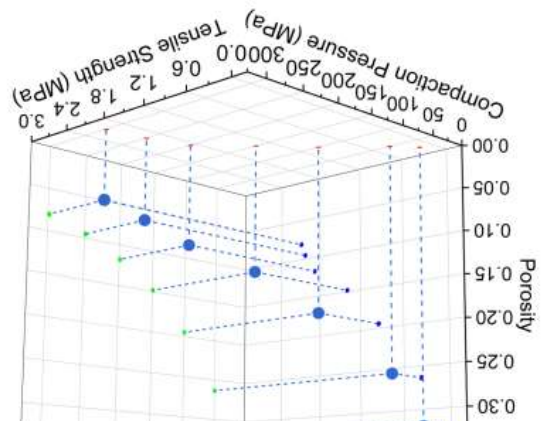
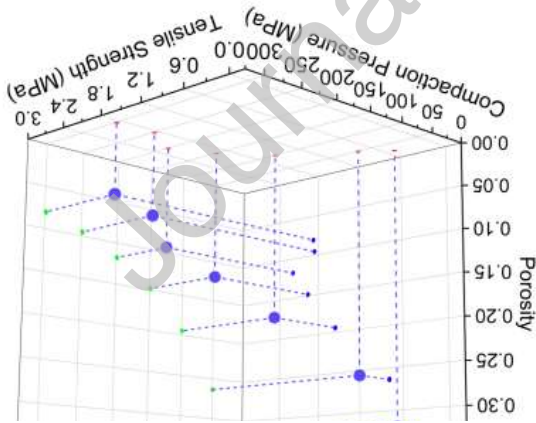
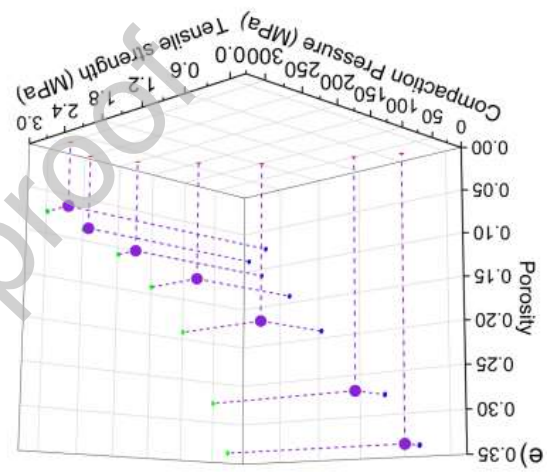
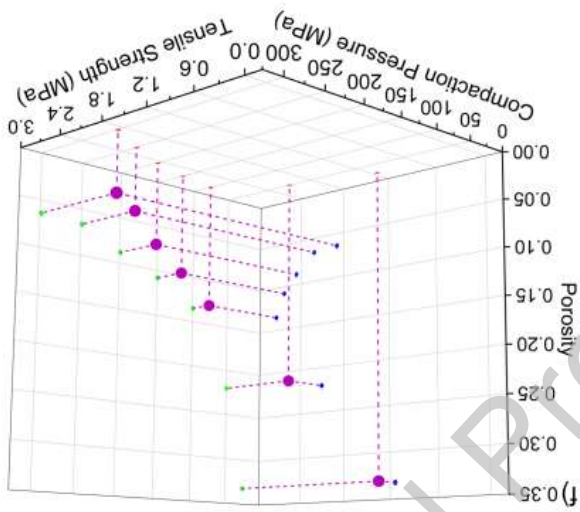


Figure 6. Friability (a) and disintegration (b) profiles of tablets made of PAR + $\text{Li}\cdot\text{H}_2\text{O}$ CC-SD mixtures. For friability testing, a weight loss < 1% is a pass [39] and for disintegration testing, a disintegration time < 15 minutes for uncoated immediate release tablets is a pass [40]. Solid lines are to guide between datapoints only. Dashed lines represent the criteria for passing.

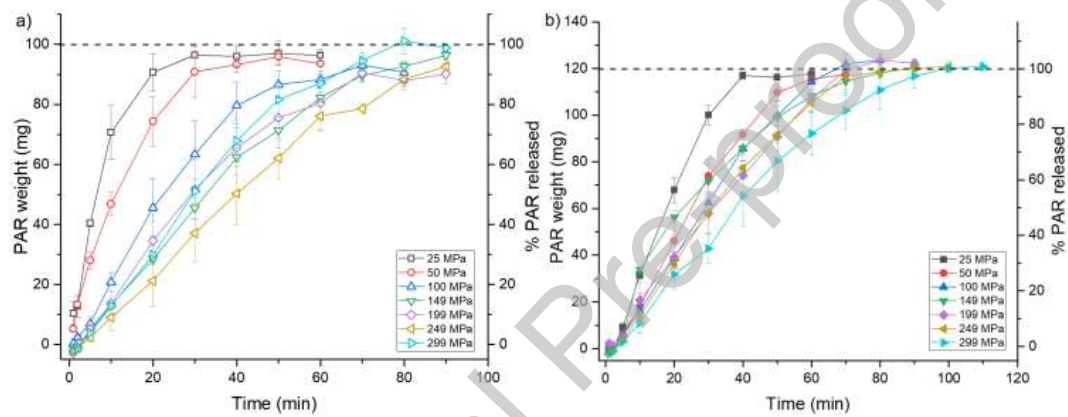


Figure 7. Dissolution profiles of tablets made of: a) the physically mixed PAR + $\text{L}\alpha\text{-H}_2\text{O}$ sample that was not spray dried (PM non-SD and b) CC-SD #6 sample at various compression pressures showing the weight and percentage of PAR released over time. Total tablet weight was 200 mg, the broken lines indicate the drug loading. Error bars represent standard deviation.

Journal Pre-proof

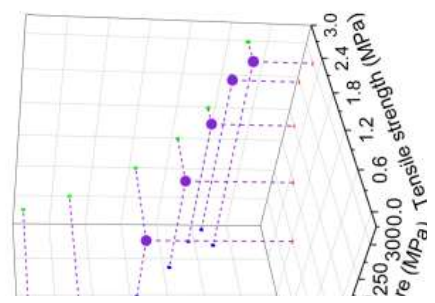
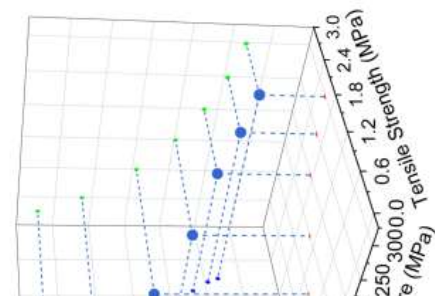
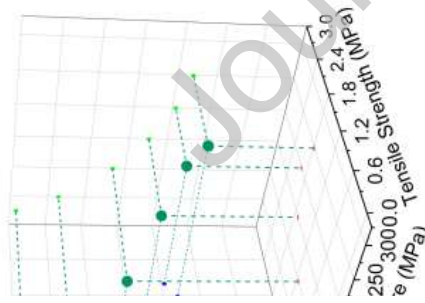
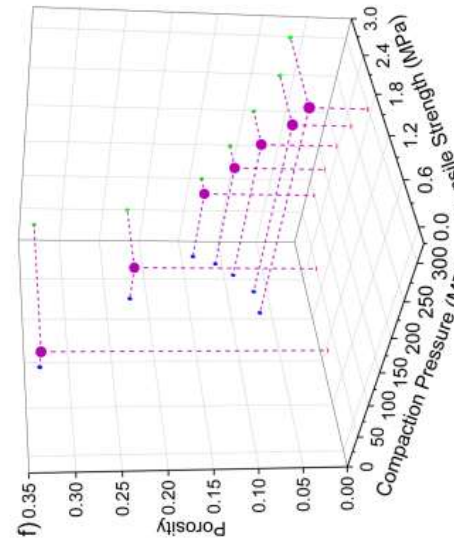
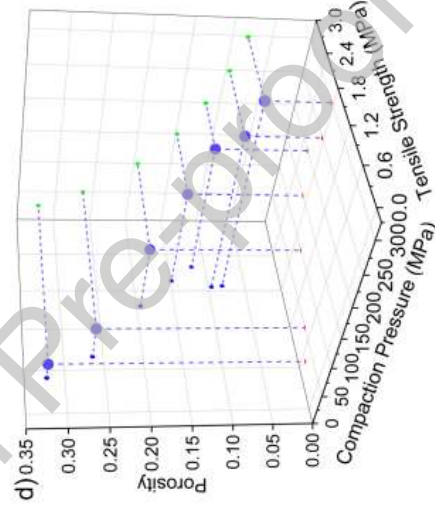
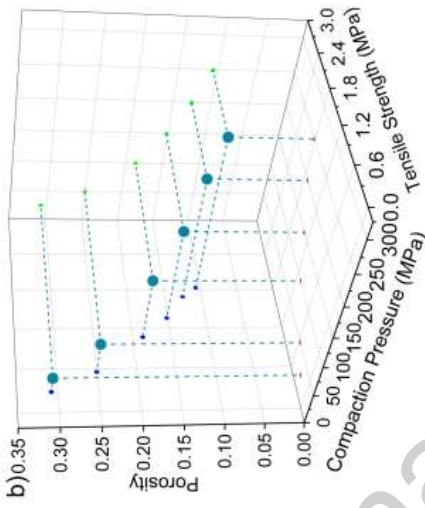


Figure 8. 3D surface plots of tablet characterisation for PAR + $\text{L}\alpha\text{-H}_2\text{O}$ CC-SD agglomerates SD using inlet feed solvent compositions: a) #1, b) #2, c) #3, d) #4, e) #5 and f) #6.

Journal Pre-proof