This is a peer-reviewed, accepted author manuscript of the following research article: Ottoboni, S., Šimurda, M., Wilson, S., Irvine, A., Ramsay, F., & Price, C. J. (2020). Understanding effect of filtration and washing on dried product: paracetamol case study. *Powder Technology*. https://doi.org/10.1016/j.powtec.2020.02.064

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Understanding effect of filtration and washing on dried product. Paracetamol case study.

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Abstract

One of the key challenges that the pharmaceutical industry is trying to address is to maintain particle properties across the entire purification and isolation process.

This research focuses on the effect of slurry properties, wash solvent, filtration and washing mechanisms on API agglomeration/granulation during the processes of downstream isolation and the impact on the physical properties of the product. In this investigation, each isolation step was analysed to identify factors that have the potential to affect the final product qualities using a multivariate statistical design of experiments approach.

The factors which were most detrimental in increasing particle agglomeration, were found to be the particle size of the input material, the quantity and identity of wash solvent and the drying mode. Low boiling point aliphatic

hydrocarbons are shown to be desirable final wash solvents to reduce the extent and strength of agglomerates and to produce free flowing powder/readily disrupted agglomerates.

Key Words: Agglomeration, lab-scale static drying, crystallization/wash solvent, paracetamol, particle size distribution, agglomerate brittleness index.

1. Introduction

Typically, the Critical Quality Attributes (CQAs) which must be established during API isolation are purity and particle size distribution. Both are achieved principally by the upstream process of crystallization in which particles of the required size and purity are generated in suspension in impure mother liquors.[1] Filtration, washing and drying steps are necessary to isolate the API and ideally should accomplish this without breaking or granulating the crystals or precipitating dissolved product or impurities on the crystal surfaces. In order to develop an isolation strategy it is necessary to consider the different materials and processing steps to identify conditions which allow production of dry API with the PSD established during primary crystallization whilst simultaneously meeting the purity requirements consistent with use as a drug substance (i.e. compliant with regulatory guidance e.g. ICH).[2] According to Murugesan et al and Beckmann[3,4], typical industrial practice is to wash a filter cake with at least three cake volumes of solvent, which approximates to between 5 to 7 mL of solvent per gram of API produced. Improving wash efficiency would reduce solvent use and improves environmental metrics.

Crystallization solvent selection and variability in particle properties can significantly affect the efficacy and operation of each of the individual processing step during filter cake processing. Understanding how these factors influence the process enables a suitable sequence of steps and combination of processing conditions to be selected to achieve consistent product quality and maximise equipment utilization.

Isolation can be divided in five stages: cake formation (sometimes called sedimentation), filtration, washing, deliquoring and drying.[5-8] At the end of final washing step, a common industrial practise is to introduce a deliquoring step, which is conducted to mechanically displace as much as possible of the remaining liquor phase trapped in cake pore structure. Mechanical displacement can be conducted by using pressure, vacuum or by physical compression using a piston (which is likely to be accompanied by particle breakage for fragile particles)

all with the objective of displacing solvent residues from the inter-particle voids. Subsequently, a thermal drying process is conducted to remove any residual intra-particle solvent further reducing the solvent content to achieve a target level of dryness.[9] Drying is the activity within the isolation step that is most frequently responsible of particle size variation (either by breakage or agglomeration or sometimes both) and in extreme cases even large lump formation.[10-14] Washing, on the other hand, has an essential role in delivering cake purity. By selection of appropriate filtration and washing strategies drying can be improved to facilitate production of pure product particles with comparable size as to the material produced in the crystallizer.

Considering which properties are likely to affect slurry filterability, the liquid phase properties and particle properties have the most marked effect slurry filterability. For example, Wakeman investigated the influence of particle properties on filtration.[15] From Darcy's theory of filtration at constant pressure, the volumetric flow rate (dV/dt), the filtrate is related to the resistance of the cake and the resistance of the medium, as shown in the Equation 1:

$$\frac{dV}{dt} = \frac{A^2 \Delta P}{\mu (\alpha_{av} c V + A R_m)} \quad (1)$$

Where ΔP (kg m^{-1} s^{-2}) is the pressure drop along the filter axis, A (m^2) is the filter surface area, μ (kg m^{-1} s^{-1}) is the filtrate viscosity, α_{av} (m kg^{-1}) the specific cake resistance is related to the cake filterability, R_m (m^{-1}) is the filter medium resistance and c (kg m^{-3}) is the dry cake mass per unit volume of filtrate.

From Carman-Kozeny equation cake resistance is correlated with cake porosity and the square of the particle size (Equation 2).

$$\alpha_{av} = \frac{180}{\rho_s x_{av}^2} \frac{1-\varepsilon}{\varepsilon^3} \quad (2)$$

Where ε (-) is the void ratio ρ_s (kg/m^3) is the crystallographic density of the API. Therefore, reducing particle size[16] and/or widening particle size distribution increases the resistance of the cake, reducing filterability of the system and increasing the probability of trapping higher quantities of mother liquor between particles. A similar effect is reported for widening the particle size distribution. As reported by Wakeman[14] and later by Beckmann [4], particle shape affects filtration rate, cake porosity and cake resistance.

Filterability[30, 31, 32] of slurries is also affected significantly by the physical properties of the liquid phase. A low viscosity mother liquor encounters less resistance when passing through cake pores than a more viscous mother liquor. This influences both filterability and filtration duration. Mass transfer for a viscous liquid is reduced due

to its difficulty in overcoming capillary forces in order to penetrate into the smallest capillaries in the cake This is explained in the Hagen-Poiseuille equation[17] (Equation 3) that is used to describe the fluid flow within capillaries.

$$dV = \frac{r^4 \Delta P \pi}{8 \mu h} dt \quad (3)$$

where dV (m^3) is the infinitesimal volume, r (m) is the capillary radius, μ (kg m^{-1} s^{-1}) is the liquid phase viscosity, h (m) is defined as the liquid rise inside a capillary and ΔP (kg m^{-1} s^{-2}) is the pressure drop inside the porous bed.[15,18]

API particle size and mother liquor properties are also affected by the cake washing process. Different approaches are used across the pharmaceutical industry. Some use the same solvent or solvent mixture attained at the end of the crystallization step, others select wash solvents with lower viscosity than the crystallization solvent, which along with dissolved API and impurities composes the mother liquor.[19] In general, less viscous wash liquors tend to be more effective in entering small capillaries and favour effective solvent displacement and diffusion washing.

Miscibility of crystallization and wash solvent is another critical parameter to consider when seeking to improve washing efficiency. Various researches have investigated the work to evaluate flow of immiscible fluids in porous media.[20-23]

At the start of the washing process, wash solvent enters the largest pores in the cake and displaces the filtrate from the connected network of large pores and channels, once this has occurred filtrate in adjacent network of fine pores held up between the product crystals may diffuse into the wash liquid, thus solvent and solute transport occurs due to axial dispersion.

During displacement washing there is no capillary equilibrium in the system, but the pressure difference between the two sides of a meniscus at any microscopic point in the system has been assumed to be equal to the capillary pressure as predicted by Laplace's equation for the continuum existing at that point. During this process pressure variation along a sequence of capillaries may be observed.[24] During this second washing phase, a combination of diffusion and dispersion processes occur.[25] To achieve a perfect displacement wash the wash solvent has to penetrate the entire cake pore network without mixing with the original mother liquor and thus plug flow must occur. In this idealised model of displacement washing, the washing process is completed when a wash solvent volume corresponding to the cake void volume is flushed through the cake.[26]

Ideal displacement washing in a real situation is never achieved in either a laboratory or manufacturing setting. In fact a combination of displacement and diffusion is required to enhance cake purity, so a combination of miscible crystallization and wash solvent is required, as Burisch and Peuker report.[26] Solvent miscibility, as described by Burisch and Peuker leads to variations in the wettability of the liquid phase on the product crystals as the solvents mix during penetration of the filter cake pore network; an awerness of liquid surface tension and product wettability is needed to understand the mechanism of washing.[27-29]

API particle solubility is another important property to consider during washing. Making a solvent switch between the crystallization solvent and a different wash solvent is a frequently used strategy in the pharmaceutical industry. For example, switching to a more volatile solvent in which the API has low solubility aids drying. This procedure needs to be carefully designed to minimise the formation of particle aggregates.[33] The extent, strength and friability of such granules (or aggregates) vary significantly vary depending on the choice of solvents and is strongly linked to the difference in solubility of the solute in the two solvents. In general, the higher the solubility of the API in the crystallization solvent at the isolation point and the lower its solubility in the wash solvent the greater the extent of granule formation and the harder the final granules produced during washing. When granules are formed during isolation further processing to disrupt the granules and attain the desired size distribution is usually necessary, typically this is accomplished by introducing a milling step.[14] Wash solvent selection can also lead to dissolution of small particles which may narrowing the PSD and/or reduce the isolated yield. This can occur either because the API has appreciable solubility in the wash solvent or in mixtures of the wash solvent and the crystallization solvent. The phenomenon of a maximum solubility being reached in mixtures of solvents is relatively common for example.[34-35]

Drying performance and the impact of drying on product attributes is influenced by both particle and process properties including; input particle size distribution and crystal shape, the flow rate of the drying gas (typically nitrogen) through the cake, the residual solvent content and composition at the start of drying, the heat applied and the design and operation of the drying device.[10-14, 36]

Many researchers have reported and examined possible causes of agglomeration during drying.[33, 36, 37] Common hypotheses suggest that if the API solubility in the wash solvent is high and sufficient solvent is present then inter-particle bridges of polycrystalline material are deposited at the points of contact between particles due to the evaporation of solvent saturated with dissolved API. One approach to reduce agglomeration is therefore to tailor the wash solvent composition to minimize concentration of the solute during the drying operation. Papageorgiou

et al.[38] investigated the propensity of particles to undergo agglomeration analysing the effect of solvent selection and the amount of residual solvent present.[39] An appropriate solvent selection can have a larger impact on particle clustering than initial particle size. Birch and Marziano (2013)[35], Zhang and Lamberto (2013)[40] and Tamrakar *et al.* (2016)[14] have all studied the effect of solvent choice on drying, analysing the role of solvent polarity in the formation of strong granules. Generally, the higher the solubility of the product in the wash solvent, the greater the chance of solid bridge formation. In addition to solubility, another reason for the increased formation of inter-particle bridges with polar solvents is the increased viscosity of the thin liquid layer surrounding the particles.[14] Lim *et al.* (2016)[39] and Zhang and Lamberto (2013)[40] investigated the effect of surface tension on agglomeration using different solvent mixtures highlighting that surface tension of the saturated solution can be a good indicator of the cohesive force experienced in the wet cake.

Wakeman[15], reports that particle size and shape play a noticeable role in deliquoring performance. Increasing particle size shortens deliquoring time when blowing nitrogen through the cake due to increased gas flow rate through the cake. Solvent removal during constant-rate period of drying is controlled in part by the accessible particle surface area, while internal particle morphology (e.g. for agglomerated material) limits drying kinetics during the falling-rate period.[9, 41-44] Moreover, PSD also affects heat transfer: as a composite particle (agglomerate) dries, the outer layers insulate the core shielding it from further heat propagation. It also forms a diffusion barrier. This is seen in case of large porous particles, removing all the solvent from the core requires extra drying time. Dryer geometry and impeller design and agitation strategy can significantly change the mixing patterns and mixing intensity and so affect the ultimate product size distribution. Agitators and orbiting elements serve to induce attrition and increase particle collisions resulting in attrition and breakage changing both particle size and shape.[12] The same agitation can also be responsible for lump formation. Typically, agglomeration occurs in agitated dryers when the material with a relatively high level of residual solvent is intensively agitated.[45]

Other parameters affecting drying are the drying temperature, pressure, agitation speed, solid loading, length of blow-down period and height of solid bed.[10-14, 46, 47, 48]

The goal of this paper is to provide useful guidance on how to minimise agglomeration during API isolation by developing optimal filtration and washing strategies and by analysing different drying strategies to evaluate the impact of key factors that affect the properties of final dried product. The API selected for this investigation is paracetamol (acetaminophen), used as a widely studied model compound with an extensive range of background data facilitates interpretation of the experimental results.[49-53] This has allowed the project to focus on questions

related to equipment capability, chemical and physical interactions of the API and the solvents during filtration, washing and drying. A further objective of the experimental work was to examine the effect of particle size on API filtration and washing with a focus on the selecting suitable wash solvents and washing regimes to minimise particle agglomeration during filtration and washing and to decouple this from granule formation during drying. The extent of granule formation during drying was determined and linked with friability analysis of the dried particles.

Solvent combinations were selected to investigate the effect washing by switching between a crystallization solvent and wash solvent. In particular, analysing the consequence of solvent switching on the tendency for particles to agglomerate during drying. Mass loss on drying and residual solvent content were used as parameters to evaluate the roles of crystallization and wash solvent and of wash quantity on agglomeration tendency. Three distinct populations of paracetamol particles were used in the experiments; micronised, typical powder and rather larger granular material. This allowed the effect of particle size to be evaluated over a broad range of processing conditions. A multivariate design of experiments (DoE) was used to allow the combined impact of multiple factors to be evaluated in terms of the tendency to form agglomerates / granules during filtration and washing and drying, and to understand the impact of cake washing on the robustness of resulting agglomerates. Solubility of the drug substance in the wash solvent, the viscosity of the wash solvent and wettability of the API with crystallization solvent and wash solvent, the mother liquor /solvent hold up in the wet filter cake were selected as some of the system variables.

Different dryer configurations are used in pharmaceutical industry. Dryers are classified by the dominant mechanism of heat transfer, the principle distinction as being conductive or convective. Three different convective static drying combinations were investigated. Static drying took place in a vacuum oven which was used without heat or moving the particles. The other two experiments used flowing gas (nitrogen); at ambient temperature and at 60°C. From Figure 1 the overview of the experimental workflow used for this work is described.

Figure 1 Experimental workflow. Three different paracetamol grades were selected, micronised, powder and granular. Slurries were prepared by creating a saturated solution and then pouring the solid load required to build the cake with the selected paracetamol grade. Filtration was then performed to form the cake for the washing step. The selection of wash strategy for each experiment was set using DoE approach. After the drying process, the final material was analysed to evaluate loss on drying, residual solvent composition and quantity, extent of agglomeration and agglomerate strength using a friability analysis.

An optimisation test was run to calculate a single combination of factors minimizing agglomerate hardness, extent of agglomeration and particle size. The same set of parameters were used to analyse the impact of wash solvent characteristics on drying.

Material attributes such as the particle size distribution of different grades of paracetamol and the solubility of paracetamol in the different wash solvents were examined. Also the mother liquor viscosity was determined experimentally.

The final dried product was characterised in order to quantify the effect of filtration, washing and drying methodology on the product. Specifically, the loss of mass on drying and the composition and quantity of residual solvents were measured as well as the extent of agglomeration and the friability of any isolated agglomerated were measured.

2. Materials

Micronised, conventionally crystallized (powder) and special granular as pharmaceutical grade paracetamol ($C_8H_9NO_2$) were supplied by Mallinckrodt Inc., Raleigh, N.C., USA. Micronised batch number 042213E407, powder batch number 637514D001 and granular batch number 161713J561 were used throughout the work reported here. The basis for selecting these three grades of material is that; the micronised material is challenging to filter, wash and dry because of its small particle size; it shows wide size distribution and damaged particle surfaces; the conventional powder represents typical API and the special granular material poses a challenge because of its large particle size. In pharmaceutical industry, these three grades are generally used. The polymorphic form, x_{10}, x_{50} and x_{90}, the Sauter mean diameter (SMD), the volume mean diameter (VMD) and true density were measured experimentally and are reported in Table 1.

Table 1 Material characteristics of the three paracetamol grades. True density values were determined with Helium pycnometer, x_{10}, x_{50} and x_{90}, SMD and VDM were determined using a QICPIC particle size analyser[a].

The crystallization solvents selected for this study were ethanol (purity ≥ 99.8% (GC), from Sigma Aldrich), isopropanol (IPA) (purity ≥ 99.5 % (GC), from Sigma Aldrich) and 3-methylbutan-1-ol, commonly called isoamyl alcohol (purity ≥ 99.5% (GC), from Sigma Aldrich). All three solvents are appropriate crystallization solvents for paracetamol.[49] The wash solvents selected were n-heptane (purity 99%, from Alfa Aesar), isopropyl acetate (purity 99+ %, from Alfa Aesar), toluene (purity 99%, from Alfa Aesar), anisole (purity 99%, from Alfa Aesar), n-dodecane (purity 99%, from Alfa Aesar), tert-butyl-methyl ether (TBME) (purity 98%, from Sigma Aldrich),

[a] * Helium pycnometer: AccuPyc 1330 V1.30
† QICPIC Particle Size Analyser (Sympatec VIBRI/L), Sympatec GmbH System-Partikel-Technik

cyclohexane (purity 99+ %, from Alfa Aesar), 4-methylpentan-2-one (purity ≥ 99.5% (GC), from Sigma Aldrich), propylene carbonate (purity 99%, from Alfa Aesar) and acetonitrile (ACN) (purity 99.5%+, from Alfa Aesar). Each of the wash solvents listed above were selected for their different chemical and physical properties (surface tension, density, viscosity and paracetamol solubility) and their miscibility with the chosen crystallization solvents. Propylene carbonate was selected for its green solvent credentials. n-heptane, isopropyl acetate, toluene, TBME, cyclohexane, propylene carbonate, 4-methylpentan-2-one, and acetonitrile are harmful if ingested and can cause respiratory difficulty, and are harmful by eye contact. n-dodecane is toxic when in contact with skin or eyes.

3. Method

In order to investigate the propensity of different grades of paracetamol to agglomerate under different process conditions, the experimental procedure was divided into a series of consecutive steps: filtration to recover suspended solid material, filter cake washing and product drying, as seen in Figure 1.

A multivariate design of experiment (DoE) approach was used to investigate the combined effects of these key parameters on the quality of the final dried material because of the complexity of the interactions between material and process parameters in this multi stage process. The ultimate aim is to use the data and understanding obtained to identify an isolation strategy which is effective and reproducible in reducing particle agglomeration. MOODE Pro V11.0.1 developed by MKS Umetrics[54] was selected as DoE software to build a statistical model to identify how the selected responses can be correlated with the multi-variate parameters. The range of values explored for each variable were selected to lie within the range of conditions typically employed during isolation. A linear D-Optimal approach was used to reduce number of experiments from 2048 (full factorial) to 31 experiments with 3 centre points used to determine the reproducibility of the experimental procedure.

The D-Optimal approach is appropriate in this case because the experimental variables investigated comprise of a combination of quantitative and qualitative factors.[55, 56] A number of potential factors were held constant and were not included in the DoE; those potential variables are intrinsically related for example to the nature of solvent or grade of the paracetamol used. Those properties include the solubility of paracetamol in the solvent investigated, other examples include the, viscosity of the pure solvent, the viscosity of mother liquor, the density of the pure solvent, density of the saturated solution (mother liquor) and tapped and bulk density of the paracetamol samples, surface tension and contact angle of paracetamol with different solvents. Other fixed parameters not included as factors are process parameters: pore size of the filter used for the isolation, (nominal

pore size 10μm), the temperature of the suspension and wash solvent during filtration and washing was held at 20°C. Finally, cake height was treated as a fixed parameter, because it is strictly related to the solid loading of the slurry; cake compressibility was also excluded from design factors, because cake compressibility index is a parameter strictly defined by the slurry attributes imparted by the other factors. Based on the preliminary characterization of the paracetamol cake obtained during constant pressure filtration experiments, the different slurries all show partially compressible behaviour ($n<1$).[9, 15, 16, 57]

Table 2 comprises of the list of variables, responses and the analytical techniques used to gather the selected responses.

Table 2 Table of factors, responses and analytical techniques used to quantify the responses in the first DOE.

To evaluate the pre-settling of the cake prior to filtration, another DoE was produced. In Table 3, the list of variables and responses is reported.

Table 3 Table of factor for pre-settling DoE (second DoE).

A third DoE used to understand the effect of wash solvent on the dried material was designed (Table 4), based on the optimal values of parameters determined in the first DoE (optimum parameters are reported in Table 15).

The values of several parameters were intentionally modified from the optimal parameters gathered from the first DoE. Micronised paracetamol was chosen as the mechanical properties of agglomerates generated can be more readily studied by sieving than in agglomerates formed from the larger crystalline material. Four cake void volumes were selected as the initial amount of wash solvent to be used and evaluated by ^{1H}NMR analysis. This quantity of wash solvent was chosen to be enough to remove the mother liquor from the cake. The isolated dry material from each experiment was analysed by using the same analytical methods as presented in the first DoE.

Table 4 Fixed parameters and variables of the third DoE.

3.1 Preliminary characterization

The three different paracetamol grades were characterized to determine raw material particle size distribution (x_{10}, x_{50} and x_{90}, SMD, VMD). Paracetamol solubility was measured in the solvent used as well the contact angle of

paracetamol with the different solvents and the density and viscosity of paracetamol saturated solutions (mother liquor in each crystallization solvent).

The particle size distributions of the different grades of paracetamol were determined using Sympatec QICPIC particle size analyser[58] with VIBRI/L setup at feed pressure of 0.5bar, feed rate of 25% and 0.5mm gap width. Same methodology was used to analyse the sub 1mm particles isolated after drying. The mass of sample used for the PSD characterization was around 1g. The feed rate was initially set to 0.5bar to allow comparison with the input paracetamol. The test was then repeated with a feed pressure of 2 and 4bar to evaluate particle breakage due to shear stress.

The solubility of paracetamol in the different solvents was determined by equilibration. Pre-weighed suspensions of paracetamol in each solvent were prepared and placed in an incubator (Incubator S160D, Stuart, UK) on a multi-position stirrer plate (CamLab, UK) and held isothermally at the selected equilibration temperature of 25°C, and equilibrated with agitation for 24 hours. At the end of the 24 hours equilibration period 1ml samples were taken, the mass recorded and the samples were then placed in a fume hood for 24 hours for the solvent to evaporate. After 24 hours, the sample masses were recorded and the sample vials were placed in a vacuum oven (Gallenamp, UK) for 24 hours at room temperature and (20mbar) prior to determining the final dry residue mass which was used to calculate the solubilities (Table 1 and Table 2 of the supplementary information).

The contact angle of paracetamol with the different solvents was determined using the Washburn capillary rise method in which a liquid phase (with known properties) migrates through the pore network of a packed bed of sample particles due to capillary forces.

Measuring the mass increase of the powder sample vs time during the capillary rise process allows the contact angle to be determined (Equation 4, supplementary information).[59]

To determine contact angle of paracetamol in ethanol, IPA and isoamyl alcohol, saturated solutions of each solvent were created to avoid paracetamol dissolution during capillary rise measurements (Table 5).

Table 5 Geometric coefficient K and contact angle for the three saturated solutions of crystallization solvent. The contact angles for ethanol and 2 propanol where calculated using the K value determined for isoamyl alcohol solution.

The true density of the three grades of paracetamol were determined using a helium pycnometer AccuPyc 1330 V1.30 and are reported in supplementary information.

The viscosities of the saturated solutions were determined by using a GV500 viscometer (Hydramotion UK). Comparison of the mother liquor viscosity with pure solvent viscosity data shows the importance of measuring the viscosity of the mother liquor, rather than using published viscosity values for pure solvents. (The data is available in the supplementary information, Table 4).

3.2. Filtration and washing procedure

A modified Biotage VacMaster[61] was used for conducting filtration and washing of the paracetamol suspensions using manual best practice. A detailed description of the unit is reported elsewhere.[62]

The paracetamol suspensions evaluated in this study were prepared by first saturating the solvent with paracetamol at 20°C. The quantity of paracetamol required to saturate the solution was calculated from the solubility data in each of the crystallization solvents. In order to produce paracetamol suspensions with 10, 20 or 30% by volume of undissolved paracetamol, 3, 6 or 9g of paracetamol was respectively added to the saturated solution. By preparing the particle suspensions in this way and filtering, washing and drying them immediately the particle size distribution of the different grades of paracetamol was preserved in the filtration experiments.

To determine the filtrate flow rate, filter cake resistance, filter medium resistance and cake porosity, the filtration time required to collect specific filtrate volumes were recorded (equations are reported in supporting information section).

The focus of washing is to remove the mother liquor from the cake by replacing the mother liquor retained in the cake pores with the wash solvent. Generally, the solubility of the solute (API) in the crystallization solvent is substantially higher than in the wash solvent. Therefore, to avoid formation of inter crystal bridges during drying due to the API crystallizing from evaporation of the residual solvent during drying, all the crystallization solvent needs to be displaced from the cake. A key parameter is therefore the wash volume that corresponds to the cake pore volume (Equation 4).

$$Vvoid = Vcake - Vsolid = \frac{\pi\, d^2\, h}{4} - \frac{m_s}{\rho_s} \quad (4)$$

Where d is the cake diameter (m), h is to the cake height and m_s is the mass of the API in the filter cake (kg) and ρ_s is the API particle density (kg/m^3).

Murugesen and Beckman[3, 4] report the amount of wash solvent required to completely remove the crystallization solvent from a filter cake is more than one cake pore volume. During this study, the role of wash volume was investigated by adjusting both the wash quantity relative to the cake void volume and the number of washes used.

To determine the effect of pre-settling cake on top of the filter medium prior to filtration, a set of experiments using 10-30% V/V of solid load in slurry was prepared using; micronised, powder or special granular paracetamol and using; ethanol, isopropanol or isoamyl alcohol as crystallization solvent. Three pressure driving forces (300, 500 and 900mbar) were investigated to evaluate the effect of sedimentation on final cake and media resistance. These experiments were performed using three different Biotage filter tube media grades; 5, 10 and 20µm. The experiments were conducted in either filter and reload mode or settle and reload mode. The filter and reload experiments were performed using 30ml of slurry that were poured into the filter tube with care to avoid slurry wetting the tube walls with slurry. The filtration was then halted at dryland and the filtrate removed from the cake was re-dispensed onto the top of the cake without disturbing the cake surface. A second filtration was then run. The settle and reload experiments were performed by dispensing the slurry into the filter tube with care to avoid leaving slurry on the walls, the suspension was then allowed to settle pre-forming a cake, the filtration was performed and the collected filtrate was re-dispensed onto the top of the cake without disturbing the surface and re-filtered again. The collection of filtration flow rate was conducted for both steps to allow for comparison of the cake and the medium resistance in the two steps of filtration where the cake is comprised from the same source material but formed in different ways.

3.3 Drying methodologies

Three different static drying approaches were evaluated in this investigation: The first drying method was vacuum driven using a vacuum oven (Gallenamp) at room temperature and 20mbar pressure. The static drying process allowed moisture evaporation by thermodynamic equilibrium of vapour pressure in the closed system of the vacuum oven. Two static drying experiments with flowing gas were also used; room temperature flowing nitrogen and 60°C flowing hot nitrogen. The drying apparatus took nitrogen form the 5bar fume hood gas distribution system, the gas pressure was lowered to 2bar and controlled using a pressure reducer. The nitrogen flow rate was adjusted using a rotameter capable of adjusting the nitrogen flow rate from 0.1L/min up to a maximum of 1.0L/min. To allow the drying rate of the more volatile solvents, to be determined, the nitrogen flow rate of 0.3L/min was selected. Nitrogen flow rate was fixed at 0.3 L/min for both the drying setups. In the case of the

experiments conducted at 60°C, nitrogen flowed through a coil of copper pipe to allow for thermal equilibration as the entire experiment was held in an incubator.

The filter tube containing the wet cake was connected to the nitrogen supply by a tube and a rubber stopper fixed to the open end of the filter tube. This allowed nitrogen gas to flow through the cake in the same direction as the filtrate and the wash could pass through the filter medium. A schematic figure of the dynamic drying apparatus is shown in Figure 2. For drying with heated nitrogen the incubator temperature was controlled by thermocouples placed in different positions in the incubator to allow system temperature to be monitored and controlled. One of the thermocouples penetrated the stopper in the filter tube to allow the temperature of the nitrogen to be measured just above the surface of the wet cake to ensure the gas was heated to the required temperature.

Figure 2 Scheme of static drying with flowing nitrogen apparatus at room temperature (without the incubator) and at 60°C temperature (with the incubator).

Loss on drying was monitored periodically by closing valve 1, removing the stopper from the filter tube and determining the wet mass of the filter cake.

3.4 Offline characterization

3.4.1 Residual moisture content and composition

Cakes were dried to stable mass in vacuum oven (Gallenkamp) to determine residual solvent content (LOD %).

To determine the solvent composition of the retained solvent content, i.e. the % of residual crystallization and wash solvent, an AVII+600 NMR Spectrometer and BRUKER Advance 2+ (Bruker, UK) were used to collect proton NMR spectra. A few mg of cake was dissolved in 0.75ml of DMSO-d6. To determine the number of scansions, a T1/T2 relaxation time evaluation was performed for all the solvent combinations (process parameters: frequency axis F1 equals to 32, pulse program t1ir, 4 scans, 2 replicas of T1/T2 analysis to evaluate T1 relaxation). In the light of this, wet cake, samples were analysed using 64 scans, corresponding to approximately 5 time T1. The time determined from the T1T2 relaxation time test (5T1) was required to maximize peak to noise intensity and be able to detect very small proton signals arising from traces of solvent residue. Each sample was analysed in duplicate.

3.4.2 Extent of agglomeration and friability test to determine agglomerate brittleness index (ABI)

The procedure to determine whether a particle aggregate is considered as an agglomerate, a lump or an aggregate is not well defined in literature. Birch and Marziano[35] arbitrary decided to consider agglomerates as particle aggregates that were retained by a 1mm sieve. A similar arbitrary decision in this work has been made to consider particle aggregates with size at least of 1mm as agglomerates.

The extent of agglomeration was thus defined as in Equation 5:

$$Extent\ of\ agglomeration = \frac{mass\ of\ agglomerates\ above\ 1mm}{mass\ of\ total\ cake} \quad (5)$$

To separate the dried particles into two size fractions, a 1mm sieve (Endecotts Ltd UK) was used along with a lid and receiver pan. The sieve was shaken gently by hand to avoid breakage of agglomerates.

3.4.3 Mechanical properties of agglomerates

Birch and Marziano[35] developed a qualitative technique to calculate an agglomerate brittleness index (ABI) which is related to the strength of agglomerates. Approximately 500mg of particles (previously retained on the 1mm sieve) were shaken in a sieve column comprising of 1mm sieve and the receiving pan (both pre-weighted), using a Variable Speed Mini Vortex Mixer (Fisherbrand™) at 2800rpm for 1 minute. After the shaking, the sieves were weighted to determine the fraction of sample in each sieve and then the test was repeated 4 times. The mass loss of the upper fraction recorded within all cycles was then plotted and the gradient of the fitted curve reflected the mechanical properties as an agglomerate brittleness index (ABI).

4. Results and discussions

4.1 Parameters affecting filtration

Figure 3 DoE variables affecting cake resistance during filtration.

Figure 3 shows the overview plot of factors affecting the cake resistance during filtration. PSD, the nature of the crystallization solvent, the pressure driving force (Pre) and the solid loading (Loa) mainly affect the resistance to the flow of the liquid phase passing through the cake.

Analysing the two extremes of the paracetamol PSD, micronised and special granular, it can be inferred that using small particles with broad particle size distribution results in increased filtration time, reduction of filtrate flow rate and increase of cake resistance. As reported by Wakeman[15, 63], during the course of filtration, finer particles migrate through the filter cake toward the filter medium, depositing in close proximity to the filter medium, causing an increase of cake tortuosity in the proximity of the filter medium. This migration of fine particles impacts the cake resistance resulting in a gradient of alpha along the axis of the cake[64, 65], slowing washing and deliquoring step and potentially leading to increased solvent retention in the deliquored cake. Conversely, the special granular paracetamol has a large particle size and contains large inter-particle pores.It has low surface area and narrow PSD which both result in negligible cake resistance and results in the highest observable filtrate flow rate.

The identity and characteristics of the crystallization solvent are the second main contributions affecting filtration performance. Ethanol and isopropanol show similar properties in terms of solubility, density and viscosity, while isoamyl alcohol has a higher viscosity. As seen from Figure 4 ethanol and isopropanol exhibit similar cake resistances, while an increase of cake resistance is obtained using isoamyl alcohol[36]: hence the data confirm that faster flow rate and lower cake resistance are observed for less viscous solvents.

Figure 4 4D contour plot of the effect of solid load and driving force on cake resistance for slurry prepared with ethanol as crystallization solvent.

Analysing Figure 4, the effect of cake height (solid load) and driving force (pressure difference) can be observed: a high solid loading in the feed material yields high cake resistance. Applying a high driving force (high pressure difference) leads to increased pressure drop through the solid bed and therefore increased resistance due to paracetamol cake compression[15] (micronised paracetamol compressibility index calculated to be 0.233 compared with 0.398 for typical crystalline paracetamol).

Filtration parameters also affect filter medium resistance: a large variance in the collected data has been observed, this may probably be attributed to the solid particles sedimentation behaviour where the settled particles contribute extra resistance to filtrate flow.[9, 66, 67] To verify this hypothesis, a DoE was run to test the effect of pre-settling to

form a cake prior to filtration and to compare this with the effect of forming a filter cake conventionally (plot available in the supplementary information, Figure 7). The filtration time for the primary filtration is shorter than the secondary filtration due to the increase of resistance to the filtrate flow. During the first filtration, cake resistance was found to increase during cake formation, reaching its maximum value when filter cake was completely formed. This contrasts with filtering a pre-formed cake arising from settling; the cake resistance is constant throughout the filtration process. The filtration rate for secondary filtrations in both mode of experiments is relatively constant throughout the secondary filtration process which is consistent with filtration taking place on an already formed cake, in contrast with the primary filtration rate which decreases with increasing time. The effect of; filtering, reloading the filtrate and then re-filtering the filtrate on medium resistance is shown Table 6. Cake resistance from step 1 and 2 slightly increase, while medium resistance from step 1 to step 2 increases by an order of magnitude. This effect is caused by the already formed cake acting as a "second filter medium" increasing resistance to the flow of the filtrate.

Table 6 Cake resistance and medium resistance for experiments where filtration followed by reloading the filtrate and filtering using a slurry made with 30% V/V of micronised paracetamol in isopropanol and filtered at 900mbar driving force (the data correspond to the Darcy plot shown in Figure 7 of the supplementary information).

Comparison of the 4D contour plots of cake resistance in the first and second steps of settling and reload and filter and reload experiments, with ethanol as crystallization solvent, are reported in Figure 5. No major difference in cake resistance was seen between steps 1 and 2 of the settling and reload and filter and reload experiments. The effect of filter pore size is clearly visible: the smaller the pore size of the filter medium, the more pronounced the variation of cake resistance from step 1 to 2. A similar effect is seen using both the micronised and powder grades of paracetamol with the overall change in cake resistance from 5 x 10^9 to 1 x10^{10}.

Figure 5 4D Response contour plot of cake resistance in step 1 (settled and then filtered) in the DoE addressing solids loading, driving force, filter medium pore size and paracetamol particle size range (powder and micronised). Factors selected are reported in Table 5 of the supplementary information.

Two extremes of filtration behaviour were encountered in this DoE:

- Very rapid filtration was challenging to record manually; this was encountered when filtering granular paracetamol slurry with a low solids content and employing a high driving force. In this case rapid filtration is likely to be accompanied by rather inefficient cake washing due to the very short contact time

between the wash solvent and the filter cake; however, the low particle surface area associated with the large particles compensates for this due to the lower mother liquor hold up in the filter cake.

- Very slow filtration arising from the combination of a high solids loading, low driving force using micronised paracetamol suspended in isoamyl alcohol as the mother liquor. In this case the filtration time increased from a few of minutes (a typical time for a laboratory filtration) to over an hour. The prolonged filtration involved extended contact between the mother liquors and the crystals. This extended contact time may enable changes to occur to the particle size distribution for example by the formation of inter-particle solid bridges, i.e. agglomerate formation.

4.2 Parameters affecting washing

The DoE was not focused particularly on washing and as consequences there were few responses which correlate to the washing step which makes evaluation of possible parameters affecting washing difficult. Nevertheless, a few observations can be made:

- In few cases where a second washing step was included, the duration of the second washing step was noticeably shorter than for the first wash step. This effect may be caused by the reduction of solvent viscosity between the mother liquor to the pure wash solvent (see Table 10). During the first wash a major portion of mother liquor is displaced from the cake, predominantly the mother liquor which was occupying the network of large pores in the filter cake. During the second wash further residual mother liquor is removed from the cake[68-70], however when the second wash is removed from the cake it is principally composed of wash solvent in which some paracetamol is likely to have dissolved depending on the identity of the wash solvent and the contact time.
- During filter cake washing with propylene carbonate an unusual process of filter cake disturbance was observed. Propylene carbonate density is higher than the mother liquor (1.21g/mL), causing the floating of mother liquor to the top of the wash solvent with consequence disturbance of the cake due to the liquids movements. This buoyancy driven movement of mother liquors was observed to disturb the upper layers of the cake.
- In all cases cake washing was immediately followed by cake deliquoring which was allowed to continue for around 10 seconds after the bubble point was detected and a break in the steady flow of filtrate was observed.

Other effects of the wash solvents on the dried cake properties are discussed in the model optimization section (4.5).

4.3 Parameters affecting drying

Static drying was either conducted in vacuum oven at ambient temperature at a reduced pressure of 20mbar or was carried out using nitrogen flow at ambient temperature and also at 60°C, to study the effect of temperature on the dried material. All the three drying methodologies were conducted with cakes after few seconds of deliquoring using the Biotage unit. After drying, the cake was gently removed from the tube to avoid breakage of agglomerates or lumps to determine the effect of the different variables considered in the DoE on the final dried cake quality.

From Figure 6, the parameters which have the larger effect on the residual solvent content after drying, are the grade of the particles forming the cake (the lower the particle size the higher the quantity of solvent retained), the identity of the wash solvent, the number of washes (and hence the quantity of crystallization solvent remaining in the cake prior to drying), the stopping point of the filtration (dry land or break through), the solid quantity (cake thickness) and the drying methodology.

The boiling point, enthalpy of vaporization and viscosity of solvents are all important parameters affecting the residual solvent content after drying. The boiling point and enthalpy of vaporization of the wash solvent affect the ease of solvent removal during drying, while higher viscosity may be associated with an increase in the extent of solvent retention in the cake. From Figure 6, it is apparent that solvents with high boiling points require longer drying times to be removed, such as n-dodecane, anisole and propylene carbonate. Anisole and n-dodecane extended the drying times from hours to days. Propylene carbonate showed an extremely slow evaporation rate, drying being complete after almost 75 days.

Analysing the effect of crystallization solvent; isoamyl alcohol resulted in an increased in the residual moisture content of the deliquored cake due to its high viscosity. Literature values of; boiling point, enthalpy of vaporization, viscosity, density and surface tension of the different solvents used in this investigation are reported in supplementary information section.

Figure 6 Parameters affecting residual solvent content.

From Figure 6, also the drying method influence the residual moisture content. Lekhal et al.[11] report that wet particles tend to agglomerate during static drying under reduced pressure. The lack of agitation and consequent absence of disruption of aggregates allows strong inter-particle bridges to be formed as consequence of saturated solvent evaporation and solid bridges formation at the points of contact between particles. In case of the use of the drying apparatus, where a flow of gas passes through the cake, agglomeration tendency was marginally reduced. From Figure 7 also the drying time is seen to be affected from the drying methodology. As previously explained, vacuum oven drying for solvents presenting both relative low boiling points and heat of vaporization, required approximately few hours to dry. However, for static drying with higher gas flow rate, time to dry was reduced to few tens of minutes for low boiling and heat of vaporization solvents, even when room temperature nitrogen was used. Further reduction of drying time is achieved when the gas was heated up. This was due to the reduction of the constant rate drying period where the free moisture trapped between particles is removed causing the increase of drying rate.[47] High drying temperature also decreases viscosity of the residual solvent implying weaker adhesion forces between the liquid and solid material.

Figure 7 Top figure: drying profile of wet cake samples where drying was achieved by flowing nitrogen at ambient temperature through the filter cake with a flow rate of 0.3l/min. Bottom: Drying profile of wet cake samples where drying was achieved by flowing nitrogen at 60°C through the filter cake with a flow rate of 0.3l/min.

As seen in Figure 7, volatile solvents with low boiling points such as; TBME, cyclohexane, n-heptane and ethanol, evaporated within 15 minutes; solvents with medium boiling points, such as toluene and 4-methylpentan-2-one, required approximately 25 minutes and high boiling point solvents, such as anisole and n-dodecane, only reached steady-state after many hours. Propylene carbonate has an extremely low evaporation rate, under vacuum drying conditions the sample dried over 75 days. Using hot flowing nitrogen, static drying generally resulted in the drying time being shortened approximately by half. Cyclohexane and acetonitrile are two exceptions. The data for cyclohexane plotted in Figure 7 relates to a micronised paracetamol slurry with isoamyl alcohol as crystallization solvent, washed once with just 1 wash volume; it is likely that the inefficiency of crystallization solvent displacement resulted in extended drying time due to the high residual quantity of isoamyl alcohol which has boiling point approximately of 50°C higher and higher heat of vaporization by two thirds than cyclohexane.

Another key solvent property that can affect the quality of dried material is the paracetamol solubility. As reported in supplementary information section (Table 2) acetonitrile shows the highest paracetamol solubility in the entire

set of the wash solvents. This tendency of acetonitrile to dissolve more paracetamol than the other wash solvents serves to promote the formation of solid bridges, to some extent this effect may have been enhanced when hot nitrogen was used as drying agent (paracetamol solubility in acetonitrile at 25ºC is 0.0294g paracetamol/g of solvent, the corresponding values at 40ºC is 0.0313g/g and at 55ºC is 0.0707g/g).

The quantity of wash solvent used to wash the cake and displace mother liquor exhibits its greatest effect by influencing the residual mother liquor (crystallization solvent) content and hence influencing the drying time. The remaining crystallization solvent can promote inter-particle bridge formation during drying. The formation of lumps and granules causes further obstacles to solvent evaporation when the solvent is trapped between "cemented" particles, prolonging the already slow falling-rate drying step driven by capillary forces.[35, 39]

A further factor affecting the starting point of drying is identified in Figure 6: the procedure selected to halt the filtration can influence the final moisture content. Analysing the 4D Contour plots (Figure 8) shows that halting filtration at breakthrough leads to a greater decrease in the final solvent quantity trapped in the cake on the completion of deliquoring. Two extremes are observed when:

- The slurry solid loading was high and the driving force was low: this represents the best case because although the cake was thicker, the lower driving force results in the wash being more efficient in displacing the crystallization solvent, leaving the cake richer in the more volatile solvent which was more easily removable during the drying step
- When the slurry solid load and driving force were both high, the quantity of solvent left behind in the cake reached a maximum: using a high driving force during washing negatively affected the final solvent content; the reduced contact time between the mother liquors and the wash solvent reduced the capability of wash solvent to displace the mother liquor due to lack of diffusion time.

Figure 8 4D response contour plot of residual solvent content after deliquoring in case of filtration halted at dryland/breakthrough showing dependence on solids loading of the slurry, pressure driving force and paracetamol grade for an input suspension in ethanol washed twice with n-heptane and then dried using the static drying methodology. Factor selected are reported in Table 9 of the supplementary information.

4.4 Agglomeration, mechanical properties and particle size of dried products

Generally, micronised paracetamol tended to form agglomerates during isolation. Typically, the samples recovered are angular with sharp edges consistent with breakage of larger particle assemblies (Figure 9 of the

supplementary information). The slightly coarser grade of paracetamol (powder) formed a mixture of fine particles and agglomerates with slightly more friable edges. The granular grade of paracetamol never formed agglomerates, with the exception of samples where propylene carbonate was selected as wash solvent. Solvents that exhibit high boiling points, tend in general to produce more agglomerated particles on isolation.

In the experiments where micronised or powder grades of paracetamol were isolated and the volume of wash solvent used in the DoE was insufficient to displace and fully remove the crystallization solvent, the bulk of the isolated material took the form of a single lump (Figure 10 of the supplementary information).

In this study, three drying approaches were evaluated, in each case the particles were stationary throughout the drying process maximising the potential for particles to be fused together into agglomerates as solute was deposited when the residual solvent evaporated. In addition, maintaining the particles in a stationary state eliminated the particle breakage typically encountered during agitated drying and the formation of granular material frequently seen when solvent wet particles are agitated:

1) Ambient (unheated) vacuum drier. On the initial application of vacuum, there is usually a brief burst of evaporation accompanied by cooling since solvent evaporation is an endothermic process[74]. As the solvent wet product cools, the rate of evaporation declines until the system eventually reaches a thermal equilibrium where the rate of entry of heat energy into the system through conduction from the outside in, is balanced by the rate of heat loss caused by further solvent evaporation. The system continues in this constant rate period until the quantity of solvent available for evaporation is insufficient to sustain this evaporation rate and the drying process enters the falling rate regime.

2) Ambient temperature flowing nitrogen drier, here the flow of nitrogen provides a modest contribution to the heat balance leading (the specific heat capacity of nitrogen is small, 1.04kJ/kg/K compared with the latent heat of vaporisation of solvents, for example ethanol 42.3kJ/mol) to the solvent evaporation rate. As indicated, the particles at the point of entry for the drying gas encounter solvent free gas at ambient temperature. As the gas passes through the filter cake it cools below ambient as solvent evaporates from the particle surfaces, the gas leaving the filter cake is the coolest and most solvent laden. Depending on the cake thickness, the solvent volatility and the gas flow rate, it may be that the gas approaches saturation at its exit temperature. The particle size distribution plays a major part in defining the filter cake pore network dimensions and tortuosity which is also an important contributor to the resistance to gas flow and hence gas velocity and the opportunity for the gas to contact the wet crystal surfaces.

3) Elevated temperature flowing nitrogen drier, the process is very similar to that described in 2 above, the difference being that the solvent molecules on the surfaces of the initial crystals encountering the warm gas are subject to a greater driving force for evaporation and the temperature gradient through the cake is larger.

When a stationary bed of wet particles is dried, the solvent leaves the open surface by evaporation and for a time the lost solvent is replenished by capillary transport from the bulk to the surface. After a time, the rate of fresh solvent delivery declines as the reservoir of residual solvent diminishes and a drying front is established. The solvent content in the cake decreases along the axis of the cake[47] and in cases 2 & 3 the main limitation on the drying rate is the gas flow. Based on this model which presumes that solvent is carried to the evaporative surface by capillary forces it is reasonable to speculate that the formation of the solid crust of paracetamol starts from the upper surface and slowly progresses through the bulk where the transport of unboned moisture is occurring through particle-particle capillaries. In case of thin cake (in this study thin cakes are the cakes formed with slurry containing 10% of volume of solid content), if the material in the upper cake part stays in contact with the solvent for a long period the material after drying has rather hard shell or crust and relatively soft core. Whereas, for much thicker cakes, the capillary forces cannot effectively transport the solvent throughout the entire cake volume to the surface. In this case, after a constant rate drying, the process is driven by solvent diffusion through the cake (slower drying rate), causing an even distribution of cake moisture and formation of a single solid block. For the case of the three centre points experiments, where the solubility of the system in wash solvent is negligible, as the material in the upper part stays in contact with the solvent for longer period the material, after drying has rather hard crust and relatively soft core.

As discussed above, the main parameters that affect the extent of agglomeration of the final dried cake are; the PSD of the particles forming the cake, the characteristics of the crystallization and wash solvents, wash solvent volume and drying protocol. The susceptibility of particles to form agglomerates can be correlated with; the solvents propensity to evaporate, API solubility, solvent viscosity and system wettability. If the wettability of the crystallization solvent is high, then the wash solvent needs to present similar wettability to be capable of removing the mother liquor and therefore to reduce the tendency for agglomerates formation.[26]

The agglomerate brittleness index (ABI) was selected as a descriptor to evaluate agglomerate mechanical properties.[35] The dried samples are not necessarily homogeneous in character but varies between the surface and

the bulk, this variability is especially noticeable with the mechanical properties of agglomerates collected from the surface or from the bulk of the cake.

Table 7 describes the relationship between isolation conditions, the extent of agglomeration and the strength of the agglomerates formed. The three DoE centre point experiments shown in bold print in the table provide evidence of the consistency of the measurement of ABI (0.076 ± 0.01) and the extent of agglomeration (93.8% ± 1.3%). The data in Table 7 indicate that the strength of agglomerates depends principally on the PSD of the suspended particles being isolated. Micronised material usually formed hard agglomerates with a low ABI index, whereas the typical crystalline powder particles formed softer agglomerates with a higher ABI index. The link between size of the input particles and both the extent of agglomeration and in the PSD of the agglomerated particles with size smaller than 1 mm. may be linked with the surface area per unit mass available to form solid inter particle bridges during drying.[15] There is insufficient evidence to make a link between the drying methodology and these two responses; further investigation is required. Another key factor discussed previously is the role of API solubility in crystallization and wash solvent which determines the quantity of material that could be deposited to form inter particle crystal bridges. Solvent volatility also is likely to play an important role in determining how quickly the solvent evaporates and the corresponding opportunity for crystallization to take place on the surfaces of the existing bulk crystals vs at points of contact between crystals.

Table 7 ABI index and extent of agglomeration values of some of the experiments of the DoE.

Figure 9 shows which isolation parameters can modify the size of single particles during filtration, washing and drying steps. Each profile was characterized by cumulative distribution, distribution density and several discrete values – x10, x50, x90, Sauter mean diameter SMD, the volume mean diameter VMD and compared with raw material values. Experiments forming large agglomerates fitting within the dimensions of the filter tube usually did not produce enough particulate material for further PSD analysis. Granular material isolated under comparable conditions remained as free flowing powder exhibiting almost uniform PSD in all cases, indicating a threshold in granule formation. Conversely, large increases of PSD where observed for micronised samples. The PSD of the dried samples were comparable to the input material. Analysing Figure 9, it also appears that; slurry solid load, crystallization solvent viscosity and the filtration and washing stopping points influence the final particle size expressed as the SMD. The same reasons used to explain the level of agglomeration can be easily transferred also

for the SMD of single particles. No major effect is observed modifying the drying equipment mechanism and its operation while API PSD increases with the solubility of API in wash solvent.

Figure 9 Investigating the effect of crystallization solvent. A 4D response contour plot of Sauter mean diameter (SMD) of the isolated product particles passing through the 1mm screen. In the case of filtration halted at dryland or breakthrough in the range of solid load of the slurry, driving force, paracetamol grade for an ethanol/isoamyl alcohol slurry washed 1/2 times with n-heptane/acetonitrile and static drying methodology. SMD of raw powder and micronised paracetamol are respectively 46.35 and 18.66μm. Factors used for these plots are reported in the supplementary information section, Table 12.

4.5 Model optimization and wash solvent screening

The data gathered from the initial screening DoE (first DoE, Table 2) used to evaluate the effect of different filtration, washing and drying conditions on the final product, the conditions that can maximize process performance and product quality were extracted. Filtration and washing driving force was fixed at 500mbar to reduce filtration time. In Table 8 the experimental parameters selected to minimize agglomeration, to get soft agglomerates and to reduce PSD variation of single crystals are reported.

Table 8 Ideal isolation parameters to minimize increase of agglomerates and PSD of single particles and formation of soft agglomerates.

Based on the optimum parameters a validation DoE was designed to understand the impact of wash solvent.

By using 4 void volumes divided between two separate washing steps, it was demonstrated that almost complete removal of the mother liquor (Table 9) could be achieved. The highest quantity of residual crystallization solvent encountered in the experiments was when acetonitrile and 4-methyl-2-pentanone were used. This is due to the high solubility of paracetamol in those two solvents that cause entrapment of mother liquor between particles agglomerated during drying. Also sample washed with n-dodecane shows high crystallization content after drying due to the lack of washing solvent used.

Table 9 Residual wash and crystallization solvent remained in cake after drying and drying time related to the nature of wash solvent.

The propensity to agglomerate and the mechanical property of the agglomerates are evaluated in Table 10. The sample that showed highest agglomeration was isolated from isopropyl acetate due to its propensity to dissolve paracetamol, while the lowest agglomeration is seen in samples washed with n-dodecane (showing the impact of

very low API solubility). The hardest agglomerates are formed with acetonitrile (high API solubility), while the softest agglomerates are generated by washing with n-heptane. From this observation, if the objective is to combine a low propensity for agglomeration and to make soft agglomerates, the best processing option is to use cyclohexane, as seen in Figure 10.

Table 10 Mechanical properties of agglomerates produced from second DoE.

Figure 10 Visual appearance of samples generated during the validation DoE after drying. The best solvent selection to reduce agglomeration and obtain soft agglomerates is cyclohexane.

The particle size was determined using approximately 1g of dried material, the particle size analysis confirmed the best wash solvents for producing the least agglomerated product are cyclohexane and n-heptane which is consistent with previous observations (Figure 13 of supplementary information).

5. Conclusions

The aim of this work was to identify which filtration, washing and drying parameters affect the size of single particles, formation of agglomerates and the mechanical properties of agglomerates formed during the isolation process. Three different DoEs were designed to evaluate the effect of:

- Filtration and drying procedure on the quality of final product
- Evaluation of sedimentation on filtration parameters: pre-settling cake prior to filtration, reloading the filtrate on top of the cake to re-filtering it again. ~~and the more complicated filter and reload the filtrate on top of the cake to re-filter it again. This DoE was used to evaluate how cake and media resistance are influenced by cake sedimentation prior to filtration.~~
- Wash solvent identity on the dried product properties (PSD, extent of agglomeration and strength of agglomerates).

~~A model compound – paracetamol – was used in the study and the effect of particle size was explored as a categorical variable using micronised, powder and granular grades of paracetamol. Three different crystallization solvents, appropriate for crystallization and isolation of paracetamol (ethanol, isopropanol and isoamyl alcohol) and ten different wash solvent were used to evaluate the effect of solvent properties (viscosity, density, solubility and evaporation capability). A series of filtration, washing and drying variables were evaluated in the DoE screening: solid load in slurry, filtration and washing driving force, filtration and washing endpoint, volume and~~

~~number of wash solvent used, and drying mechanism. Cake and media resistance, residual moisture content, and characteristics of the dried material; extent of agglomeration, ABI index and PSD of single particles were selected as responses in the initial screening DoE.~~

~~Two different sedimentation approaches were investigated: pre-settling cake prior to filtration and the more complicated filter and reload the filtrate on top of the cake to re-filter it again. This DoE was used to evaluate how cake and media resistance are influenced by cake sedimentation prior to filtration.~~

To analyse the effect of drying on the final product, the extent of agglomeration and PSD of the single particles were selected as responses to evaluate the effect of residual moisture content, drying time and using different drying approaches. The major parameters affecting the percentage of residual moisture content are:

- The size distribution (grade) ~~grade~~ of the particles forming the cake: the lower the particle size the higher the quantity of residual solvent retained.
- The nature of the wash solvent, high boiling point, enthalpy of vaporization and solute solubility promote particle bridge formation during drying. ~~due to its boiling point, enthalpy of vaporization and solubility that can promote or impede particle bridge formation during drying.~~
- The number of washes: if insufficient wash solvent is used ineffective washing is ineffective causing entrapment of mother liquor between particles which promotes particle cementation during drying. ~~washing occurs causing the entrapment of mother liquor between particles that can then promote particle cementation during drying.~~
- The crystallization solvent characteristics ~~identity~~ and quantity remaining at the start of drying influence agglomeration, high API solubility, ~~and~~ large solvent quantity and high solvent viscosity favour agglomeration.
- The drying methodology: when particles remain stationary under vacuum drying agglomeration was promoted, while drying with a flowing gas marginally reduced agglomerate formation. ~~drying under vacuum promoted agglomeration, while drying with a flowing gas marginally reduced agglomerate formation.~~

~~Analysing the agglomeration propensity and mechanical properties of the agglomerates formed, sieving provided accurate results only in case of micronised agglomerates.~~ Agglomeration extent and agglomerate strength were found to correlate strongly with particle size. Fewer agglomerates were formed using the powder grade paracetamol and they were softer than those formed with the micronised input. ~~showing that the PSD of the raw~~

~~material is a major parameter that affects the nature of agglomeration.~~ No agglomeration was observed with special granular particle samples, with the exception to samples washed with propylene carbonate, where extremely hard and highly agglomerated products were formed under all conditions. ~~where it always produced extremely hard and highly agglomerated products.~~ From the analysis of the parameters affecting agglomeration and agglomerate mechanical properties are; the PSD of the particles forming the cake, and crystallization and wash solvent characteristics (evaporation propensity, API solubility, viscosity and wettability washing step), wash solvent volume and drying mechanism.

Sedimentation prior to filtration influences the cake and media resistance. The increase in media resistance after sedimentation can be treated ~~considered~~ as the sum of resistance of the cake sedimented prior filtration and the filter medium resistance. ~~media resistance of the filter medium.~~

An experimental design was performed to identify the best combination of process conditions to suppress agglomeration. This was followed by a solvent screening study ~~(with exception of propylene carbonate)~~ where the effect of wash solvent would play a dominant role. ~~Proton NMR spectroscopy was used to monitor cake washing efficiency identifying washing conditions where agglomeration would not be driven by residual mother liquor acting as a binding agent.~~ In general, solvents presenting high API solubility and/or high boiling point show increased ~~favour the increase of~~ agglomeration propensity with the formation of hard agglomerates. From the validation DoE; low boiling aliphatic hydrocarbons (cyclohexane and n-heptane) were shown to be the best wash solvents for paracetamol, they reduce the tendency for agglomerate formation, yielding soft and easy to break agglomerates. These findings were further confirmed from PSD analysis of non-agglomerated fraction.

This work has delivered useful guidance and analytical approaches to design API isolation strategy to minimize agglomeration and to measure agglomerate mechanical properties.

6. Abbreviations

Engineering and Physical Sciences Research Council (EPSRC), Active Pharmaceutical Ingredient (API), particle size distribution (PSD), proton nuclear magnetic resonance (^{1}H-NMR), critical quality attributes (CQAs), International Conference on Harmonisation (ICH), design of experiments (DoE), paracetamol (PCM), Sauter mean diameter (SDM), volume mean diameter (VMD), isopropanol (IPA), gas chromatography (GC), tert butyl methyl ether (TBME), acetonitrile (ACN), polytetrafluoroethylene (PTFE), residual solvent content (LOD %), agglomerate brittleness index (ABI).

7. Aknowledgement

The authors gratefully acknowledge the financial support of the University of Strathclyde and the UK Engineering and Physical Sciences Research Council (EPSRC) research grants [Grant Ref. EP/L014971/1] awarded to CJP, and Doctoral Training Centre for Innovative Manufacturing in Continuous Manufacturing and Crystallization grant [Grant Ref. EPK503289] awarded to SO. All data underpinning this publication are openly available from the University of Strathclyde Knowledge Base.

Declaration of interest: none.

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10. Supplementary information

- Figure 1 Cumulative distribution and distribution density of raw granular paracetamol
- Figure 2 Cumulative distribution and distribution density of raw micronised paracetamol.
- Figure 3 Cumulative distribution and distribution density of raw powder paracetamol.
- Figure 4 Isopropanol - Paracetamol Saturated Solution Viscosity at different temperatures. [75]
- Figure 5 Ethanol - Paracetamol Saturated Solution Viscosity at different temperatures. [76]
- Figure 6 Isoamyl alcohol - Paracetamol Saturated Solution Viscosity at different temperatures. [77]
- Table 1 Experiments parameters of the cake shown in Figure 23 and Figure 24 of the main manuscript.
- Figure 7 Factors selected for the screening DoE (first DoE).
- Figure 8 Responses of the screening DoE (first DoE).
- Figure 9 Factors selected for the pre-settling DoE (second DoE).
- Figure 10 Responses of the pre-settling DoE (second DoE).

11. Vitae

This is a peer-reviewed, accepted author manuscript of the following research article: Ottoboni, S., Šimurda, M., Wilson, S., Irvine, A., Ramsay, F., & Price, C. J. (2020). Understanding effect of filtration and washing on dried product: paracetamol case study. *Powder Technology*. https://doi.org/10.1016/j.powtec.2020.02.064

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Chris Price is an EPSRC Manufacturing Fellow and Director of Knowledge Exchange based in Chemical & Process Engineering at Strathclyde University. His research is focused in two areas; enhancing purification during crystallization using ultrasound, and addressing the technology gap associated with continuous isolation (filtration washing and drying) of pharmaceuticals. He has been active in industrial crystallization for over 30 years, mostly in the pharmaceutical industry. Chris is a Fellow of the Royal Society of Chemistry and a chartered chemist and holds a BSc in Chemistry from York University and, MSc and PhD degrees from Manchester University.