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UNDESIRED AGGLOMERATION IN AGITATED FILTER DRYERS: A CRITICAL REVIEW

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Abstract

Agitated filter dryers (AFDs) are commonly used in many industries, however the mechanisms driving undesired agglomeration remain poorly understood. Undesired agglomeration can have several consequences, including out of specification product, equipment damage, additional downstream processing and increased cycle times and cost. This review explores the influence of key material and process parameters on agglomeration in AFDs, highlighting the lack of mechanistic understanding that has hindered the development of accurate predictive models.

To address this, insights from wet granulation are applied to propose a novel mechanism consisting of three rate processes governing agglomeration during agitated drying: (1) formation of loosely bound agglomerates, (2) consolidation and coalescence, and (3) solidification of liquid bridges. The review examines how various parameters influence each rate process in this mechanism, offering a more predictive framework for agglomeration behaviour.

Additionally, existing modelling efforts for AFDs are reviewed, revealing that many studies focus on heat transfer while neglecting agglomeration. Comparisons with wet granulation models highlight opportunities to integrate established agglomeration and scale-up approaches into AFD models. By advancing the mechanistic understanding, this work aims to improve prediction, control, and scalability of agglomeration in agitated drying.

1. Introduction

The manufacturing of active pharmaceutical ingredients (API) is a lengthy process with many downstream processing steps involved after crystallisation, such as filtration, washing and drying (Figure 1). It is important to streamline these steps to avoid affecting the API properties achieved during crystallisation. Drying is typically the last step in the manufacturing process and is required to lower the solvent content to acceptable levels but is often a bottleneck in the overall manufacturing process.[1] To improve the efficiency of this, agitated filter dryers (AFDs) are commonly used and non-agitated drying is typically no longer used for large scale manufacture.[2] This is because AFDs have the following advantages over non-agitated dryers, such as:

1. An improved rate of mass transfer leading to an increased drying rate.
2. An increase in shear stresses within the power bed leading to:
    a. Increased homogeneity
    b. Breakdown of agglomerates formed during the filtration stage.

However, these advantages need to be weighed against an increased potential for undesired agglomeration of primary particles during the drying stage. The formation of agglomerates and the resulting impact to final product properties are a common problem in many industries.[3] In this paper, we present a review of undesired agglomeration in agitated filter dryers.

Figure 1 - Pharmaceutical manufacturing process.[4]

Filtration and drying can be carried out in separate units, such as centrifuges for filtration followed by drying in dedicated equipment. However, AFDs can be used as an integrated solution, particularly in pharmaceutical manufacturing, allowing for filtration and drying within a single item of equipment. This integration eliminates the need for multiple handling steps, reducing product loss, and minimises the required floor space, resulting in a smaller physical footprint and a reduced capital investment.[5] Despite their widespread use, there remains a limited mechanistic understanding of the agglomeration processes occurring within AFDs, which can impact final product properties.

Filter dryers are typically equipped with an agitator, which can increase the efficiency of filtration, cake washing and drying by improving mass and heat transfer and enabling more homogeneous mixing. The agitator can be heated to allow particles to be periodically exposed to heated surfaces, which further increases the rate of heat transfer and leads to shorter drying times.[6] AFDs are often used in the pharmaceutical industry as they can operate drying under low pressure or vacuum conditions. Many APIs are heat sensitive and prone to degradation at high temperatures. Operating at low temperatures has typically resulted in long drying times, but working at low pressures allows for high levels of heat and mass transfer even at lower temperatures.

Ideally, the API should be dried without altering the physical properties imparted during crystallisation to ensure better control and suitability for downstream formulation. However, intense agitation and rapid moisture loss can cause particle agglomeration, attrition, or other modifications that impact drug performance. Undesired agglomeration can lead to out of specification products due to deviations in particle size, appearance, or residual solvent content, and may require further milling. It can also lead to difficulties in batch removal from equipment, longer cycle times, and, in extreme cases, damage to the equipment due to the formation of hard agglomerates.[7] Attrition of primary material can also occur as a result of agitated drying but is beyond the scope of this paper.

The exact causes and mechanisms underlying undesired agglomeration in AFDs are not yet fully understood. In this review paper, we will cover the construction and operating stages of AFDs (Section 2 and 3). Our proposed mechanism for undesired agglomeration is presented, drawing parallels between the wet granulation process and agglomeration in AFDs to develop a comprehensive understanding. The key parameters affecting each of the underlying rate

processes are discussed (Section 4). This is followed by a comprehensive review of the current modelling work on AFDs as well as advancements in modelling wet granulation (Section 5).

The existing literature on agglomeration in agitated filter dryers is critically reviewed, including the direct effect of changing material and process parameters. However, the focus of this review is to investigate the underlying rate processes and how they may interact, offering mechanistic insights into undesired agglomeration.

2. Construction of agitated filter dryers

A schematic of an AFD is shown in Figure 2, and the agitator can be lowered or raised as needed, and accommodate low and high speed rotations.[2] The agitator can be heated to enhance heat transfer, and the heated agitator contributes to roughly 45 % of the total energy input, with the vessel walls and filter plate providing 30 % and 25 % respectively.[6] Agitation can also aid in cake washing by smoothing out cracks in the wet cake to prevent channelling of wash solvents. To avoid disturbing the filter cloth, there is an offset between this and the agitator base, but this causes residual cake build-up, known as the heel.[2]

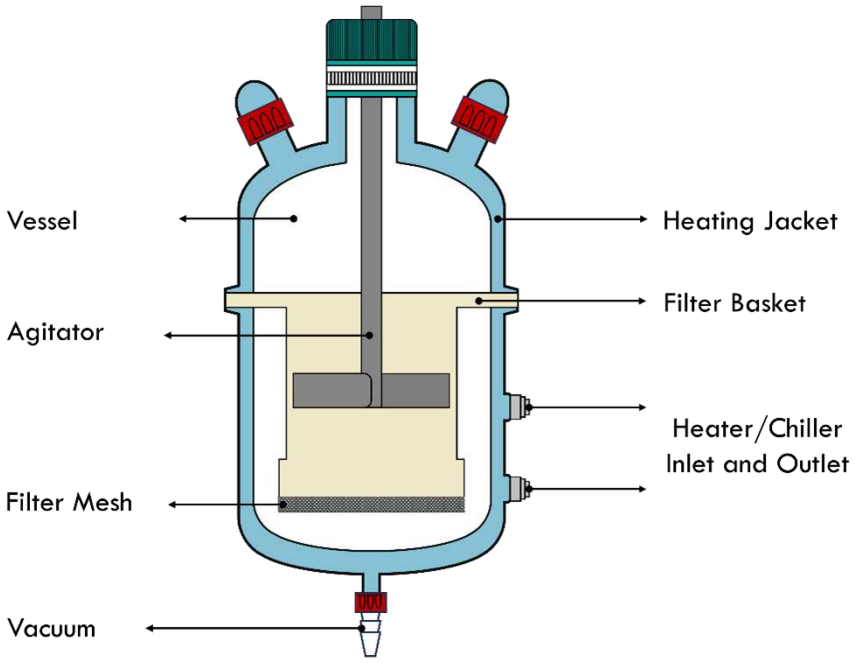

Figure 2 - Cross-sectional representation of a lab-scale agitated filter dryer (AFD).

AFDs are fitted with a jacket to provide heat for drying but this is also used to conduct filtration at various temperatures.[2] The heat is usually supplied by circulating heating fluid throughout the insulated jacket surrounding the vessel.[8] The slurry passes through the filter media above the filter plate and solids are retained. The most common filter media are filter cloths and

sintered metal screens.[9,10] These components can all be altered for specific functions, increasing the applicability of AFDs.

3. Operating stages of agitated filter dryers

An AFD tends to operate in three stages: filtration, washing and drying. These are discussed briefly in the following sections.

3.1 Filtration

Filtration is the process of separating solids from a liquid suspension by passing the slurry through a filter medium and applying a pressure gradient across the medium. The slurry is transferred into the AFD and given time to settle and form the powder bed before filtration.[3] Filtration occurs by creating a pressure drop across the filter medium, either by applying pressure above the cake or vacuum below it.

3.2 Washing

Following filtration, cake washing is typically conducted. This is to remove any impurities remaining but also remove the crystallisation solvent to acceptable levels. The level of solvent is of particular importance if increased solubility is expected at the drying temperature. By lowering the level of solvent, the redissolution of crystals in the solvent which can later form agglomerates is minimised.[11]

There are two primary types of cake washes, displacement and reslurry. Displacement washes pass a large volume of solvent through the wet cake to displace trapped crystallisation solvent and are preferred for insoluble contaminants.[2,12] Reslurry washes involve adding fresh wash solvent and agitating the wet cake to form a slurry which is filtered. This is preferred for soluble impurities, and results in less cake cracking.[12] Using both displacement and reslurry washes gives the highest purity, and a washing sequence of displacement, reslurry, displacement is often used in agitated vessels.[2]

3.3 Drying

Following filtration and washing, the cake can be dried within the same equipment. There is often a nitrogen or cold air blow through to reduce the moisture content of the wet cake before drying.[7] Drying occurs primarily by contact drying where heat is transferred to wet solids from heated surfaces such as heated vessel walls, agitator and filter plate. Contact dryers are

useful in pharmaceuticals where many APIs and excipients are heat sensitive and prone to degradation.[13] They also operate under vacuum and vacuum conditions can lower the boiling point of solvents.[7] Contact heating from heated surfaces coupled with agitation and vacuum produces dried solids with low moisture contents. Once dried, the cake is discharged through the discharge port and the agitator is slowly lowered to facilitate this.[2]

Agglomeration during drying is a widespread problem in AFDs. AFDs commonly use heated agitator blades, enhancing heat and mass transfer, resulting in more uniform drying.[14] However, this agitation contributes to agglomeration or attrition (breakage). Agglomeration during drying occurs when particles with residual solvent become bound during agitation. As solvent evaporates, a viscous API solution film forms around the particles. Upon evaporation, the viscous film forms crystalline bridges, cementing the agglomerates.[15]

4. Parameters affecting agglomeration in agitated filter dryers

Although agglomerates are only characterised after drying, there are many parameters in the filtration and washing regimes that may encourage agglomeration. The key parameters influencing agglomeration are shown in the Ishikawa diagram in Figure 3.

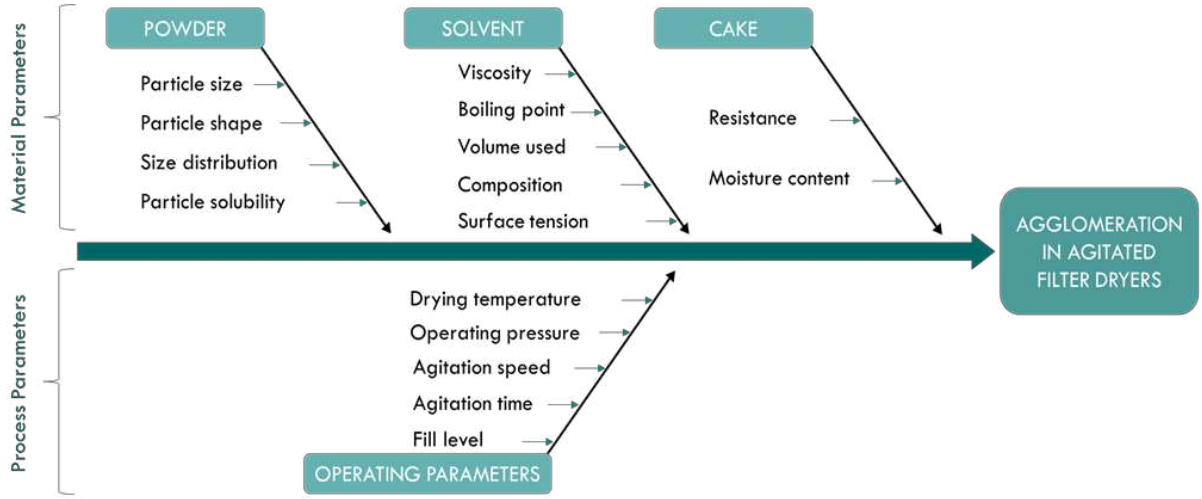

Figure 3 – Ishikawa diagram of different parameters influencing agglomeration in agitated filter dryers – modified from Tamrakar *et al.*[14]

Due to a lack of understanding of the rate processes involved, these studies mainly report correlations between experimental conditions and resulting agglomeration. In this review, we propose the underlying mechanisms of agglomerate formation. To do this, we drew parallels between agglomeration in AFDs and wet granulation.

Wet granulation is a particle size enlargement technique that involves agglomerating particles into larger granules where the original particles are still distinguishable.[16] This is achieved by spraying particles with liquid binder over an agitated particle bed, where the liquid binds particles together through capillary and viscous forces. This is an important unit operation used in many industries including pharmaceuticals where the aim is to produce larger granules.

Wet granulation is commonly described as a combination of three rate processes (Figure 4).

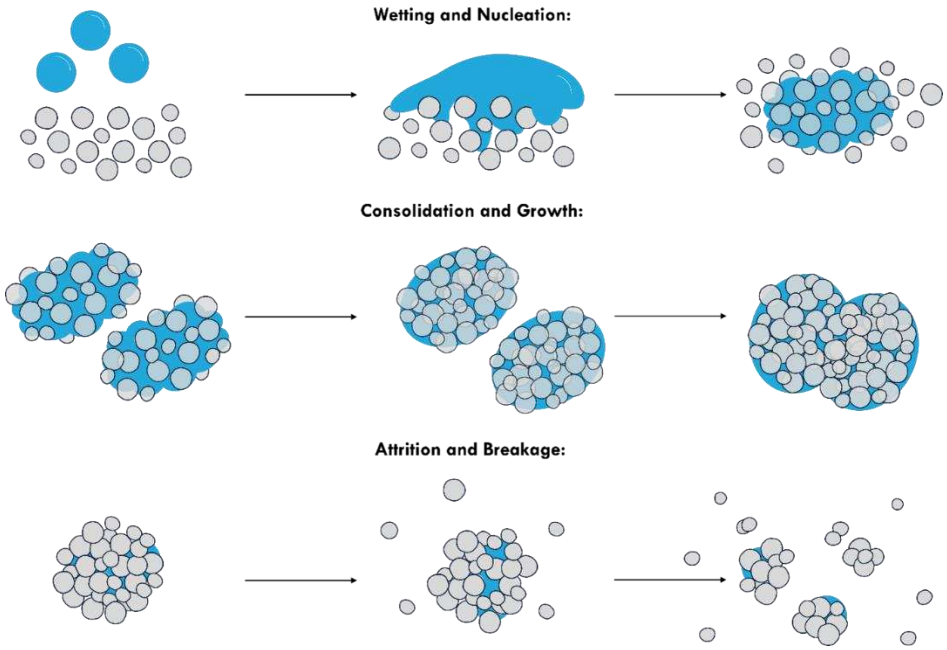

Figure 4 - Wet Granulation Mechanism reproduced.[16]

Wet granulation is a well-established field, and this existing knowledge can be used to guide AFD operations due to their similarities.[15] Wet granulation aims to take a dry solid, which is then wetted and agitated to form granules. In contrast, drying in AFDs starts with a damp solid, and solvent is removed while agitating the wet cake, but agglomeration is undesired in this process (Figure 5).

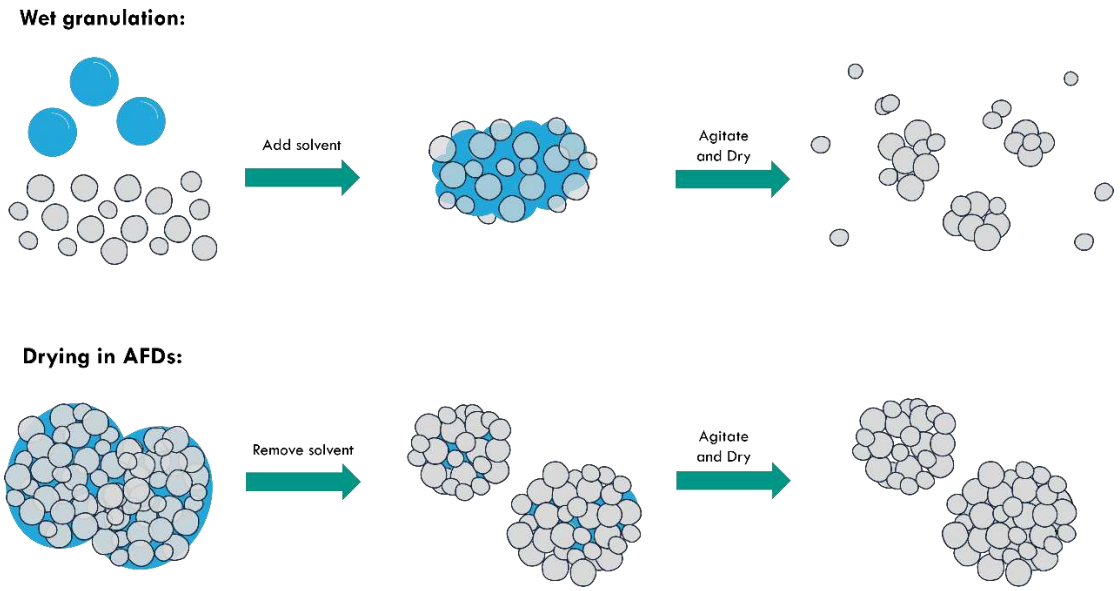

Figure 5 - Contrasting wet granulation to drying in AFD.

In this review, we propose the rate processes governing undesired agglomeration during agitated drying to be:

1) Formation of loosely bound agglomerates

The slurry produced during crystallisation is filtered and typically deliquored to form a wet cake (or filter cake). Within this wet cake, there are loosely bound agglomerates, and the extent of their formation depends on the efficiency of the filtration and washing procedures.

2) Consolidation and coalescence

Agitation of these wet solids encourages initial consolidation of agglomerates followed by growth by coalescence and/or layering.

3) Solidification of liquid bridges

Wet agglomerates are subjected to agitation during drying, and those able to withstand these shear forces will experience evaporation of solvent from these liquid bridges resulting in solid crystalline bridges cementing the agglomerates.

These proposed mechanisms are discussed in detail in the following sections.

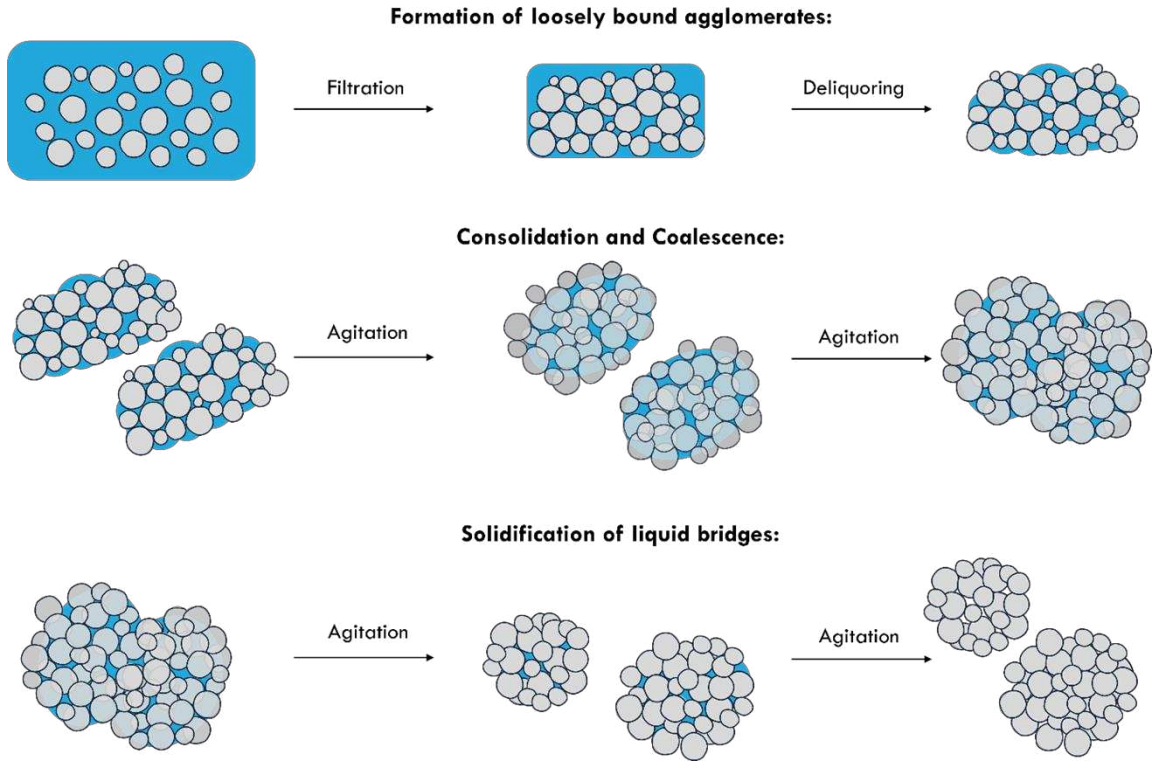

Figure 6 - Proposed mechanism of undesired agglomeration.

4.1 Formation of loosely bound agglomerates

The wet cake is formed during the filtration step but may be reformed after the washing step. Poor filtration and washing result in wet cakes with higher moisture content, increasing contact between the crystallisation solvent and crystals, which promotes the formation of liquid bridges. These liquid bridges lead to loosely bound agglomerates that act as nuclei for further agglomerate growth. The size of these agglomerates and the strength of liquid bridges influence agglomerate growth and resistance to shear forces from agitation. Therefore, the properties of these initial agglomerates impact the overall agglomeration at the end of the drying process. Key parameters that influence the properties of the resulting wet cake during both filtration and washing are discussed.

4.1.1 Filtration rates

Filtration theory is well established and more in-depth explanations of the parameters affecting the filtration performance can be found in studies by Wakeman and others.[2,17,18] These studies are useful for designing AFD processes with efficient filtration where the filter cake is deliquored to low moisture contents, particularly in the absence of a washing procedure. The key parameters that influence filtration performance and properties of the resulting wet cake can be classified as particle and solvent properties and a brief overview is given in Table 1.

Table 1 - Summary of effect of particle and solvent parameters on filtration rates.

Parameter	Effect on filtration rate
Particle Size	By having larger particles, the solvent can readily flow through the openings in the cake, resulting in lower specific cake resistance and better filtration rates. [17,19]
Particle Size Distribution (PSD)	Having a narrow PSD is ideal for lower cake resistance and greater filtration rates as the filter cake has more open voids for solvent flow. When the PSD is wide, finer particles fill the gaps between larger particles, resulting in higher resistance to solvent flow. [20–22]
Particle Shape	Particle shapes with greater aspect ratios such as needles result in high specific cake resistance and poor filtration rates. [17,22]
Solvent Viscosity	Low viscosity crystallisation solutions will have less resistance passing through cake pores and this results in better filtration rates. [21,23]

The parameters in Table 1 and their effect on filtration rate and cake resistance is significant due to the consequence of slow filtration rates. High cake resistance gives slow filtration rates which results in longer period of contact between the crystallisation solution and crystals. This can enable the formation of liquid bridges between particles in the wet cake, which solidify upon drying to give agglomerates.[15,21] Even though agglomeration occurring in AFDs is commonly attributed to the drying process, these findings indicate that agglomeration may be initiated much earlier during downstream processing. This emphasises the need for more meticulous design of filtration processes to not only improve filtration times but reduce the possibility of agglomeration occurring.

4.1.2 Design of washing procedure

The reduction in agglomeration as a result of washing was clearly shown by Löbnitz *et al.* when looking at *L*-phenylalanine crystals washed with ethanol.[24] Figure 7 shows a clear reduction in the number of agglomerates when washed with ethanol compared to the unwashed filter cake, due to the crystallisation solvent being replaced by ethanol. By preventing and/or reducing the formation of strong liquid bridges within the wet cake, agglomeration can be reduced. When designing an optimal washing procedure, various parameters must be

considered to minimise the potential for agglomeration to occur and these will be discussed in the following sections.

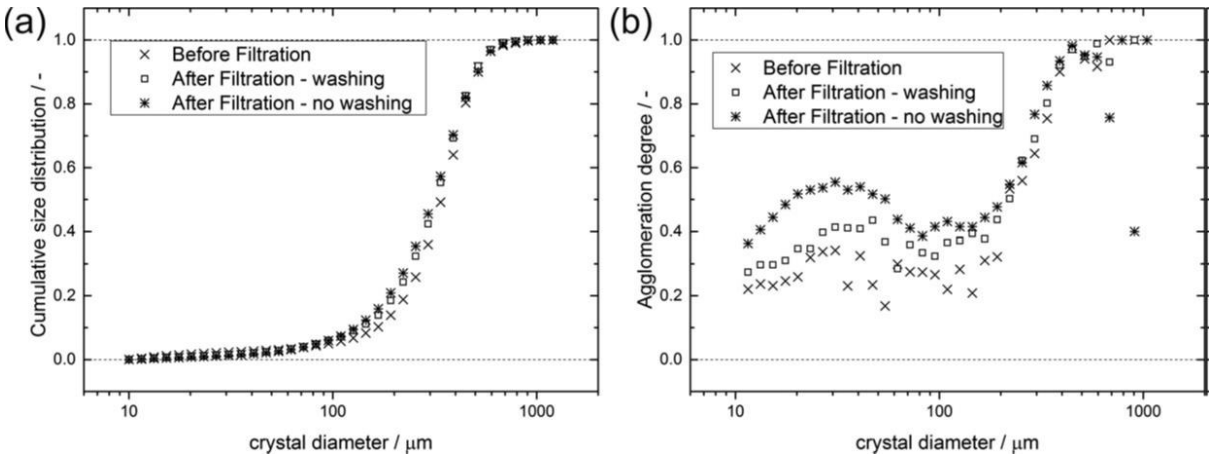

Figure 7 – (a) the PSD and (b) agglomeration degree (AgD) of *L*-phenylalanine before and after filtration with ethanol wash. [24]

4.1.2.1 Solubility of API in the wash solvent

The solubility of the product in the solvent should be minimal to prevent dissolution of the crystals and product loss during washing.[2,25] High solubility of the API in the solvent promotes agglomerate formation and this was investigated by Birch and Marziano.[26] Compound A, was washed with four solvent systems of varying solubility and at lower solubilities, there was not only a reduced likelihood of agglomeration but agglomerates were also more friable. Ottoboni *et al.* investigated the effect of various wash solvents on the extent of agglomeration and agglomerate brittleness index (ABI) for paracetamol (Table 2).[21] The greatest extent of agglomeration was seen for isopropyl acetate in which paracetamol is highly soluble, whereas the least agglomeration was seen with cyclohexane in which paracetamol has a low solubility. Figure 8 highlights the striking difference between the two samples. The ABI was also calculated which is a qualitative measure of agglomerate strength using successive cycles of sieving.[26] The highest API solubility was in acetonitrile, which produced the hardest agglomerates as shown by the ABI value in Table 2 and images in Figure 8. The increased solubility allows for more liquid bridges with dissolved API which solidify upon drying to form hard agglomerates. However, the solubility of impurities present should be high to be removed efficiently. A low solubility may facilitate impurities crystallising with the product crystals.[11]

Table 2 - Agglomerate characterisation for paracetamol with various wash solvents.[21]

Wash solvent	Extent of agglomeration (%)	ABI index
n-heptane,	91.42	**0.223**
Isopropyl acetate	**99.48**	0.113
Toluene	95.52	0.146
Anisole	95.33	0.19
Dodecane	94.59	0.111
TBME	92.57	0.127
Cyclohexane	**87.57**	0.218
4-methylpentan-2-one	95.47	0.197
Acetonitrile	98.29	**0.066**

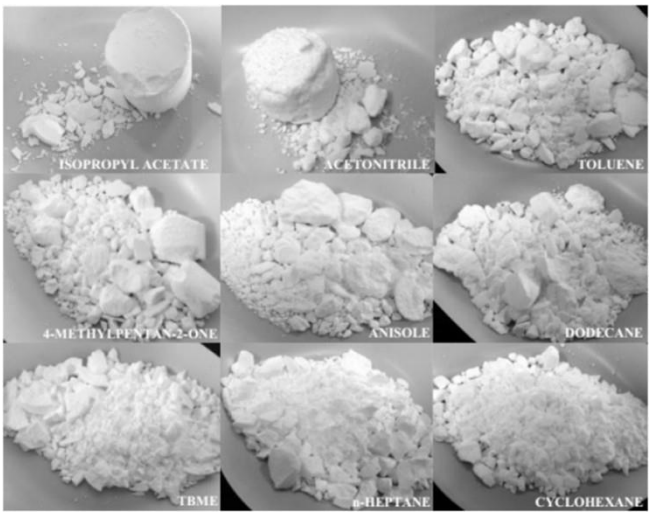

Figure 8 – Images of paracetamol agglomerates produced with different wash solvents.[21]

It is crucial to minimise the solubility difference between the crystallisation and wash solvents to avoid an anti-solvent effect. This results in precipitation of the product with high impurity, which can lead to extensive agglomeration.[27] Although this is a useful tool in anti-solvent crystallisation, controlling it during washing can be challenging, especially if a large volume of crystallisation solvent remains, potentially resulting in significant agglomeration. Shahid *et al.* compared paracetamol isolated from three different crystallisation solvents (ethanol, isopropyl alcohol and isoamyl alcohol) with three wash solvents (heptane, acetonitrile, and isopropyl acetate).[27] Paracetamol has the lowest solubility in heptane and using this as the wash solvent resulted in precipitation regardless of the crystallisation solvent used. This anti-solvent effect is to be expected given the large solubility difference between heptane and the

crystallisation solvents. One way to mitigate this is to first perform an initial wash with the crystallisation solvent before introducing a wash solvent (i.e., an anti-solvent).

The effect of solvent solubility on agglomeration behaviour is not always clear. Lim *et al.* investigated two food grade model powders and an API with four different wash solvents and observed significantly reduced agglomeration for sodium hydrogencarbonate ($NaHCO_3$) with reduced solubility.[3] The API intermediate investigated had 82 wt % agglomerates regardless of the solvent system. Both calcium carbonate ($CaCO_3$) and the API are only sparingly soluble in water, but extensive agglomeration was observed suggesting a different underlying agglomeration mechanism to liquid bridges forming. Agglomeration was reduced when washing $CaCO_3$ with binary solvents, possibly due to the reduced surface tension. Therefore, solubility of the API in the solvent may not be the only solvent parameter influencing liquid bridge formation and subsequent agglomeration.

4.1.2.2 Viscosity of the wash solvent

Various approaches are used in the pharmaceutical industry for the washing procedure, with some using the same solvent from crystallisation. However, wash solvents often have a lower viscosity than the crystallisation solvent, allowing them to penetrate smaller capillaries within the cake more effectively and displace the crystallisation solvent.[28] To achieve effective displacement, the contact time with the wash solvent must be sufficient and low viscosity wash solvents tend to pass through the wet cake rapidly.[27] Additionally, if there is a large viscosity difference between crystallisation and wash solvents, the less viscous wash solvent would preferentially travel through any cracks or passages between particles as opposed to forcing out the crystallisation solvent.[29]

Tamrakar *et al.* suggested the wash solvent's effect on agglomeration may be due to solvent viscosity, contrasting previous literature which indicate that the solubility is the most influential factor.[7] Micronized acetaminophen (APAP) exhibited greater solubility in methanol but formed more agglomerates with ethanol, which were also more resistant to the agitation. The authors attributed this to ethanol's higher heat of vaporisation and boiling point which allows it to remain at a higher moisture content, as well as its higher viscosity. This resulted in the formation of strong solid bridges, as demonstrated by the agglomerates increased yield strength. Solvent viscosity can impact the deliquoring of wet cakes with more viscous solvents deliquoring less efficiently and resulting in solvent retention.[30] However, the viscosity difference is minimal and so it is difficult to conclude that viscosity is the dominating factor

for the agglomeration behaviour observed. The effect of viscosity was also highlighted by Zhang *et al.* when investigating Compound A, which was tested in two solvent systems of methanol/water and isobutyl acetate/heptane using mixer torque rheometry (MTR).[31] MTR gives torque measurements at various solvent contents, indicating the resistance of the mixing blades to movement through the wet solid. Surprisingly, the results indicated a significantly higher agglomeration potential for Compound A in the methanol/water system, despite Compound A's solubility being approximately five times higher in isobutyl acetate/heptane. This could be due to the methanol/water system exhibiting not only a higher viscosity but increased surface tension.

As suggested by Tamrakar *et al.*, the properties of the wash solvent might be the most crucial and controllable parameter to reduce agglomeration during agitated drying.[7] However, the existing literature on the effect of solvents on agglomeration shows disparities and needs further research. This shows the need to move away from viewing agglomeration in AFDs as a function of various parameters and instead identify the underlying rate processes for a better understanding.

4.1.2.3 Particle size

The effect of particle size on washing performance is analogous to the effect on filtration. Larger particle sizes have lower cake resistance and allow a higher flow rate of wash solvent. Conversely, small particles have smaller pore networks, and the wash solvent has a much lower flow rate. This results in a prolonged period of contact between the API particles and the solvent, and these liquid bridges facilitate agglomeration upon drying.[17] However, Shahid *et al.* demonstrated that smaller particles also run the risk of being lost during washing. Compared to the granular paracetamol, the micronized and crystalline material have a larger surface area and hence are more likely to dissolve during the washing process. [29]

4.2 Consolidation and coalescence

As the wet cake is agitated during the drying process, the particles and agglomerates collide with each other, the vessel walls and impeller allowing them to consolidate. This results in smaller, more dense agglomerates. In some cases, this can also squeeze solvent from within the agglomerate to the surface. The presence of wet surfaces then encourages coalescence of agglomerates. In this work, we consider type II coalescence, where colliding particles come into contact for a finite time, and a bond is formed. The coalescence is only permanent should the bond be able to resist the shear forces from collisions and agitation.

4.2.1 Moisture content of wet cake

Numerous studies have highlighted the relationship between the moisture content of the wet cake before agitation and the extent of agglomeration. This is due to agglomerates forming by liquid bridges, which is dependent on the amount of solvent. The moisture content defines the saturation state of the agglomerates, which transition through the various states with increasing moisture (Figure 9).[16] In the pendular state, particles are held together by lens-shaped rings of liquid (i.e. liquid bridges). Increasing the moisture results in a more continuous network of liquid, which is the funicular state. When the particles are fully saturated and all pores are filled, the capillary state is reached. The droplet stage is when the particles are held within a liquid drop. Using MTR to investigate these saturation states has shown that the torque peaks when particles are within the capillary state. [26,32] This moisture content is known as the 'sticky point' at which agglomeration is most likely, and this varies for different solid/solvent systems. The combined effect of capillary forces peaks at the sticky point so agitation would promote agglomeration.[26]

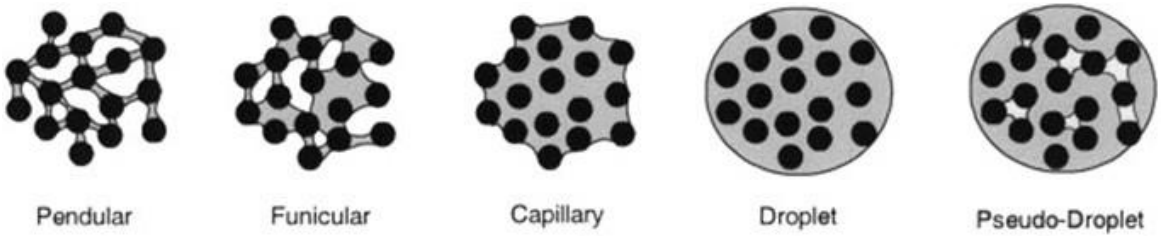

Figure 9 - States of liquid saturation for agglomerates.[16]

As MTR gives a measure of torque at different solvent contents, it is often used to determine the sticky point so agitation can be avoided until the moisture content is lower than this value. This has been experimentally validated by various researchers who observed increased agglomeration when the wet solid was agitated at or beyond the sticky point.[15,32] Shin *et al.*

used MTR to investigate an AbbVie compound (ABT-089) where torque readings at various moisture contents were validated by characterisation of the dry agglomerates.[32] This allowed them to define a 'risky zone' for the compound, as shown in Figure 10, which describes moisture contents of the sticky point and higher, which also corresponds to a change in granule saturation from funicular to capillary state. The sticky point is not only important to assess optimal moisture content but also gives an indication of the hardness of agglomerates, relative to the maximum torque value. However, using a sieving method can be more accurate and straightforward. The percentage of the initial mass sieved that is retained by the sieve also indicates the extent of agglomeration.[26]

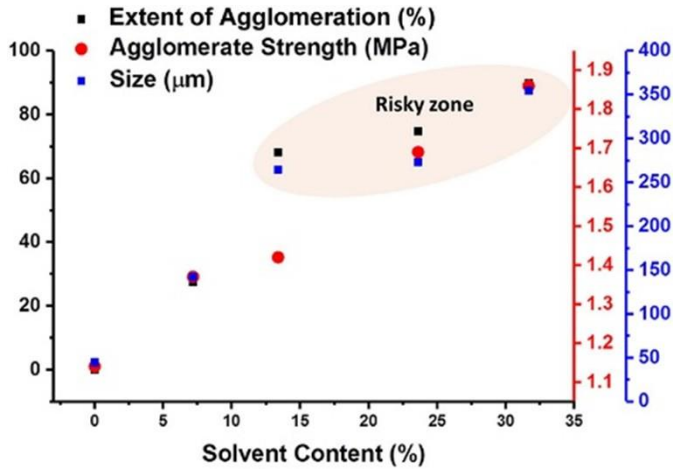

Figure 10 – The variation in extent of agglomeration, agglomerate strength, and size as a function of the solvent content.[32]

Zhang and Lamberto probed the validity of MTR as a useful tool by using an acoustic mixer. The results from MTR were not only in agreement with the acoustic mixer but also pilot plant data.[31] In lab scale experiments, the torque was measured as increasing amount of solvent was added to the powder bed, but at pilot scale the torque was recorded as the wet cake dried. Despite this difference, the torque profiles for both showed good agreement, with both having a maximum torque at a loss on drying (LOD) of 38 %, validating the use of MTR. However, MTR experiments function as a guide but do not fully simulate agitated drying. It gives a measure of the potential to agglomerate when a wet mass is agitated but is not definitive. Some materials show a high propensity for agglomeration but are deliquored well and have a low moisture content prior to drying, showing little agglomeration upon scale-up. For better accuracy, MTR data should be used alongside the moisture content post filtration to assess the risk of agglomeration, particularly upon scale-up.[15]

Birch and Marziano measured the sticky point of different particle sizes of the same compound with solvent and observed that smaller particles required larger amounts of solvent to reach the sticky point.[26] The capillary forces act on a larger surface area and smaller particles need more binder to achieve the same capillary forces as larger particles. This highlights the variance of the sticky point with different particle sizes, even in the same solid/liquid system. However, the sticky point and the relationship between moisture content and extent of agglomeration has been well researched on both lab scale equipment and pilot plant AFDs.[15,33]

4.2.2 Solvent viscosity

Ottoboni *et al.* showed that the solvent viscosity has a knock-on effect on the residual moisture content prior to drying, with more viscous solvents resulting in greater solvent retention in the wet cake.[21] By having more wet surfaces, this not only increases particle mobility for consolidation but also facilitates coalescence of agglomerates. Viscous solvents are also effective in dissipating kinetic energy of collisions, which also promotes coalescence. The effect of solvent viscosity is a complex phenomenon as observed with Avicel, a microcrystalline cellulose, which was wetted with both water and isopropyl alcohol. Despite having a low solubility in both solvents, Avicel demonstrated a greater potential for agglomeration in water, the less viscous solvent, and this was confirmed experimentally.[15] However, this may not be due to the viscosity difference but rather the swelling behaviour often seen with Avicel in water. More investigation is required for a more comprehensive understanding of the interplay between solvent properties such as solubility and viscosity to be able to predict agglomeration more accurately.

4.2.3 Solvent surface tension

Solvents with high surface tension, such as water, may encourage more and stronger liquid bridges due to their hydrogen bonding ability, leading to increased agglomeration. Lim *et al.* found that using a binary solvent mixture with a lower surface tension reduced the agglomeration of calcium carbonate ($CaCO_3$).[3] The reduced surface tension can modify the critical moisture content (CMC) or ‘sticky point’ and reduce agglomeration, as well as agglomerate strength. The correlation between the surface tension of the solvent and agglomeration for $CaCO_3$ can be seen in Figure 11. This finding was further supported by Zhang and Lamberto who used MTR and observed that solvents with high surface tension resulted in higher torque readings, indicating a higher risk of agglomeration during drying.[31] This effect has also been reported in wet granulation literature, where although reducing the surface tension may increase the rate of consolidation, the extent of this is lower.[34]

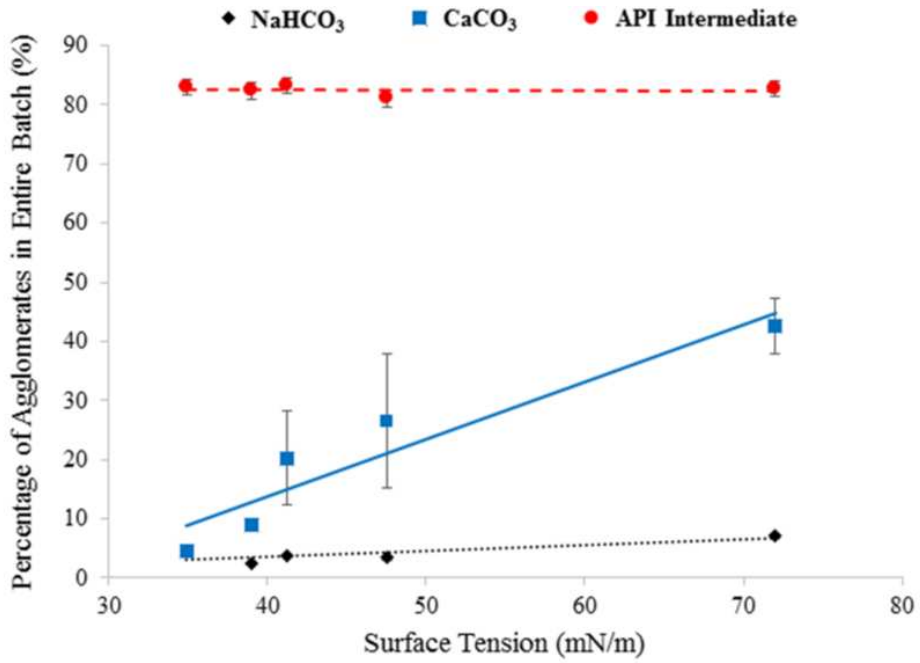

Figure 11 – Effect of increasing surface tension on agglomeration of $NaHCO_3$, $CaCO_3$ and an API intermediate.[3]

A different study examining the effect of eight different solvents on a Takeda API showed no correlation between viscosity or surface tension and the agglomeration potential.[35] This may be due to the contrasting effects of reducing surface tension on consolidation and coalescence. Although it may increase the consolidation, it results in agglomerates with weaker bonds, which therefore reduces the chance of permanent coalescence.

4.2.4 Particle size

The effect of particle size on solvent retention was discussed in the previous section, and as a result of poor solvent removal, smaller particles tend to stay wetter which naturally facilitates both consolidation and coalescence. Smaller particles also tend to agglomerate due to a greater contact area with the solvent allowing liquid bridges to form.[36] This was observed by Papageorgiou *et al.* when coarse (d_{10} = 4.6 µm, d_{50} = 14.1 µm, d_{90} = 40.5 µm), fine (d_{10} = 2.5 µm, d_{50} = 6.2 µm, d_{90} = 13.8 µm) and micronized (d_{10} = 0.4 µm, d_{50} = 1.9 µm, d_{90} = 4.3 µm) grades of a Takeda API (TAK-117) were compared. As seen in Figure 12, the micronized API had the lowest friability and hence exhibited the highest potential for agglomeration. This behaviour has been reported in wet granulation literature where small particles produce very strong granules that do not deform and cannot coalesce with other granules unless there is solvent available at the surface.[37] A blend of 75 % coarse API and 25 % micronized API was also investigated, and this showed a significantly higher agglomeration risk compared to the

coarse API. This demonstrates how even a small number of fines can exacerbate agglomeration.[35] The presence of finer particles leads to less void space and higher compaction, resulting in higher cohesion between particles, and potentially cake hardening and heel formation. Therefore, wide PSDs are not ideal when aiming to minimise agglomeration.[15]

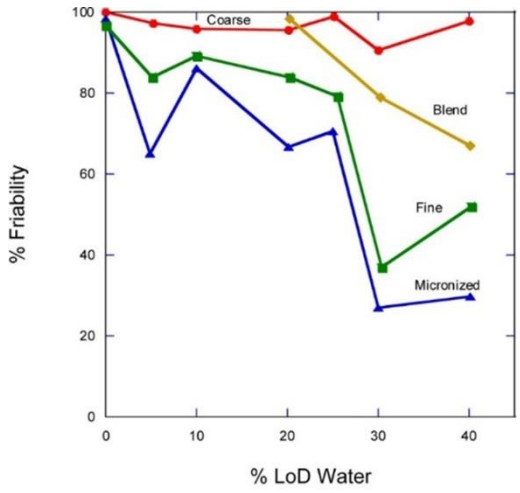

Figure 12 – Effect of particle size on agglomerate friability for Takeda API TAK-117 with water.[35]

4.2.5 Particle shape

Agglomeration is greatly influenced by crystal properties including morphology, and it was shown by Schæfer that interlocking between plate or needle morphologies often results in weak agglomerates.[38] Irregularly shaped particles such as needles are sensitive to attrition and more likely to be broken down whereas spherical particles are less prone to attrition or breakage.[7,39] However, a mixture of needle or plate crystals with spherical crystals generates stronger agglomerates, with the strength increasing as a function of shape irregularity.[38] This is because coarse, irregular particles increase the internal friction of the packed bed and reduce the flowability, resulting in poor mixing. This leads to increased solvent retention which encourages consolidation and coalescence of agglomerates.[14]

4.2.6 Agitation time

By agitating the wet cake, consolidation and coalescence of agglomerates are promoted. However, agitating for prolonged periods may result in breakage or fragmentation. This can be seen in the work by Tamrakar *et al.* where the median particle diameter reaches a peak at approximately 7 minutes into the 24-minute agitation period, for moisture contents of 5, 15 and 25 %.[7] Further agitation results in breakage of agglomerates. However, there may be an upper

limit for this as reported for carbamazepine dihydrate, where there is an increase in breakage for up to 20 minutes agitation, but further agitation for 40 minutes shows no further breakage.[40] This may be due to smaller crystals being harder to break. This is also seen in the wet granulation literature where some authors report larger granules with increased wet massing times, whilst others observed a decrease in granule size.[41–43]

4.3 Solidification of liquid bridges

The drying stage in AFDs is most commonly associated with undesired agglomeration, as it is during the post-drying phase that agglomeration is typically characterised. Drying involves simultaneous heat and mass transfer and is influenced by a multitude of material and process parameters. This complex interplay of powder, solvent and equipment parameters has resulted in significant challenges in predicting drying performance. Kemp and Oakley have even gone as far to describe drying as the 'the graveyard of academic theory' due to the lack of accurate, predictive models.[44] The reported effects of various material and process parameters on the final rate process, solidification of liquid bridges, are discussed in the following sections.

4.3.1 Particle solubility in solvent

Although the choice of crystallisation and wash solvents and the influence of the particle solubility has been discussed in the previous sections, it is essential to consider how solvent selection affects the drying process itself. The solubility of the solids in the solvent/solvent mixture influences agglomeration. When solvent is removed during drying, any compounds dissolved in the solvent will precipitate, potentially forming solid bridges that facilitate agglomeration. The greater the solubility of solids in the solvent, the more likely solid bridges will form.[7] When particles have a high solubility in the crystallisation solvent, the agglomerates formed also tend to be harder and difficult to break.[21]

4.3.2 Boiling point of solvent

The agglomeration of wet particles is usually facilitated when the residual solvent around the particles becomes more viscous during drying, and this viscous film binds the particles together.[45] However, solvents with low vaporisation enthalpies and boiling points evaporate quickly and do not allow this to occur. This was seen by Tamrakar *et al.* when investigating the use of four different solvents (methanol, ethanol, water and acetone) with APAP.[7] The lowest vaporisation enthalpy and boiling point was for acetone, and the APAP/acetone samples showed the least agglomerate growth. Solvents with higher boiling points require longer drying times which prolongs the time in which the wet cake is agitated. This promotes solid bridge formation and was observed in the drying of APAP with ethanol and methanol, where the APAP/ethanol system resulted in more agglomeration. The boiling point of ethanol is higher and allowed the system to remain at a higher moisture content resulting in worsened agglomeration.[7] This highlights the importance of considering solvent boiling points when designing an optimal drying process.

4.3.3 Solvent composition

Multicomponent solvents are used to reduce the surface tension and particle solubility and remove impurities more effectively in filtration. It is important for solvents to have similar boiling points to reduce agglomeration as otherwise, one solvent may become more enriched in drying. If the particles have a higher solubility in this solvent, this can lead to dissolution and recrystallisation and bridging of crystals.[15] Also, if the wettability of the crystallisation solvent is high then the wash solvent needs a similar wettability to efficiently remove the crystallisation solvent and reduce agglomerate formation.[21]

Hydrophobic compounds have been shown to form agglomerates in aqueous systems, where the water molecules form hydrogen bonds with each other. This excludes the hydrophobic particles and leads to mutual attraction between them.[46] Research has shown that the surface hydrophobicity of particles has a linear correlation with the potential energy for hydrophobic attraction between particles and the degree of agglomeration.[47]

Lim *et al.* reported another interesting observation where alcohol washes not only reduced agglomeration but formed much weaker agglomerates. Alcohols such as ethanol form surface alcoholic functional groups such as ethoxy groups and this reduces hydrogen bonding between hydroxyl groups on the surface of the molecule.[48] Hydrogen bonds cannot form between terminal ethoxy groups of different particles, unlike water. This results in a steric effect where individual particles are prevented from being attracted to each other which inhibits agglomerate formation as no chemical bonds form between particles.[3] This is different to the agglomerate formation in water washes, where although bridging water molecules are lost during drying, the terminal hydroxy groups of particles are in proximity and form hydrogen bonds. As drying continues, chemical bonds are formed between the powder particles, resulting in agglomerates.[48] This is illustrated in Figure 13, highlighting the contrasting bonding interactions between water and ethanol washes.

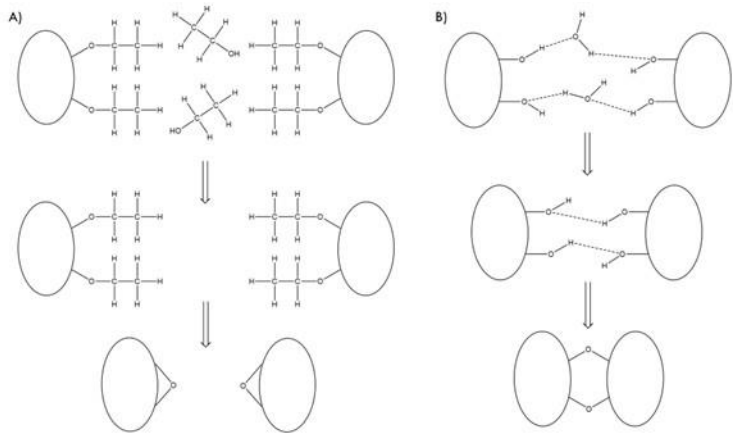

Figure 13 - Proposed mechanism for agglomerate formation in a) ethanol and b) water washes.[48]

4.3.4 Particle shape

Lekhal *et al.* investigated the drying behaviour of *L*-threonine (needle shaped) and potassium chloride (cubic) and observed different relationships between the critical moisture content and agglomeration.[33,39] While the critical moisture content for potassium chloride was consistent across batches, it showed variation for *L*-threonine with no single value for critical moisture content being established. This can be explained by the difference in particle shape and a wider PSD for *L*-threonine. Particle shape and size will influence the amount of solvent retained during the drying process and hence facilitating agglomeration at various moisture contents. However, these findings are limited to only two potential crystal morphologies and more work is needed to establish a more precise understanding of the relationship between particle shape and agglomeration during agitated drying.

4.3.5 Particle size

Experiments by Ottoboni *et al.* demonstrated that not only do micronized materials show increased agglomeration compared to original and granular API, but the agglomerates formed are much harder.[21] The increased hardness of these agglomerates makes them less susceptible to breakage by the shearing action of the impeller, in contrast to the softer agglomerates formed with the original API. The enhanced agglomerate strength for micronized material may be related to the increased surface area available for solid bridge formation during drying. However, further investigation is necessary to establish a definitive link, as the agglomerate strength will also have been influenced by the different crystallisation and wash solvents used and the particle solubilities. Unless these factors are isolated, it is difficult to confirm the effect of particle size alone on agglomeration behaviour.

4.3.6 Agitation speed

Lekhal *et al.* measured the moisture content as a function of time at different agitation speeds and drying times decreased at higher agitation speeds.[33] Similar drying rates were observed at lower agitation rates but at higher agitation rates, the drying rate increased. Agitation enhances heat and mass transfer by improving the mixing which increases the rate of drying.[39] The average diameter of particles decreased at higher agitation speeds. This suggests less agglomeration with increased agitation, due to greater shearing action and more particle collisions. At low agitation speeds, a higher fraction of larger particle sizes was observed after drying compared to before, as shown in Figure 14. This suggests that agglomeration is more prevalent at lower agitation rates as a result of the sample experiencing less shearing action from the impeller, and therefore solid bridges holding agglomerates together are less likely to break. The drying rates are also lower at lower agitation speeds which allows prolonged periods of contact between crystals, further increasing the likelihood of agglomeration.

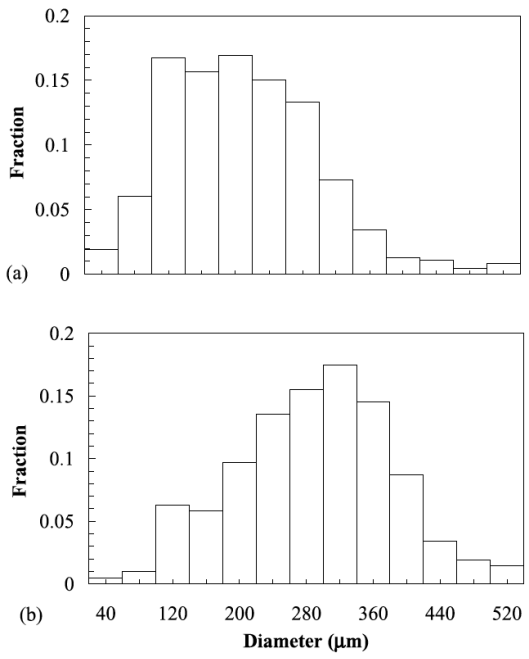

Figure 14 – Particle size distribution of *L*-threonine prior to (a) drying and (b) after drying.[39]

Sahni *et al.* observed a sharper decrease in solvent content at higher agitation speeds as well as a shift to the left in the PSD, indicating attrition has occurred.[5] Further analysis of the PSD suggested that more fines are generated at lower impeller speeds as attrition occurs. At higher agitation speeds, there are less fines produced, and fragmentation dominates. Several studies

have reported a decrease in particle size with increased agitation. [39,49] Schæfer *et al.* proposed that the agglomeration behaviour is a function of the impeller speed and power input.[50]

The impact of increased agitation speeds on agglomeration shows variation between materials as demonstrated by Lim *et al.*[3] Increasing the agitation speed fivefold led to a threefold reduction in agglomerates for $NaHCO_3$ but had a negligible effect on $CaCO_3$. For $CaCO_3$, some snowballing was observed as soon as agitation began, and although greater agitation helped to break down agglomerates into smaller fragments, it was not possible to completely remove agglomerates. This was also seen with carbamazepine hydrate crystals where the effect of increasing the agitation speed on the PSD was minimal.[40] This contrasts other studies where there is a significant change in the PSD with increased agitation and shows the importance of considering material properties. Some materials are sensitive to strain rate and likely to show a greater change in their PSD. Therefore, it is crucial to consider the strength of materials when investigating the effect of increased agitation. If the liquid bridges can withstand the shear forces of agitation, they will solidify upon drying and result in agglomerates.

4.3.7 Agitation time

The agitation time can also impact the extent of agglomeration. Experiments conducted by Tamrakar *et al.* showed an interesting trend in particle size distribution (PSD) over the agitation period for various moisture contents.[7] Even at 0 % moisture content, due to cohesive nature of the APAP powder used, agglomerates formed from the impeller agitation and these agglomerates maintained their size throughout the agitation period. However, for 5 to 25 % moisture content, the agglomerates showed almost identical behaviour of alternating increase and decrease in PSD span over the drying period, as shown in Figure 15. The initial nuclei formed will grow by layering of fines to a certain size, but the free solvent will evaporate as the drying continues, and only weak agglomerates will remain. These weak agglomerates subsequently break, resulting in a continuous cycle of agglomeration and breakage. This cyclic behaviour is evident in the larger PSD spans observed at higher moisture contents.

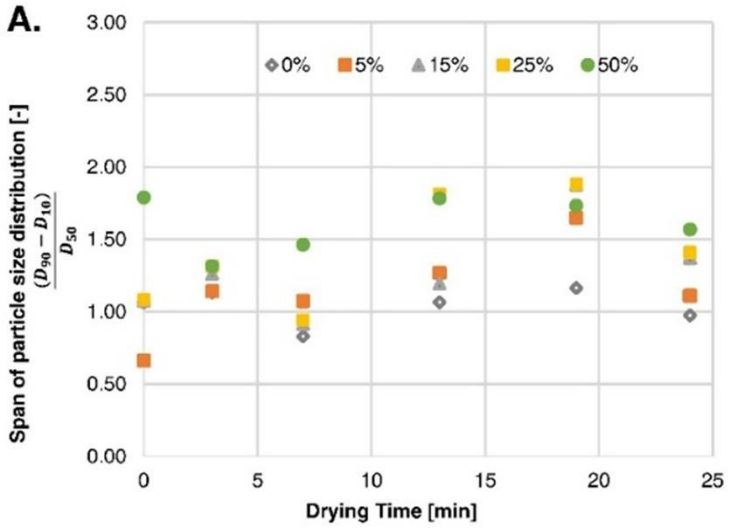

Figure 15 – PSD span of APAP-methanol samples over time at different L/S ratios.[7]

These results show good agreement with previous studies that also investigated the effect of agitation time on agglomeration.[39,51] However, to determine the underlying mechanisms occurring and apply these observations to various powder/solvent systems and drying conditions, more work is needed.

4.3.8 Drying temperature

Lim *et al.* reported an increase in temperature resulted in more agglomerates in the drying of $NaHCO_3$ and $CaCO_3$.[3] Drying at higher temperatures reduces drying time and minimises the particles' exposure to the agitator, allowing more liquid bridges to solidify during drying.[39] Agglomerates produced at higher drying temperatures are often stronger and require intense milling, as seen with potassium chloride in a study by Lekhal *et al*.[33] This is due to particles having a higher solubility at increased temperatures, allowing stronger solid bridges to form.

Contrasting effects were seen for $NaHCO_3$ where despite increased agglomeration at higher drying temperatures, the agglomerates formed were weaker.[3] This may be due to the surface crust formed on agglomerates being thicker and denser because of increased dissolution of solids. At higher drying temperatures, there will be significant stresses within agglomerates as they shrink due to moisture evaporation. A thick dense crust will be unable to shrink, resulting in cracking of the agglomerates, hence reducing their strength.[39] There was also no significant change in the strength of $CaCO_3$ and API intermediate agglomerates investigated at higher temperatures.[3]

There is a vast amount of literature on the effect of drying temperature on agglomeration, both in agitated dryers and other systems.[5,45,52,53] However, additional studies are required for

a more comprehensive understanding of how drying temperature can affect the agglomerate strength, which will also determine if agglomerates are likely to be broken during agitated drying.

4.3.9 Operating pressure

Lower pressures are used to reduce drying times, but this faster rate of drying means particles experience less shear and agglomeration occurs. Lekhal *et al.* investigated the change in the average particle diameter of potassium chloride with temperature at three different pressures, as shown in Figure 16.[33]

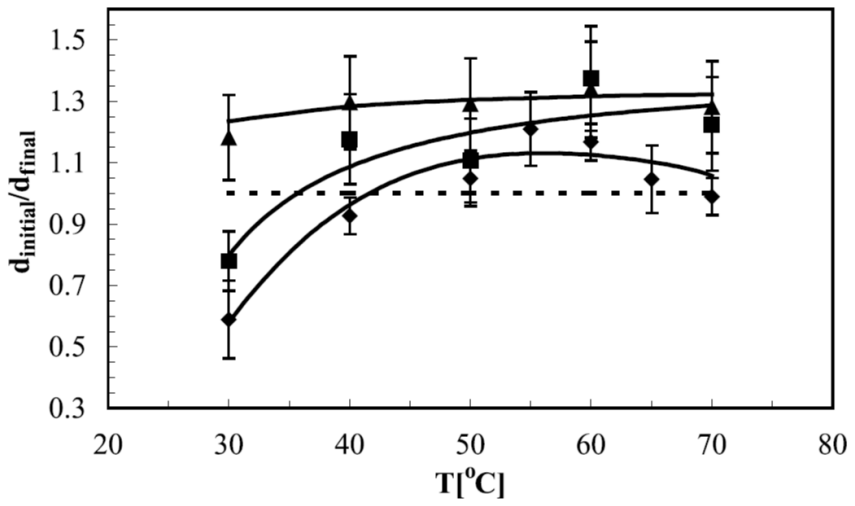

Figure 16 – Change in average diameter with increasing temperature at different pressures (♦ P =1 atm, ■ P=200 Torr, ▲P=80 Torr).[33]

It is evident that the average diameter experiences a general increase as the pressure is decreased, regardless of the temperature. However, this becomes less pronounced at higher temperatures where the drying rate is high and hence changing the pressure has minimal effects. However, at lower temperatures at approximately 30 °C, reducing the pressure switches the drying from a regime where attrition dominates to an agglomeration dominated regime. This transition can be attributed to the improved drying rates observed. As seen in Figure 16, when the pressure is very low (80 Torr), the average diameter has little variation with increasing temperatures. This phenomenon occurs as the low pressure means the liquid is boiling at any given temperature and the drying time is constant. Therefore, at very low pressures, the agglomerate size is independent of the drying temperature. Overall, the findings highlight the relationship between pressure, temperature, and average diameter. However, a significant limitation of this study is that it does not account for the potential variations in results based on

different particle properties, such as hardness. Therefore, further investigation is necessary to gain a more comprehensive understanding of the influence of pressure on drying processes.

4.3.10 Fill level

The fill volume of the dryer also affects agglomeration, and this was reported by Sahni *et al*.[5] At lower fill levels, narrower PSDs are seen alongside smaller average particle sizes. Lower fill levels allow more particles to experience the shearing action of the impeller as well as more particle-particle collisions. At higher fill levels, less particles encounter the impeller blades and there is an increase in particle size and a wider PSD. There is also a greater resistance to heat transfer which results in longer drying times. Also, the PSD for the highest fill level was bimodal due to attrition occurring near the impeller and agglomeration occurring above the impeller. Similar observations were reported by other authors who also observed reduced agglomeration at lower fill levels.[3,54]

5. Computational modelling of agitated filter dryers

Simulating drying processes and the resulting agglomeration (or attrition) has long been a challenging task due to the simultaneous heat, mass and momentum transfer. There is also no universal drying protocol for pharmaceutical compounds due to variations in the physicochemical properties of the wet cake.

The different approaches to modelling AFDs can be broadly categorised as continuous and discrete particle models and will be discussed in the following sections. The limited modelling work on AFDs and gaps in the work will also be outlined.

5.1 Continuous models

The continuous approach, developed by Schlünder and colleagues, is based on modelling heat penetration through a particle bed. This penetration model has significantly advanced our understanding of contact drying in mechanically agitated powder beds.[55–58] In this penetration model, the particle bed is considered as a quasi-continuous phase, and the mixing process is divided into a series of contact drying and mixing periods. During the hypothetical contact drying period (t_R), the agitated bed is assumed to be static, and a distinct drying front penetrates from the hot surface into the bulk. Any particles between the drying front and heated surface are considered dry whereas particles beyond the drying front are uniformly wet. The bed temperature is assumed to be uniform, and the bulk material is assumed to be perfectly mixed at the end of the contact time. The contact time (t_R) can be described as a function of the dimensionless mixing number (N_{mix}) and the inverse of the rotational frequency (t_{mix}):

$$t_R = t_{mix} N_{mix} \tag{3}$$

The mixing number is related to the Froude number and is also dependent on agitator type.[58] The penetration model states that the overall heat transfer coefficient, α, can be expressed as the sum of the inverse of the wall to first layer heat transfer coefficient α_{ws} and the heat transfer coefficient of the dry bed α_{bed}:

$$\frac{1}{\alpha} = \frac{1}{\alpha_{ws}} + \frac{1}{\alpha_{bed}} \tag{4}$$

There is extensive literature available on all the relevant equations and summaries of the penetration model developed by Schlünder and co-workers so this will not be repeated

here.[59,60] The widespread use of the penetration model can be attributed to its ability to be applied to various contact drying operations. It has been extended to various conditions such as vacuum drying, hygroscopic materials, drying under atmospheric pressure and drying paste like materials, and is widely covered in literature.[56–58,61–63]

Despite the prevalent use of continuous models, which are also an industry standard, there are several limitations to be considered. One caveat is the key parameters of the model, contact time (t_R) and the mixing number (N_{mix}), are not based on theory and are empirical. This particular limitation was addressed by Mollekopf by correlating the mixing number to the Froude number (Fr) as shown in Eq 5, where C and x are constants that vary for various dryer types.[58]

$$N_{mix} = CFr^x \tag{5}$$

The values of C and x were experimentally determined, and these values can be found in the literature.[60] However, it is important to note that the data available to Mollekopf was limited and was based on two tray dryers, two paddle dryers and a tray dryer. It is difficult to find values of N_{mix} for different applications as it will vary for different agitators and dryer type and size. The penetration model also does not account for the behaviour of particles and any inter-particle interactions and neglects the mechanics of particle motion.

5.2 Discrete models

The weaknesses of the penetration model can be addressed by using discrete approaches such as the discrete element method (DEM). In DEM, individual particles within a dryer can be simulated and it can resolve the motion of each particle as well as calculate temperature changes as a result of collisions. The key assumption of DEM is that the time step chosen in the simulation is small enough for the interaction force to only apply to adjacent particles. As DEM considers the properties of individual particles and their properties, it is a useful tool for modelling granular systems and discontinuous materials and addresses the limitations of the penetration model. A comprehensive review of DEM and its application in the pharmaceutical industry was published by Yeom *et al.* and can be consulted for further information.[64]

It is important to note that a key limitation of DEM is the computational time required for simulations, especially for systems like AFDs which contain trillions of particles. The computational time required can be expressed as a function of various properties, and the time

step (ΔT_{step}) between each iteration of the simulation is set to be less than the critical time step ($\Delta T_{critical}$). The critical time step is also referred to as the Rayleigh time step and can be calculated using Equation 6:

$$\Delta T_{step} < \Delta T_{critical} = T_{Rayleigh} = \frac{\pi R \sqrt{\frac{\rho}{G}}}{0.1631\upsilon + 0.8766} \quad (6)$$

Where R is the particle radius, ρ is the particle density, G is the shear modulus and υ is Poisson's ratio.[65] It is evident from this equation that the computational time required is directly related to particle properties such as density and size. Therefore, one common solution to reduce computational burden is to lessen the number of particles by using larger ones.[66] However, one caveat of this 'particle scaling' approach is that it can have significant effects on calculated particle velocities and often overestimates the degree of mixing. The other method often mentioned in literature is to reduce the shear modulus value, as this can also reduce the simulation time.[67] It was shown by Lommen *et al.* that this approach is not always accurate and can lead to misleading simulation results.[68] Therefore, it is important to ensure that the effect of varying particle properties to reduce computational burden should be considered.

Numerous researchers have worked on the simulation of particles in agitated vessels, such as rotary drums and bladed mixers, which share similarities with AFDs.[69,70] One study of note was done by Kwapinska *et al.* where heat transfer in agitated beds was modelled, and the results of the DEM simulations were in good agreement with both experimental data and the classic penetration model. Although these results were limited to specific cases, it highlighted that DEM has the potential to not only simulate the heat and mass transfer in agitated beds but also provide more information than the penetration model, such as the thermal behaviour.[69] There has also been various work done in the field of wet granulation to look at the flow of wet granular materials.[71–74] Some of the key models for force calculations will be discussed.

5.2.1 Contact forces

In DEM, various contact models can be used to calculate the forces experienced by colliding particles, and these various models can be categorised as soft sphere or hard sphere approaches. In the hard sphere approach, particles are considered as rigid and collisions are instantaneous, with forces between particles not considered. This model is usually best for highly agitated systems with rapid granular flow. Conversely, the soft sphere approach considers particles to

deform when there are overlaps and assumes that multiple contacts between particles is possible.[75] This model is more commonly used for powder systems as particles tend to be deformable.

Particles interact with adjacent particles at contact points and the contact forces calculated are based on the normal and tangential force components. In order to calculate these forces, various models have been developed, and a detailed review of these can be found in the well-known review paper by Zhu *et al.*[76]

It is important to note that due to the reduced computational cost and simple contact detection, most DEM studies have used spheres to represent particle shapes, despite the effect of particle morphology on granular systems being well established. Representing non-spherical particles in DEM can be achieved using either the multi-sphere approach or the geometrically exact approach.[77]

In the multi-sphere approach, non-spherical particles are represented by clusters of spheres of varying sizes, linked together to approximate irregular shapes, while still using the same contact detection method as spherical particles.[78] This approach is widely used as it is easy to implement but comes with certain limitations. Not only is it difficult to specify the design of these multi-sphere clusters, but often many spheres are needed to accurately represent irregular particles, which increases the computational time. Having more spheres can then result in incorrect centre of mass and moment of inertia, thus reducing computational efficiency.[77]

The geometrically exact method is a single particle approach that represents a non-spherical particle using complex geometry such as an ellipsoid, super-quadric or polyhedron. Although this approach improves the accuracy compared to the multi-sphere approach, it requires more complicated contact detection models.[78] This increased complexity, and the high computational costs remains a significant limitation of the geometrically exact method. [79]

The high computational cost of simulations has long been a bottleneck for DEM, but the use of graphics processing units (GPUs) has shown promise for more realistic simulations of APIs with non-spherical particles.[80,81] Using GPUs can allow for less restrictions on particle number and size, facilitating large scale simulations due to its parallel computation. Although GPUs have significantly improved simulations of spherical particles to be conducted on much larger scales, advancements in simulating non-spherical particles remains relatively limited.

5.2.2 Liquid bridge force calculation

Non-contact forces such as liquid bridge force and van der Waals tend to become more dominant for wet or fine particles and so is especially important when modelling pharmaceutical processes.[82] Liquid bridge models which account for the capillary and viscous forces are often used in DEM.

The capillary force of a liquid bridge can be described by the Young-Laplace equation but as this cannot be solved analytically, work by Fisher and Lian *et al.* showed the capillary force can be estimated by using a toroidal approximation for the liquid bridge shape.[83,84] Lian *et al.* also showed that the toroidal approximation has an error of less than 10 %.[84] The capillary liquid bridge force (F_c) can be described by the following equation:

$$F_c = 2\pi\gamma R \sin\phi \sin(\phi + \theta) + \pi R^2 \Delta P \sin^2\phi \tag{7}$$

Where γ is the liquid surface tension, R is the particle radius, ϕ is the half-filling angle, θ is the contact angle and ΔP is the reduced hydrostatic pressure, given by the Young-Laplace equation. The viscous forces of a liquid bridge can be calculated using the normal and tangential components which are given in Equations 8 and 9 respectively.[85] There is no analytical solution for the tangential viscous force, but the asymptotic solution shown in Eq 9 was derived by Goldman *et al.* for sufficiently small separation distances.[86]

$$F_{vis}^{n} = \frac{6\pi\eta R^{*2} v_n}{S} \tag{8}$$

$$F_{vis}^{t} = \left(\frac{8}{15}\ln\frac{R}{S} + 0.9588\right) 6\pi\eta R v_t \tag{9}$$

Where η is the fluid viscosity, R^* is the reduced radius, S is the separation distance, R is the radius and v_n and v_t are the relative velocities in the normal and tangential direction.

Instead of using an approximate solution for the Young-Laplace equation, Willett *et al.* employed an appropriate fit of the results for the Young-Laplace equation for a range of liquid volumes.[87] The error of the approximation was 4 % for a liquid-solid volume ratio of 0.1 %, but the error increases with increasing ratios. However, a more complex expression was

presented which showed errors less than 3 % up to a liquid-solid volume ratio of 10 %. Willet *et al.* also demonstrated the Derjaguin approximation can be used to accurately calculate the capillary forces between spheres of unequal sizes for small bridge volumes and also a range of separation distances except near the rupture distance or close contact.[87] A similar approach was taken by Mikami *et al.* to predict the capillary force, but with improved accuracy compared to Willet's solution for larger size ratios as it is obtained by fitting to the limiting case where one of the spheres radii becomes infinite.[88] This liquid bridge model was also experimentally validated by Remy *et al.* when investigating wet granular flow in a bladed mixer.[89] Radl *et al.* used Willet's solution for particle-particle interactions and Mikami's solution for particle-wall interactions to optimise the accuracy.[90] Both Remy *et al.* and Radl *et al.* investigated the effect of moisture on powder flow patterns in bladed mixers and observed increased particle velocities compared to dry material. Remy *et al.* investigated a larger range of moisture content, and saw this effect deteriorated at higher moisture contents. This work was also the first to extend the modelling of wet granular systems to look at the resulting undesired agglomeration using DEM.[89] Mikami and co-workers' model was later expanded on by Soulie *et al.* to incorporate polydisperse materials.[91]

Tamrakar *et al.* proposed a model which implemented both wet granular flow and heat transfer models to demonstrate the simultaneous processes occurring during the operation of an AFD.[14] As well as accounting for capillary and viscous forces using the aforementioned equations, their model also calculates a critical separation distance for each contact where exceeding this distance results in the liquid bridge being broken. This reflects the dynamic bonding occurring between wet granules. They also applied the capillary number, Ca, which can be described by the following equation:

$$Ca = \frac{\mu U}{\gamma} \tag{10}$$

Where μ is the average viscosity of the fluid, U is the relative particle velocity and γ is the surface tension of liquid in the liquid bridge. The capillary number is a dimensionless group which describes the ratio of viscous forces (F_{vis}) to capillary forces (F_c) in the liquid bridge.[92] To reflect the dynamic nature of the drying process where the viscosity of liquid is continuously changing, the model also implemented two conditions for liquid bridge formation. For low capillary numbers ($Ca < 0.001$), capillary forces dominate the liquid bridge force and so only

the capillary force is used. However, for higher capillary forces (Ca > 0.001), both capillary and viscous force components are used. This novel model incorporates many of the phenomena occurring in AFDs and was used to investigate the effect of multiple material and process parameters on both drying and agglomeration behaviour. Although experimental validation is required, this is a great advancement in the modelling of agglomeration behaviour in AFDs.

5.2.3 Heat transfer calculations

Heat transfer can occur via various mechanisms such as thermal conduction through the interstitial fluid, thermal conduction through the contact area of particles, heat transfer by fluid convection or radiation between particle surfaces. It is common practice to only focus on the first two mechanisms as they are expected to dominate.[93] This is because the interstitial fluid is stagnant and possesses a thermal conductivity lower than that of the particles. Batchelor and O'Brien demonstrated that this assumption is valid as long as Equation 10 is satisfied where k_s and k_f are the conductivities of the particles and the interstitial fluid, respectively.[94]

$$\left(\frac{k_s}{k_f}\right) \gg 1 \tag{10}$$

The heat flux ($Q_{i,j}$) between two particles i and j can be described as a function of the interparticle conductance (h_c) and temperature difference between particles ($\Delta T_{i,j}$).

$$Q_{i,j} = h_c \Delta T_{i,j} \tag{11}$$

The interparticle conductance (h_c) is given by the following equation:

$$h_c = 2k_s \left[\frac{3F_N r^*}{4E^*}\right]^{1/3} \tag{12}$$

Where k_s is the solid's thermal conductivity, F_N is the normal force during contact, r^* is the hertzian contact radius and E^* is the effective Young's modulus of the two particles.[95] The temperature change of particle i is given by:

$$\frac{dT_i}{dt} = \frac{Q_i}{\rho_i C_i V_i}$$

(13)

Where Q_i is the sum of the heat fluxes of particle i and $\rho_i C_i V_i$ is the thermal heat capacity of particle i and is the product of its density, specific heat capacity and volume.[96] Equations 11 – 13 can be used to calculate the progression of temperature for individual particles and were used by Chaudhuri *et al.* to look at the heat transfer of granular material in rotating vessels.[93] One of the main assumptions of their model was that the temperature inside each particle is uniform during each time period of the simulation. This is a valid assumption when the resistance to heat transfer inside the particle is less than between particles, as shown by Vargas and McCarthy.[97] A similar approach was taken by Hartmanshenn *et al.* when investigating the effect of agitation rate on the heating process.[98] They only considered heat transfer between particles and between particles and vessel walls to isolate one aspect of the drying process and avoid having several parameters at play. Experiments were conducted in a laboratory scale agitated dryer and an infrared (IR) camera was used to take temperature readings. The experiments and simulations showed good agreement, where increasing the agitation led to a hotter, more uniform powder bed surface after a few minutes of heating. However, the simulation results for 0 rpm had much lower particle temperatures compared to experimental results, and this may be due to the value of thermal conductivity used being derived from agitated bed experiments. Static beds are likely to have different thermal behaviour to agitated beds and so the model needs to consider this. However, the model can be a good starting point for understanding the effect of agitation on heat transfer and temperature uniformity in agitated dryers. The authors also noted that the use of glass beads in this work does not account for the behaviour of APIs such as attrition and agglomeration, and this should also be investigated going forward.

Earlier models often neglected heat transfer through the liquid bridges, perhaps for simplicity, and Sahni *et al.* observed variations between their experimental findings and simulations when looking at the drying behaviour in a filter dryer.[99] The key variation was the decrease of solvent content over time during drying which was greater in experiments, but there were also disparities in the average bed temperature for different fill levels. This was improved on in a later model by Sahni and Chaudhuri where heat transfer through liquid bridges was accounted for in numerical simulations of contact drying in a filter dryer.[100] The change in temperature of particle i (ΔT_i) can be calculated using the following equation:

$$\Delta T_i = \left(T_{avg} - T_i\right)\left(1.0 - exp\left(-Q_{ij}dt/\left(MC_p\right)\right)\right)$$

(14)

Where T_{avg} is the average temperature of particles i and j (which is assumed to be the temperature of the solvent forming the liquid bridge), T_i is the temperature of particle i, M is the mass of particles, C_p is the specific heat capacity and Q_{ij} is the heat flow between the particles and solvent. Heat transfer through the liquid bridge is applicable while the particle temperature is less than the boiling point of the solvent, and when this is exceeded, the heat transfer occurs by direct particle-particle contact.

Particles can heat up as a result of collisions between particles or particles and the vessel wall and drying will occur if the surface temperature can maintain the slurry at a temperature greater than the boiling point for vacuum conditions.[99] A coupled heat and mass transfer equation is used to find the change in mass of solvent:

$$Qdt = m\Delta H_v + m_s c\Delta T$$

(15)

Where Q is the total heat, m is the mass of solvent, ΔH_v is the heat of vaporisation, m_s is the sample mass, c is the specific heat capacity and ΔT is the temperature change. This improved model by Sahni *et al.* was validated with experiments and indicated that vessel wall temperatures and impeller speeds have a considerable influence on the drying rate, as a result of increased drying temperatures. Another interesting observation was the greater impact of agitation speed on lactose compared to glass beads. For lactose, stable contact force chains form which results in deformation of the powder bed as heaps are formed, leading to recirculation zones. This was attributed to the high friction coefficient of lactose and this phenomenon has been reported by other researchers.[101,102] On the contrary, glass beads have low friction coefficients, so particle are able to slide past each other and no heaps are formed. This work further indicated that the drying performance should not only be considered as a function of process parameters but also material properties. Some disparities between the simulation and experiments were observed and suggested to be due to the slight variations in particle properties and the assumption that particles were monodisperse. Sahni and Chaudhuri also highlighted that models often did not account for the change in particle size during drying as a result of agglomeration and/or attrition.[100]

5.3 Advancements in wet granulation modelling

The modelling of agglomeration in AFDs proves to be difficult and there is currently limited work on this, with many reported models neglecting the agglomeration behaviour. However, there has been significant advances in the modelling of wet granulation, which may be applied to modelling AFDs. Some interesting models of note are discussed in the following sections.

5.3.1 Population balance model (PBM)

Population balance modelling is able to track changes in particle properties for a large population over time and has been used to predict final granule properties such as the porosity, size distribution and liquid content.[103–105] It has commonly been used for modelling wet granulation on a macroscale, where nucleation, growth, attrition and breakage can all occur simultaneously. PBM groups particles by one or more properties and tracks the number of particles in each class or bin over time. These changes are determined by evaluating the rate processes of wet granulation. The general formula for PBM can be summarised as:

$$\frac{\partial n}{\partial t} + \nabla.(pn) - B + D = 0$$

Where n is the number density of particles, p is the velocity, and B and D refer to the birth rate and death rate or particles, respectively. Depending on the process being modelled, various equations are used to account for various phenomena such as nucleation, coalescence, breakage etc. These equations are grouped into kernels. Various kernels have been developed and although the population balance equation (PBE) is difficult to solve analytically, solutions are available for simple kernels. [106–108]

The full underlying principles of PBM cannot be covered within this review but a comprehensive review of modelling wet granulation by Singh *et al.* should be consulted for further reading.[109]

5.3.1.1 Modelling agglomeration using PBM

One notable study by Watano *et al.* modified a previous PBM by Ouchiyama and Tanaka to look at the effect of moisture content on the likelihood of coalescence and the effect of moisture content, damping speed and operating time on granule growth in an agitated fluidised bed.[110,111] The simulations showed good agreement with experimental data on pharmaceutical powders. Liu *et al.* used PBM to model the granule size distribution (GSD) in a pulsed spray fluidised bed, but also used partial least square (PLS) regressions to describe the relationship between operating parameters and the kernel parameters in the PBM.[112] They

were able to simulate the GSD as a function of varying the pulsed frequency, binder spray rate and atomisation pressure and the results showed very good agreement with experimental data. One strength of this model is it can accurately predict the GSD in-process as well as the final PSD. Such a tool would be invaluable for monitoring agglomeration in AFDs. Hayashi *et al.* developed a PBM for fluidised bed granulation that considered the moisture content when determining the likelihood of coalescence and breakage, which is also a very influential parameter for agglomeration in AFDs.[113] The model was validated with experimental results, however it did not consider the effect of particle collisions, which can also have a significant effect on the coalescence and breakage occurring. This is a common limitation of PBM as it does not consider the dynamics of particles inside the vessel, and also relies on experimental data for fitting, which further limits the predictive capability. Although PBM has long dominated the modelling of wet granulation, it does not consider what is occurring on a granular scale, and hence other methods have been used in recent years.[114]

5.3.2 Discrete element method (DEM)

The use of DEM offers significant advantages over PBM as interactions between individual particles can be studied. As mentioned in previous sections, DEM can be used with soft or hard sphere approaches, with the former being preferred for modelling wet granulation. It has been used to track changes in particle size and other granule material properties, but is highly limited by the computational load required, due to the small integration time-step. Often studies will reduce the number of particles or use larger particles to represent groups of smaller particles to circumvent this.[115] However, with improving computer speed, models are able to incorporate more particles with recent simulations having up to 1.9 billion particles.[116]

5.3.2.1 Coarse grain model

One method to circumvent the issue of high computational load is the coarse grain model or technique.[117] Instead of particles being represented by discrete elements even after agglomeration, agglomerates are modelled as a single discrete element, and hence this method of scaling up particle size can greatly reduce the computational cost. There are two main methods for the coarse grain technique, direct force scaling and parameter scaling. With direct force scaling, the forces acting on the agglomerate are directly scaled from the forces acting on the primary particles using similarity laws.[118] The parameter scaling method involves adjusting the physical properties or DEM parameters to achieve similarity with the original particle system, for example by scaling spring and stiffness parameters.[119,120] When evaluating various scaling methods for particles with liquid bridges and particles with van der

Waals forces, it was found that direct force scaling based on the stress experienced performs better than scaling based on the Bond number for predicting the average slip velocity.[117] Further review and comparison of various coarse grain techniques can be found in a review by these authors.[121,122]

5.3.2.2 Modelling agglomeration using DEM

Despite the computational cost of DEM simulations for large granular systems, great progress has been made in simulating the particle velocities and size distributions. These simulations have primarily focused on high shear granulators, fluidised beds, and twin-screw granulators.

An early study by Talu *et al.* looked at modelling the effect of binder content, Stokes number and capillary number on the agglomeration and breakage of both wet and dry particles.[123] However, many simplifications had to be made to reduce the computational cost, such as the transfer of liquid from wet to dry particles being neglected. A model by Gantt and Gatzke in 2005 for high shear granulation incorporated the three rate processes of wet granulation and even accounted for type I and type II coalescence. [124] The model was able to simulate the PSD for various moisture contents and impeller speeds and were in agreement with experimental results reported in the literature. Gantt *et al.* also applied periodic boundary conditions to a DEM model to represent flow, and the particle collision rates found were used to develop a coalescence kernel that could be incorporated into PBM.[125]

Tamrakar *et al.* developed a DEM model which accounted for wet and dry binder addition and incorporated the resulting capillary and viscous liquid bridge formation.[126] This model neglects breakage due to impact and focuses on agglomeration by liquid bridge formation or breakage due to the rupture of liquid bridges. Despite this, this work gives valuable insight into the viscous regions in both dry and wet systems and the effect of viscosity on liquid bridge strength. This is especially important for modelling AFDs where the dynamic drying process results in changes in viscosity throughout the drying period, which influences liquid bridge strength and the resulting agglomeration.

Considerable progress has been made in modelling wet granular systems using DEM.[114] However, these models often are not able to simulate the changes in particle properties as a result of the individual rate processes in wet granulation and often limited by computational cost.

5.3.3. Coupling PBM and DEM

By coupling PBM and DEM, the strengths of each technique can be combined, and both macroscale and microscale behaviour can be predicted. This two-way coupling works by initially performing PBM calculations using DEM simulation data, and the PBM result is fed back to the DEM model to update any changes in particle properties. This improves the accuracy of the model by accounting for the dynamic nature of the system.

Barrasso and Ramachandran reported a PBM-DEM model for continuous twin screw granulation where various rate processes such as aggregation, breakage, and consolidation were simulated.[127] The model also gave residence time information for each compartment. The simulations showed good agreement with experimental data in the literature, and any variations were accounted for by limitations of the model such as not accounting for the evolving granule properties in individual screw elements. Hayashi *et al.* developed a PBM with DEM-CFD coupling using collision frequency functions to investigate granule aggregation and breakage.[128] Many previous studies compared simulation data to experimental data obtained at a laboratory scale. In this model, the PSDs simulated were compared with experimental data at a production scale, under various operating conditions, and showed very good agreement. In particular, the accuracy of the PSDs highlights the ability of this model to simulate both granule aggregation and breakage, both of which are important phenomena in AFDs.

6. Conclusions and future outlook

The widespread use of AFDs across various industries highlights the importance of developing a thorough understanding of undesired agglomeration. Multiple parameters influence undesired agglomeration in AFDs making it increasingly complex to understand the underlying mechanisms. These parameters contribute to simultaneous and often competing rate processes. Future research into undesired agglomeration in AFDs should focus on moving away from empirical relationships to a mechanistic understanding, as this knowledge gap has long hindered the accuracy of models. While significant progress has been made in recent years through both experimental and computational efforts to develop our qualitative understanding of various parameter effects, this review emphasises the need for transitioning towards a mechanistic understanding. Without a clear understanding of the mechanisms and rate processes involved, any models developed will be significantly limited and unable to simulate the dynamic nature of agglomeration in AFDs, and the competing effects of various parameters.

In this review, we propose a mechanism consisting of three rate processes: the formation of loosely bound agglomerates, consolidation and coalescence, and the solidification of liquid bridges. These are key for developing predictive tools that account for the effect of several material and process parameters on undesired agglomeration in AFDs. However, more work is still required to develop dimensionless groups that can be utilised as prediction tools applicable to various material systems and equipment scales. Validating these tools on large scales, where mixing patterns and shear profiles are likely to differ, will be of great interest and significance. Developing dimensionless groups will enable more accurate scale up with reduced reliance on empirical correlations.

Although many modelling studies predominantly focus on simple agitated mixers, more recent studies have shifted towards investigating wet granular flow and agitation in a heated vessel. Computational approaches such as DEM are promising tools for advancing the field and investigating the mechanisms of undesired agglomeration while reducing the experimental workload. DEM can give detailed insights into particle interactions on a micro-scale, significantly reducing the experimental workload. Currently, the computational cost has resulted in oversimplified assumptions, such as only considering spherical geometries and unrealistically large particle sizes. While this may reduce the computational burden, it also reduces the reliability of these models, given particles often occur in irregular shapes. Therefore, future work should integrate more representative material properties such as the presence of fine particles and common API morphologies, typically needles, whilst optimising

computational costs by using GPUs. This will enable more realistic models that are representative of typical industrial processes.

Another key opportunity for this field is the applicability of wet granulation models and integrating both agglomeration and attrition behaviour into AFD models. This would allow for a more comprehensive understanding of the interplay between the two phenomena. Wet granulation models have also explored the challenges of scaling up. By building on these existing frameworks, more insightful models can be developed to better understand and predict agglomeration behaviour in AFDs. In doing so, this would not only further our theoretical understanding but also improve the performance and scalability of AFDs, benefitting many industries where undesired agglomeration in AFDs remains a persistent challenge.

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7. References

[1] N.K. Nere, K.C. Allen, J.C. Marek, S. v Bordawekar, Pharmaceutical Technology Drying Process Optimization for an API Solvate Using Heat Transfer Model of an Filter Dryer, J Pharm Sci 101 (2012) 3886–3895. https://doi.org/10.1002/jps.23237.

[2] S. Murugesan, P.K. Sharma, J.E. Tabora, Design of Filtration and Drying Operations, in: Chemical Engineering in the Pharmaceutical Industry: R&D to Manufacturing, John Wiley & Sons, Ltd, 2010: pp. 315–345. https://doi.org/10.1002/9780470882221.CH17.

[3] H.L. Lim, K.P. Hapgood, B. Haig, Understanding and preventing agglomeration in a filter drying process, Powder Technol 300 (2016) 146–156. https://doi.org/10.1016/J.POWTEC.2016.03.003.

[4] CMAC, CMAC | CMAC Annual Reviews, 2020. https://cmac.ac.uk/cmac-annual-reviews (accessed August 25, 2022).

[5] E.K. Sahni, R.H. Bogner, B. Chaudhuri, Systematic Investigation of Parameters Affecting the Performance of an Agitated Filter-Dryer, J Pharm Sci 102 (2013) 2198–2213. https://doi.org/10.1002/JPS.23572.

[6] T. Kudra, A.S. Mujumdar, Advanced Drying Technologies, Advanced Drying Technologies (2009) 379–395. https://doi.org/10.1201/9781420073898/ADVANCED-DRYING-TECHNOLOGIES-TADEUSZ-KUDRA-ARUN-MUJUMDAR.

[7] A. Tamrakar, A. Gunadi, P.M. Piccione, R. Ramachandran, Dynamic agglomeration profiling during the drying phase in an agitated filter dyer: Parametric investigation and regime map studies, Powder Technol 303 (2016) 109–123. https://doi.org/10.1016/J.POWTEC.2016.09.012.

[8] Agitators in Nutsche Filter / Dryers | De Dietrich Process Systems, (n.d.). https://www.dedietrich.com/en/agitators-nutsche-filter/dryers (accessed February 18, 2022).

[9] Guide to Selecting Filter Media for Nutsche Filter/Dryers, (n.d.). https://www.ddpsinc.com/blog/guide-to-selecting-filter-media-for-nutsche-filter/dryers (accessed February 18, 2022).

[10] D.B. Purchas, K. Sutherland, Screens and Meshes, Handbook of Filter Media (2002) 201–259. https://doi.org/10.1016/B978-185617375-9/50007-9.

[11] L. Svarovsky, Cake washing, Solid-Liquid Separation (2001) 335–348. https://doi.org/10.1016/B978-075064568-3/50035-3.

[12] R. Wolthuis, V.C. Dichiaria, Conventional Filtration, Handbook of Downstream Processing (1997) 20–47. https://doi.org/10.1007/978-94-009-1563-3_2.

[13] M. Murru, G. Giorgio, S. Montomoli, F. Ricard, F. Stepanek, Model-based scale-up of vacuum contact drying of pharmaceutical compounds, Chem Eng Sci 66 (2011) 5045–5054. https://doi.org/10.1016/J.CES.2011.06.059.

[14] A. Tamrakar, A. Zheng, P.M. Piccione, R. Ramachandran, Investigating particle-level dynamics to understand bulk behavior in a lab-scale Agitated Filter Dryer (AFD) using Discrete Element Method (DEM), Advanced Powder Technology 31 (2020) 477–492. https://doi.org/10.1016/J.APT.2019.11.004.

[15] D. am Ende, M. Birch, S.J. Brenek, M.T. Maloney, Development and Application of Laboratory Tools To Predict Particle Properties upon Scale-Up in Agitated Filter-Dryers, Org Process Res Dev 17 (2013) 1345–1358. https://doi.org/10.1021/OP400080X.

[16] S.M. Iveson, J.D. Litster, K. Hapgood, B.J. Ennis, Nucleation, growth and breakage phenomena in agitated wet granulation processes: a review, Powder Technol 117 (2001) 3–39. https://doi.org/10.1016/S0032-5910(01)00313-8.

[17] R. Wakeman, The influence of particle properties on filtration, Sep Purif Technol 58 (2007) 234–241. https://doi.org/10.1016/J.SEPPUR.2007.03.018.

[18] B.A. Perlmutter, Solid-Liquid Filtration: Practical Guides in Chemical Engineering, in: Solid-Liquid Filtration: Practical Guides in Chemical Engineering, Elsevier, 2015: pp. 1–122. https://doi.org/10.1016/C2014-0-00166-9.

[19] D. Martynek, J. Němeček, L. Ridvan, M. Šoóš, Impact of crystallization conditions and filtration cake washing on the clustering of metformin hydrochloride crystals, Powder Technol 405 (2022) 117522. https://doi.org/10.1016/J.POWTEC.2022.117522.

[20] K.J. Hwang, Y.S. Wu, W.M. Lu, Effect of the size distribution of spheroidal particles on the surface structure of a filter cake, Powder Technol 91 (1997) 105–113. https://doi.org/10.1016/S0032-5910(96)03237-8.

[21] S. Ottoboni, M. Simurda, S. Wilson, A. Irvine, F. Ramsay, C.J. Price, Understanding effect of filtration and washing on dried product: Paracetamol case study, Powder Technol 366 (2020) 305–323. https://doi.org/10.1016/J.POWTEC.2020.02.064.

[22] D. Wieckhusen, W. Beckmann, Downstream Processes, Crystallization: Basic Concepts and Industrial Applications (2013) 275–288. https://doi.org/10.1002/9783527650323.CH14.

[23] J.F. Richardson, J.H. Harker, J.R. Backhurst, Chemical Engineering: Particle Technology and Separation Processes: Fifth Edition, in: Chemical Engineering: Particle Technology and Separation Processes: Fifth Edition, Elsevier Inc., 2013: pp. 372–436. https://doi.org/10.1016/C2009-0-25733-3.

[24] L. Löbnitz, M. Böser, H. Nirschl, Influence of Filtration on the Agglomeration Degree of Two Crystalline Amino Acids, Chemie Ingenieur Technik 90 (2018) 464–471. https://doi.org/10.1002/CITE.201700110.

[25] E.W. Conder, A.S. Cosbie, J. Gaertner, W. Hicks, S. Huggins, C.S. MacLeod, B. Remy, B.S. Yang, J.D. Engstrom, D.J. Lamberto, C.D. Papageorgiou, The Pharmaceutical Drying Unit Operation: An Industry Perspective on Advancing the Science and Development Approach for Scale-Up and Technology Transfer, Org Process Res Dev 21 (2017) 420–429.

https://doi.org/10.1021/ACS.OPRD.6B00406/ASSET/IMAGES/LARGE/OP-2016-00406C_0006.JPEG.

[26] M. Birch, I. Marziano, Understanding and avoidance of agglomeration during drying processes: A case study, Org Process Res Dev 17 (2013) 1359–1366. https://doi.org/10.1021/OP4000972/SUPPL_FILE/OP4000972_SI_001.PDF.

[27] M. Shahid, G. Sanxaridou, S. Ottoboni, L. Lue, C. Price, Exploring the Role of Anti-solvent Effects during Washing on Active Pharmaceutical Ingredient Purity, Org Process Res Dev 25 (2021) 969–981. https://doi.org/10.1021/ACS.OPRD.1C00005/SUPPL_FILE/OP1C00005_SI_001.PDF.

[28] B. Perlmutter, A Treatise of Filter Cake Washing Mechanisms In Pressure and Vacuum Filtration Systems | AIChE, in: 2011. https://proceedings.aiche.org/conferences/aiche-spring-meeting-and-global-congress-on-process-safety/2011/proceeding/paper/110e-treatise-filter-cake-washing-mechanisms-pressure-and-vacuum-filtration-systems-0 (accessed February 17, 2025).

[29] M. Shahid, C. Faure, S. Ottoboni, L. Lue, C. Price, Employing Constant Rate Filtration To Assess Active Pharmaceutical Ingredient Washing Efficiency, Org Process Res Dev 26 (2022) 97–110. https://doi.org/10.1021/ACS.OPRD.1C00272/ASSET/IMAGES/LARGE/OP1C00272_0016.JPEG.

[30] E.W. Conder, A.S. Cosbie, J. Gaertner, W. Hicks, S. Huggins, C.S. MacLeod, B. Remy, B.S. Yang, J.D. Engstrom, D.J. Lamberto, C.D. Papageorgiou, The Pharmaceutical Drying Unit Operation: An Industry Perspective on Advancing the Science and Development Approach for Scale-Up and Technology Transfer, Org Process Res Dev 21 (2017) 420–429. https://doi.org/10.1021/ACS.OPRD.6B00406/ASSET/IMAGES/LARGE/OP-2016-00406C_0006.JPEG.

[31] S. Zhang, D.J. Lamberto, Development of new laboratory tools for assessment of granulation behavior during bulk active pharmaceutical ingredient drying, J Pharm Sci 103 (2014) 152–160. https://doi.org/10.1002/JPS.23762.

[32] Y.J. Shin, R. Ho, A.Y. Sheikh, P. Kumar, K. Sinha, N.K. Nere, L. Mlinar, Toward a Holistic Approach to Assess Particle Agglomeration: Impact of Intrinsic Materials Properties, Ind Eng Chem Res 58 (2019) 10394–10401. https://doi.org/10.1021/ACS.IECR.9B01701/SUPPL_FILE/IE9B01701_SI_001.PDF.

[33] A. Lekhal, K.P. Girard, M.A. Brown, S. Kiang, B.J. Glasser, J.G. Khinast, Impact of agitated drying on crystal morphology: KCl–water system, Powder Technol 132 (2003) 119–130. https://doi.org/10.1016/S0032-5910(03)00056-1.

[34] S.M. Iveson, J.D. Litster, Fundamental studies of granule consolidation. Part 2: Quantifying the effects of particle and binder properties, Powder Technol 99 (1998) 243–250. https://doi.org/10.1016/S0032-5910(98)00116-8.

[35] C.D. Papageorgiou, M. Langston, F. Hicks, D. Am Ende, E. Martin, S. Rothstein, J. Salan, R. Muir, Development of Screening Methodology for the Assessment of the Agglomeration Potential of APIs, Org Process Res Dev 20 (2016) 1500–1508. https://doi.org/10.1021/ACS.OPRD.6B00201/SUPPL_FILE/OP6B00201_SI_001.PDF.

[36] K. Sinha, E. Murphy, P. Kumar, K.A. Springer, R. Ho, N.K. Nere, A Novel Computational Approach Coupled with Machine Learning to Predict the Extent of Agglomeration in Particulate Processes, AAPS PharmSciTech 2021 23:1 23 (2021) 1–16. https://doi.org/10.1208/S12249-021-02083-X.

[37] S.M. Iveson, J.D. Litster, Growth regime map for liquid-bound granules, AIChE Journal 44 (1998) 1510–1518. https://doi.org/10.1002/AIC.690440705.

[38] T. Schæfer, Growth mechanisms in melt agglomeration in high shear mixers, Powder Technol 117 (2001) 68–82. https://doi.org/10.1016/S0032-5910(01)00315-1.

[39] A. Lekhal, K.P. Girard, M.A. Brown, S. Kiang, J.G. Khinast, B.J. Glasser, The effect of agitated drying on the morphology of l-threonine (needle-like) crystals, Int J Pharm 270 (2004) 263–277. https://doi.org/10.1016/J.IJPHARM.2003.10.022.

[40] W.P. Goh, K. Sinha, N.K. Nere, R. Ho, S. Bordawekar, A. Sheikh, M. Ghadiri, Breakage Assessment of Lath-Like Crystals in a Novel Laboratory-Scale Agitated Filter Bed Dryer, Pharm Res 1 (2022) 1–13. https://doi.org/10.1007/S11095-022-03411-X/FIGURES/12.

[41] I. Ohno, S. Hasegawa, S. Yada, A. Kusai, K. Moribe, K. Yamamoto, Importance of evaluating the consolidation of granules manufactured by high shear mixer, Int J Pharm 338 (2007) 79–86. https://doi.org/10.1016/J.IJPHARM.2007.01.030.

[42] O. Macho, Ľ. Gabrišová, A. Guštafík, K. Jezso, M. Juriga, J. Kabát, J. Blaško, The Influence of Wet Granulation Parameters on the Compaction Behavior and Tablet Strength of a Hydralazine Powder Mixture, Pharmaceutics 15 (2023). https://doi.org/10.3390/PHARMACEUTICS15082148.

[43] S.I.F. Badawy, M.M. Menning, M.A. Gorko, D.L. Gilbert, Effect of process parameters on compressibility of granulation manufactured in a high-shear mixer, Int J Pharm 198 (2000) 51–61. https://doi.org/10.1016/S0378-5173(99)00445-7.

[44] I.C. Kemp, D.E. Oakley, MODELLING OF PARTICULATE DRYING IN THEORY AND PRACTICE, Drying Technology 20 (2007) 1699–1750. https://doi.org/10.1081/DRT-120015410.

[45] W.B. Pietsch, The strength of agglomerates bound by salt bridges, Can J Chem Eng 47 (1969) 403–409. https://doi.org/10.1002/CJCE.5450470419.

[46] J. Adamson, N. Faiber, A. Gottlieb, L. Hamsmith, F. Hicks, C. Mitchell, B. Mittal, K. Mukai, C.D. Papageorgiou, Development of Suitable Plant-Scale Drying Conditions That Prevent API Agglomeration and Dehydration, Org Process Res Dev 20 (2015) 51–58. https://doi.org/10.1021/ACS.OPRD.5B00327.

[47] S. Lu, S. Song, Hydrophobic interaction in flocculation and flotation 1. Hydrophobic flocculation of fine mineral particles in aqueous solution, Colloids and Surfaces 57 (1991) 49–60. https://doi.org/10.1016/0166-6622(91)80179-R.

[48] M.S. Kaliszewski, A.H. Heuer, Alcohol Interaction with Zirconia Powders, Journal of the American Ceramic Society 73 (1990) 1504–1509. https://doi.org/10.1111/J.1151-2916.1990.TB09787.X.

[49] Z.Q. Yu, R.B.H. Tan, P.S. Chow, Effects of operating conditions on agglomeration and habit of paracetamol crystals in anti-solvent crystallization, J Cryst Growth 279 (2005) 477–488. https://doi.org/10.1016/J.JCRYSGRO.2005.02.050.

[50] T. Schæfer, B. Taagegaard, L.J. Thomsen, H. Gjelstrup Kristensen, Melt pelletization in a high shear mixer. IV. Effects of process variables in a laboratory scale mixer, European Journal of Pharmaceutical Sciences 1 (1993) 125–131. https://doi.org/10.1016/0928-0987(93)90002-R.

[51] Y. Kawashima, S. Aoki, H. Takenaka, SPHERICAL AGGLOMERATION OF AMINOPHYLLINE CRYSTALS DURING REACTION IN LIQUID BY THE SPHERICAL CRYSTALLIZATION TECHINIQUE, Chem Pharm Bull (Tokyo) 30 (1982) 1900–1902. https://doi.org/10.1248/CPB.30.1900.

[52] M. Maghsoodi, Z. Yari, Effect of temperature on wet agglomeration of crystals, Iran J Basic Med Sci 17 (2014) 344. /pmc/articles/PMC4069845/ (accessed June 8, 2023).

[53] F. De Leersnyder, V. Vanhoorne, H. Bekaert, J. Vercruysse, M. Ghijs, N. Bostijn, M. Verstraeten, P. Cappuyns, I. Van Assche, Y. Vander Heyden, E. Ziemons, J.P. Remon, I. Nopens, C. Vervaet, T. De Beer, Breakage and drying behaviour of granules in a continuous fluid bed dryer: Influence of process parameters and wet granule transfer, European Journal of Pharmaceutical Sciences 115 (2018) 223–232. https://doi.org/10.1016/J.EJPS.2018.01.037.

[54] M. Llusa, K. Sturm, O. Sudah, H. Stamato, D.J. Goldfarb, H. Ramachandruni, S. Hammond, M.R. Smith, F.J. Muzzio, Effect of high shear blending protocols and blender parameters on the degree of API agglomeration in solid formulations, Ind Eng Chem Res 48 (2009) 93–101. https://doi.org/10.1021/IE8007055/ASSET/IMAGES/LARGE/IE-2008-007055_0011.JPEG.

[55] E.U. Schlünder, Heat transfer to packed and stirred beds from the surface of immersed bodies, Chemical Engineering and Processing: Process Intensification 18 (1984) 31–53. https://doi.org/10.1016/0255-2701(84)85007-2.

[56] E. Tsotsas, E.U. Schlünder, Contact drying of mechanically agitated particulate material in the presence of inert gas, Chemical Engineering and Processing: Process Intensification 20 (1986) 277–285. https://doi.org/10.1016/0255-2701(86)80021-6.

[57] E. Tsotsas, E.U. Schlünder, Vacuum contact drying of mechanically agitated beds: The influence of hygroscopic behaviour on the drying rate curve, Chemical Engineering and Processing: Process Intensification 21 (1987) 199–208. https://doi.org/10.1016/0255-2701(87)80017-X.

[58] E.U. Schlünder, N. Mollekopf, Vacuum contact drying of free flowing mechanically agitated particulate material, Chemical Engineering and Processing 18 (1984). https://doi.org/10.1016/0255-2701(84)85012-6.

[59] E. Tsotsas, M. Kwapinska, G. Saage, Modeling of contact dryers, Drying Technology 25 (2007) 1377–1391. https://doi.org/10.1080/07373930701439079.

[60] A. Mujumdar, Handbook of Industrial Drying, in: Handbook of Industrial Drying, 3rd ed., CRC Press, 2006: pp. 163–164. https://doi.org/10.1201/9781420017618.

[61] J.H. Yan, W.Y. Deng, X.D. Li, F. Wang, Y. Chi, S.Y. Lu, K.F. Cen, Experimental and theoretical study of agitated contact drying of sewage sludge under partial vacuum conditions, Drying Technology 27 (2009) 787–796. https://doi.org/10.1080/07373930902900911.

[62] E. Tsotsas, E.U. Schlunder, Vacuum Contact Drying of Free Flowing Mechanically Agitated Multigranular Packings, Chem. Eng. Process. 20 (1986) 339–349.

[63] F. Heimann, E.U. Schlünder, Vacuum contact drying of mechanically agitated granular beds wetted with a binary mixture: Vakuum-Kontakttrocknung von mechanisch durchmischten Schütgütern, die mit einem binären Gemisch befeuchtet sind, Chemical Engineering and Processing: Process Intensification 24 (1988) 75–91. https://doi.org/10.1016/0255-2701(88)87016-8.

[64] S. Bin Yeom, E. Ha, M. Kim, S.H. Jeong, S.J. Hwang, D.H. Choi, Application of the Discrete Element Method for Manufacturing Process Simulation in the Pharmaceutical Industry, Pharmaceutics 11 (2019). https://doi.org/10.3390/PHARMACEUTICS11080414.

[65] M. Marigo, E.H. Stitt, Discrete Element Method (DEM) for Industrial Applications: Comments on Calibration and Validation for the Modelling of Cylindrical Pellets, KONA Powder and Particle Journal 32 (2015) 236–252. https://doi.org/10.14356/KONA.2015016.

[66] S.C. Thakur, J.Y. Ooi, H. Ahmadian, Scaling of discrete element model parameters for cohesionless and cohesive solid, Powder Technol 293 (2015) 130–137. https://doi.org/10.1016/j.powtec.2015.05.051.

[67] H. Chen, Y.G. Xiao, Y.L. Liu, Y.S. Shi, Effect of Young's modulus on DEM results regarding transverse mixing of particles within a rotating drum, Powder Technol 318 (2017) 507–517. https://doi.org/10.1016/J.POWTEC.2017.05.047.

[68] S. Lommen, D. Schott, G. Lodewijks, DEM speedup: Stiffness effects on behavior of bulk material, Particuology 12 (2014) 107–112. https://doi.org/10.1016/J.PARTIC.2013.03.006.

[69] M. Kwapinska, G. Saage, E. Tsotsas, Continuous versus discrete modelling of heat transfer to agitated beds, Powder Technol 181 (2008) 331–342. https://doi.org/10.1016/J.POWTEC.2007.05.025.

[70] B. Remy, B.J. Glasser, J.G. Khinast, The effect of mixer properties and fill level on granular flow in a bladed mixer, AIChE Journal 56 (2010) 336–353. https://doi.org/10.1002/AIC.11979.

[71] S. Sarkar, B. Chaudhuri, DEM modeling of high shear wet granulation of a simple system, Asian J Pharm Sci 13 (2018) 220–228. https://doi.org/10.1016/J.AJPS.2018.01.001.

[72] D. Barrasso, R. Ramachandran, Multi-scale modeling of granulation processes: Bi-directional coupling of PBM with DEM via collision frequencies, Chemical Engineering Research and Design 93 (2015) 304–317. https://doi.org/10.1016/J.CHERD.2014.04.016.

[73] R.M. Dhenge, K. Washino, J.J. Cartwright, M.J. Hounslow, A.D. Salman, Twin screw granulation using conveying screws: Effects of viscosity of granulation liquids and flow of powders, Powder Technol 238 (2013) 77–90. https://doi.org/10.1016/J.POWTEC.2012.05.045.

[74] M. Börner, M. Michaelis, E. Siegmann, C. Radeke, U. Schmidt, Impact of impeller design on high-shear wet granulation, Powder Technol 295 (2016) 261–271. https://doi.org/10.1016/J.POWTEC.2016.03.023.

[75] P.A. Cundall, O.D.L. Strack, A discrete numerical model for granular assemblies, Geotechnique 29 (1979) 47–65. https://doi.org/10.1680/GEOT.1979.29.1.47.

[76] H.P. Zhu, Z.Y. Zhou, R.Y. Yang, A.B. Yu, Discrete particle simulation of particulate systems: Theoretical developments, Chem Eng Sci 62 (2007) 3378–3396. https://doi.org/10.1016/J.CES.2006.12.089.

[77] G. Lu, J.R. Third, C.R. Müller, Discrete element models for non-spherical particle systems: From theoretical developments to applications, Chem Eng Sci 127 (2015) 425–465. https://doi.org/10.1016/J.CES.2014.11.050.

[78] D. Höhner, S. Wirtz, H. Kruggel-Emden, V. Scherer, Comparison of the multi-sphere and polyhedral approach to simulate non-spherical particles within the discrete element method: Influence on temporal force evolution for multiple contacts, Powder Technol 208 (2011) 643–656. https://doi.org/10.1016/J.POWTEC.2011.01.003.

[79] F. Yu, Y. Zhang, Y. Zheng, M. Han, G. Chen, Z. Yao, Comparison of different effective diameter calculating methods for sphero-cylinders by geometrically exact DEM simulations, Powder Technol 360 (2020) 1092–1101. https://doi.org/10.1016/J.POWTEC.2019.10.097.

[80] C.A. Radeke, B.J. Glasser, J.G. Khinast, Large-scale powder mixer simulations using massively parallel GPUarchitectures, Chem Eng Sci 65 (2010) 6435–6442. https://doi.org/10.1016/J.CES.2010.09.035.

[81] S. Ravjee, S.W. Jacobsz, D.N. Wilke, N. Govender, Discrete element model study into effects of particle shape on backfill response to cyclic loading behind an integral bridge abutment, Granul Matter 20 (2018) 1–14. https://doi.org/10.1007/S10035-018-0840-Z/FIGURES/19.

[82] W.R. Ketterhagen, M.T. Am Ende, B.C. Hancock, Process modeling in the pharmaceutical industry using the discrete element method, J Pharm Sci 98 (2009) 442–470. https://doi.org/10.1002/JPS.21466.

[83] R.A. Fisher, On the capillary forces in an ideal soil; correction of formulae given by W. B. Haines, J Agric Sci 16 (1926) 492–505. https://doi.org/10.1017/S0021859600007838.

[84] G. Lian, C. Thornton, M.J. Adams, A Theoretical Study of the Liquid Bridge Forces between Two Rigid Spherical Bodies, J Colloid Interface Sci 161 (1993) 138–147. https://doi.org/10.1006/JCIS.1993.1452.

[85] M.J. Adams, V. Perchard, The cohesive forces between particles with interstitial liquid., Institution of Chemical Engineers Symposium Series (1985) 147–160. https://jglobal.jst.go.jp/en/detail?JGLOBAL_ID=200902067233439729 (accessed June 27, 2023).

[86] A.J. Goldman, R.G. Cox, H. Brenner, Slow viscous motion of a sphere parallel to a plane wall—I Motion through a quiescent fluid, Chem Eng Sci 22 (1967) 637–651. https://doi.org/10.1016/0009-2509(67)80047-2.

[87] C.D. Willett, M.J. Adams, S.A. Johnson, J.P.K. Seville, Capillary bridges between two spherical bodies, Langmuir 16 (2000) 9396–9405. https://doi.org/10.1021/LA000657Y/ASSET/IMAGES/MEDIUM/LA000657YE00020.GIF.

[88] T. Mikami, H. Kamiya, M. Horio, Numerical simulation of cohesive powder behavior in a fluidized bed, Chem Eng Sci 53 (1998) 1927–1940. https://doi.org/10.1016/S0009-2509(97)00325-4.

[89] B. Remy, J.G. Khinast, B.J. Glasser, Wet granular flows in a bladed mixer: Experiments and simulations of monodisperse spheres, AIChE Journal 58 (2012) 3354–3369. https://doi.org/10.1002/AIC.13743.

[90] S. Radl, E. Kalvoda, B.J. Glasser, J.G. Khinast, Mixing characteristics of wet granular matter in a bladed mixer, Powder Technol 200 (2010) 171–189. https://doi.org/10.1016/J.POWTEC.2010.02.022.

[91] F. Soulié, F. Cherblanc, M.S. El Youssoufi, C. Saix, Influence of liquid bridges on the mechanical behaviour of polydisperse granular materials, Int J Numer Anal Methods Geomech 30 (2006) 213–228. https://doi.org/10.1002/NAG.476.

[92] B.J. Ennis, J. Li, T. Gabriel I., P. Robert, The influence of viscosity on the strength of an axially strained pendular liquid bridge, Chem Eng Sci 45 (1990) 3071–3088. https://doi.org/10.1016/0009-2509(90)80054-I.

[93] B. Chaudhuri, F.J. Muzzio, M.S. Tomassone, Modeling of heat transfer in granular flow in rotating vessels, Chem Eng Sci 61 (2006) 6348–6360. https://doi.org/10.1016/J.CES.2006.05.034.

[94] G.K. Batchelor, R.W. O'Brien, Thermal or electrical conduction through a granular material, Proceedings of the Royal Society of London. A. Mathematical and Physical Sciences 355 (1977) 313–333. https://doi.org/10.1098/RSPA.1977.0100.

[95] M.M. Yovanovich, Thermal contact resistance across elastically deformed spheres, J Spacecr Rockets 4 (1967) 119–122. https://doi.org/10.2514/3.28821.

[96] P. Chaksmithanont, G. McEntee, C. Hartmanshenn, C. Leung, J.G. Khinast, C.D. Papageorgiou, C. Mitchell, J.L. Quon, B.J. Glasser, The effect of intermittent mixing on particle heat transfer in an agitated dryer, Powder Technol 422 (2023) 118459. https://doi.org/10.1016/J.POWTEC.2023.118459.

[97] W.L. Vargas, J.J. McCarthy, Heat conduction in granular materials, AIChE Journal 47 (2001) 1052–1059. https://doi.org/10.1002/AIC.690470511.

[98] C. Hartmanshenn, P. Chaksmithanont, C. Leung, D. V. Ghare, N. Chakraborty, S. Patel, M. Halota, J.G. Khinast, C.D. Papageorgiou, C. Mitchell, J.L. Quon, B.J. Glasser, Infrared temperature measurements and DEM simulations of heat transfer in a bladed mixer, AIChE Journal (2022) e17636. https://doi.org/10.1002/AIC.17636.

[99] E. Sahni, J. Hallisey, B. Morgan, J. Strong, B. Chaudhuri, Quantifying drying performance of a filter dryer: Experiments and simulations, Advanced Powder Technology 23 (2012) 239–249. https://doi.org/10.1016/J.APT.2011.03.002.

[100] E.K. Sahni, B. Chaudhuri, Numerical simulations of contact drying in agitated filter-dryer, Chem Eng Sci 97 (2013) 34–49. https://doi.org/10.1016/J.CES.2013.04.025.

[101] C.S. Campbell, Granular shear flows at the elastic limit, J Fluid Mech 465 (2002) 261–291. https://doi.org/10.1017/S002211200200109X.

[102] B. Remy, J.G. Khinast, B.J. Glasser, Discrete element simulation of free flowing grains in a four-bladed mixer, AIChE Journal 55 (2009) 2035–2048. https://doi.org/10.1002/AIC.11876.

[103] A. Darelius, A. Rasmuson, I.N. Björn, S. Folestad, High shear wet granulation modelling—a mechanistic approach using population balances, Powder Technol 160 (2005) 209–218. https://doi.org/10.1016/J.POWTEC.2005.08.036.

[104] A. Chaudhury, H. Wu, M. Khan, R. Ramachandran, A mechanistic population balance model for granulation processes: Effect of process and formulation parameters, Chem Eng Sci 107 (2014) 76–92. https://doi.org/10.1016/J.CES.2013.11.031.

[105] H.Y. Ismail, S. Shirazian, M. Singh, D. Whitaker, A.B. Albadarin, G.M. Walker, Compartmental approach for modelling twin-screw granulation using population balances, Int J Pharm 576 (2020) 118737. https://doi.org/10.1016/J.IJPHARM.2019.118737.

[106] M. Singh, H.Y. Ismail, R. Singh, A.B. Albadarin, G. Walker, Finite volume approximation of nonlinear agglomeration population balance equation on triangular grid, J Aerosol Sci 137 (2019) 105430. https://doi.org/10.1016/J.JAEROSCI.2019.105430.

[107] I.J. Laurenzi, J.D. Bartels, S.L. Diamond, A General Algorithm for Exact Simulation of Multicomponent Aggregation Processes, J Comput Phys 177 (2002) 418–449. https://doi.org/10.1006/JCPH.2002.7017.

[108] B.J. Benjamin, G. Madras, Analytical solution for a population balance equation with aggregation and fragmentation, Chem Eng Sci 58 (2003) 3049–3051. https://doi.org/10.1016/S0009-2509(03)00159-3.

[109] M. Singh, S. Shirazian, V. Ranade, G.M. Walker, A. Kumar, Challenges and opportunities in modelling wet granulation in pharmaceutical industry – A critical review, Powder Technol 403 (2022) 117380. https://doi.org/10.1016/J.POWTEC.2022.117380.

[110] S. Watano, T. Morikawa, K. Miyanami, Mathematical Model in the Kinetics of Agitation Fluidized Bed Granulation. Effects of MOisture Content, Damping Speed and Operation Time on Granule Growth Rate, Chem Pharm Bull (Tokyo) 44 (1996) 409–415. https://doi.org/10.1248/CPB.44.409.

[111] T. Tanaka, N. Ouchiyama, Mathematical Model in the Kinetics of Granulation, Industrial and Engineering Chemistry Process Design and Development 13 (1974) 383–389. https://doi.org/10.1021/I260052A015/ASSET/I260052A015.FP.PNG_V03.

[112] H. Liu, T. O'Connor, S. Lee, S. Yoon, A process optimization strategy of a pulsed-spray fluidized bed granulation process based on predictive three-stage population balance model, Powder Technol 327 (2018) 188–200. https://doi.org/10.1016/J.POWTEC.2017.12.070.

[113] K. Hayashi, S. Watano, Novel population balance model for granule aggregation and breakage in fluidized bed granulation and drying, Powder Technol 342 (2019) 664–675. https://doi.org/10.1016/J.POWTEC.2018.10.036.

[114] S. Watano, H. Nakamura, Numerical modeling for wet granulation processes, in: Handbook of Pharmaceutical Wet Granulation: Theory and Practice in a Quality by Design Paradigm, Elsevier, 2018: pp. 737–763. https://doi.org/10.1016/B978-0-12-810460-6.00015-4.

[115] A. Hassanpour, C.C. Kwan, B.H. Ng, N. Rahmanian, Y.L. Ding, S.J. Antony, X.D. Jia, M. Ghadiri, Effect of granulation scale-up on the strength of granules, Powder Technol 189 (2009) 304–312. https://doi.org/10.1016/J.POWTEC.2008.04.023.

[116] D. Nishiura, M. Furuichi, H. Sakaguchi, Real-scale DEM simulations on the fault evolution process observed in sandbox experiments, Advanced Powder Technology 32 (2021) 4432–4441. https://doi.org/10.1016/J.APT.2021.09.007.

[117] J. Tausendschön, J. Kolehmainen, S. Sundaresan, S. Radl, Coarse graining Euler-Lagrange simulations of cohesive particle fluidization, Powder Technol 364 (2020) 167–182. https://doi.org/10.1016/J.POWTEC.2020.01.056.

[118] M. Sakai, H. Takahashi, C.C. Pain, J.P. Latham, J. Xiang, Study on a large-scale discrete element model for fine particles in a fluidized bed, Advanced Powder Technology 23 (2012) 673–681. https://doi.org/10.1016/J.APT.2011.08.006.

[119] Y. Kosaku, Y. Tsunazawa, C. Tokoro, A coarse grain model with parameter scaling of adhesion forces from liquid bridge forces and JKR theory in the discrete element method, Chem Eng Sci 268 (2023) 118428. https://doi.org/10.1016/J.CES.2022.118428.

[120] S.C. Thakur, J.Y. Ooi, H. Ahmadian, Scaling of discrete element model parameters for cohesionless and cohesive solid, Powder Technol 293 (2015) 130–137. https://doi.org/10.1016/j.powtec.2015.05.051.

[121] V. Brandt, J. Grabowski, N. Jurtz, M. Kraume, H. Kruggel-Emden, A benchmarking study of different DEM coarse graining strategies, Powder Technol 426 (2023) 118629. https://doi.org/10.1016/J.POWTEC.2023.118629.

[122] A. Di Renzo, E.S. Napolitano, F.P. Di Maio, Coarse-Grain DEM Modelling in Fluidized Bed Simulation: A Review, Processes 2021, Vol. 9, Page 279 9 (2021) 279. https://doi.org/10.3390/PR9020279.

[123] I. Talu, G.I. Tardos, M.I. Khan, Computer simulation of wet granulation, Powder Technol 110 (2000) 59–75. https://doi.org/10.1016/S0032-5910(99)00268-5.

[124] J.A. Gantt, E.P. Gatzke, High-shear granulation modeling using a discrete element simulation approach, Powder Technol 156 (2005) 195–212. https://doi.org/10.1016/J.POWTEC.2005.04.012.

[125] J.A. Gantt, I.T. Cameron, J.D. Litster, E.P. Gatzke, Determination of coalescence kernels for high-shear granulation using DEM simulations, Powder Technol 170 (2006) 53–63. https://doi.org/10.1016/J.POWTEC.2006.08.002.

[126] A. Tamrakar, S.W. Chen, R. Ramachandran, A DEM model-based study to quantitatively compare the effect of wet and dry binder addition in high-shear wet granulation processes, Chemical Engineering Research and Design 142 (2019) 307–326. https://doi.org/10.1016/J.CHERD.2018.12.016.

[127] D. Barrasso, R. Ramachandran, Qualitative Assessment of a Multi-Scale, Compartmental PBM-DEM Model of a Continuous Twin-Screw Wet Granulation Process, J Pharm Innov 11 (2016) 231–249. https://doi.org/10.1007/S12247-015-9240-7/FIGURES/11.

[128] K. Hayashi, H. Nakamura, S. Watano, Numerical study on granule aggregation and breakage in fluidized bed granulation by a novel PBM with DEM-CFD coupling approach, Powder Technol 360 (2020) 1321–1336. https://doi.org/10.1016/J.POWTEC.2019.11.027.