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Impact milling of pharmaceutical agglomerates in the wet and dry states

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Abstract

This study focused on the milling of wet granulated agglomerates at points before and after drying in a typical high-shear pharmaceutical process train. These steps, referred to here as wet and dry milling, utilized a conical screen mill. Milling of granulation in the wet state eliminated 1–10 mm size agglomerates without affecting granule porosity or inducing further agglomeration. These millimeter-size agglomerates broke down during wet milling into moderately sized fragments larger than 125 μm. In contrast, when milled after drying, these same 1–10 mm-size agglomerates broke down predominantly into fine particles less than 125 μm. Data from screen-less milling trials suggest that the mill screen served only as a classifier and did not significantly contribute to the route of breakage for either wet or dry milling. However, in the case of dry milling, mill screens with grated surface textures did result in fewer fines than non-grated screens. This may be a result of reduced residence time in the mill. Experiments varying the size fraction of feed material and the rotational speed of the mill's impeller identified impact attrition as the primary mechanism governing dry granule breakage. The findings in this study shed light into the fundamental breakdown behavior of pharmaceutical agglomerates and demonstrate how breakdown of wet agglomerates via a de-lumping step prior to drying can lead to a reduced level of fine particle generation during dry milling.

Keywords: Impact milling; Agglomerates; Wet granulation; Impact attrition

1. Introduction

Wet granulation is commonly used in the pharmaceutical industry to improve the ability to process fine powder blends. Particle size control over the granulated material is important to achieve suitable flow properties and minimize segregation potential during tablet compression. Particle size at the time of compression can also affect key tablet properties such as hardness and appearance. The focus of particle size control in a typical wet granulation process train tends to center on granule growth during the wet granulation step and size reduction during milling of granules after drying. A third, but less reported on, point of size control is milling of the wet granules prior to drying.

Prior to the 1980s, many of the wet granulation processes in the pharmaceutical industry were carried out using low-shear mixers (Kadam, 1991; Parikh et al., 1997; van den Dries et al., 2003). Since it was not uncommon for low-shear granulation to result in agglomerates that approached or even exceeded the size of golf balls, it was customary to include a wet milling step to increase drying efficiency (Parrott, 1974; Kadam, 1991; Parikh et al., 1997; Schenck et al., 2002) and to eliminate large agglomerates that might otherwise break down into fine material during dry milling (Propst, 1988; Quadro Bulletin, 1990; Kadam, 1991; Parikh et al., 1997). In recent times, most pharmaceutical companies have shifted away from the use of low-shear mixers towards the use of high-shear mixers (e.g. Diosna, Fielder, Gral) (Kadam, 1991; Parikh et al., 1997; van den Dries et al., 2003). Over that same time period, the inclusion of a wet milling step has seemingly become less routine since high-shear granulation results in less 'lump' formation relative to low-shear granulation. This reduction in lump formation can be attributed to intense mixing induced by the bottom swept impeller and utilization of high-speed side-mounted chopper blades.

Although golf ball size agglomerates are generally not associated with high-shear processing, the generation of agglomerates on the order of 1–10 mm is not uncommon, even when targeting a mean granule size of only 100–200 μm. For high-shear processing, several reports highlight the beneficial impact of wet milling in reducing drying times for high-shear granulated

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material (Parrott, 1974; Kadam, 1991; Parikh et al., 1997). We previously reported that the elimination of agglomerates greater than 6 mm in size can shorten fluid bed drying times by as much as 25%, thus demonstrating that practical drivers to include wet milling in high-shear process trains do exist (Schenck et al., 2002). In this paper, attention is turned to the use of wet milling for added downstream particle size control. The high-shear processing of a conventional pharmaceutical formulation is studied with and without a wet milling step. Milling data is presented across a range of operating conditions and breakdown models are used to assess the relationship between wet and dry milling.

2. Experimental

2.1. Materials

Table 1 shows the components of starting powder blends used in this work and highlights the intended role of each ingredient. The formulations employed excipient ratios typically applied across the pharmaceutical industry. The powdered materials used in this investigation were lactose monohydrate (Foremost 80), microcrystalline cellulose (Avicel PH 101, FMC), croscarmellose sodium (Mallinkrodt), hydroxypropylcellulose (HPC, Hercules) and polyvinylpyrolidone K29/32 (PVP, BASF).

2.2. Granulation, drying and milling

Wet granulation was carried out in a 300L high-shear mixer (Aeromatic-Fielder). All components in Table 1 were added to the mixer and dry blended for 2 min using a bottom-swept impeller operating at 216 rpm and a side-mounted chopper operating at 3400 rpm. Water was used as the granulating fluid, with fluid levels reported as a weight percentage of the dry ingredients. Data presented in these studies primarily focus on fluid levels at or near the midpoint and upper limit of an operating window representing a satisfactory balance of granule flow, granule compactability, and tablet dissolution. The optimal fluid level for HPC-based granulation was shifted downward relative to that for the PVP-based granulation. The target fluid levels were approximately 40 and 55% for the HPC and PVP systems, respectively. Note that while quantitatively (i.e. optimal fluid level) these granulations differed, qualitatively (i.e. response to processing conditions) they behaved quite similarly. Water was added to the mixed powder bed using a stainless steel, flat-spray hydraulic nozzle (Spraying Systems) and was delivered over a duration of 3–6 min while operating the granulator with an impeller speed of 108 rpm and a chopper speed of 1800 rpm. Following completion of fluid delivery, mixing continued for no more than 1 min.

Table 1
Formulation utilized during studies

Component	Role
Lactose	Filler
Microcrystalline cellulose	Filler/compression aid
Croscarmellose sodium	Disintegrant
HPC or PVP	Binder
Drug X	Active ingredient

At the targeted granulating fluid level, a sample of granulation was removed from the mixer and split into two parts of equal size. One part was placed immediately into a tray dryer and the other part was wet milled prior to tray drying. The material in the wet state was gently handled and tray drying was used in place of fluid bed drying. Although not representative of the physical conditions experienced during fluid bed drying, tray drying was utilized in an attempt to remove moisture while preserving the particle size attained at the end of the wet granulation step. With this approach, the reported particle size data is representative of that achieved from the wet granulation and milling processes and not affected by attrition or consolidation that might occur during fluid bed drying. Samples were spread on trays to a depth of ∼1/2 in. and dried in an oven at 50 °C for ∼8 h until the loss on drying at 95 °C reached ≤2% as determined by a Denver Mark 40 LOD tester. This drying endpoint represented an equilibrium relative humidity level of approximately 30%.

All wet milling trials utilized a conical screen mill (Quadro Comil model 197). The default screen for wet milling comprised 9.5 mm square-shaped apertures (vendor type 375Q) and 63% total open area. This screen was chosen to achieve sufficient breakdown of the largest agglomerates while maintaining adequate throughput rates. All wet milling trials utilized a square-bar impeller operating across a range of speeds with a nominal setting of 2000 rpm. Wet milling trials were carried out immediately following high-shear granulation, with material discharged from the mixer and manually fed through a conical screen mill. Material was fed to the mill with the intent of achieving choked as opposed to dilute feed conditions. Throughputs of approximately 5–7 kg/min were achieved. Trials with up to 115 kg of wet material resulted in no appreciable buildup of material on the mill screen or impeller.

Tray dried samples were manually fed through the same conical screen mill used for wet milling. Milling studies operated across a range of speeds with a nominal setting of 2000 rpm. Unless specified otherwise, the screen used for dry milling comprised 1.0 mm grated, round-shaped apertures (vendor type 40G) and 31% total open area. This screen was selected to achieve a particle size distribution suitable for tablet compression while maintaining adequate throughput rates during milling. Select studies were also performed with non-grated mill screens (vendor R type screens) as well as screens with apertures greater than 1.0 mm. As was the case for wet milling, dry material was fed to the mill with the intent of achieving choked feed conditions, and dry milling achieved similar throughputs to wet milling in the range of 5–7 kg/min. No screen blinding or material buildup was observed during milling trials involving upwards of 140 kg of granulation. Unless specified otherwise, dry milling studies utilized non-wet milled, tray dried granulation.

2.3. Granule characterization

Particle size analysis was performed on tray dried samples before and after dry milling using 8-in. diameter sieve screens and a sieve shaker (Tyler Ro-Tap). Before dry milling, representative samples of 1–2 kg in size were sieved using some combination of screens with apertures of 12.7, 6.3, 4.8, 2.8, 1 mm and a pan. Approximately 20 g samples were then removed from the pan and further sieved using screens with apertures of 500, 250, 180, 125, 90, 63, 45 μm and a pan. Particle size data for material before dry milling is presented as a composite of the coarse and fine mesh data. After dry milling, representative samples of ∼20 g in size were sieved using screens with apertures of 500, 250, 180, 125, 90, 63, 45 μm and a pan. Particle size data is presented in histograms with mass percent retained plotted against sieve screen aperture.

Pore volume measurements were made with a Quantachrome Poremaster 60 using tray dried granules ranging in size from 500 to 850 μm. The mercury intrusion method applied here utilized a low pressure cycle from 0 to 30 psi, followed by a high pressure intrusion cycle up to 15,000 psi. Solid volume was derived from true density measurements made with a Micromeritics Accupyc 1330 helium pycnometer. Porosity values are reported as percent total porosity, which was calculated by dividing pore volume by pore volume plus solid volume.

3. Results

3.1. Wet milling trials

Visually, the wet milling process significantly reduced the number of large agglomerates fed through the mill. Figs. 1 and 2 display particle size data for tray dried samples of wet milled and non-wet milled material that had been granulated to 55 and 65% fluid levels, respectively. Data in Figs. 1 and 2 confirm visual observations that wet milling did indeed significantly reduce the level of large agglomerates. All agglomerates larger than the screen aperture (9.5 mm) were eliminated, while most agglomerates greater than 2.8 mm were also eliminated. Wet milling of the 55% fluid level sample broke down the large agglomerates predominantly into particles larger than 125 μm, whereas wet milling of the 65% fluid level sample broke down the agglomerates predominantly into particles larger than 250 μm.

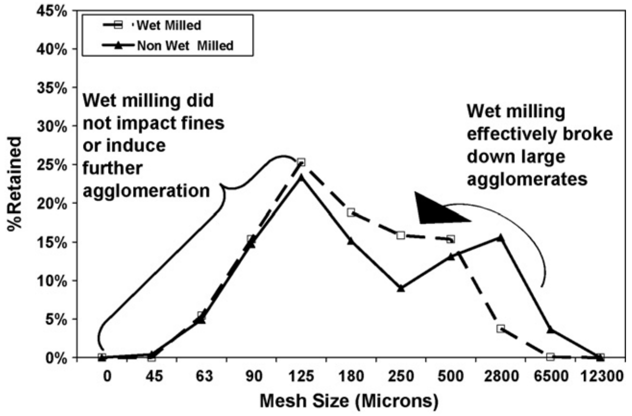

Fig. 1. Histogram showing the impact of wet milling on the particle size of PVP-based granulation at 55% fluid level (wet milled samples (□), and non-wet milled (▲)).

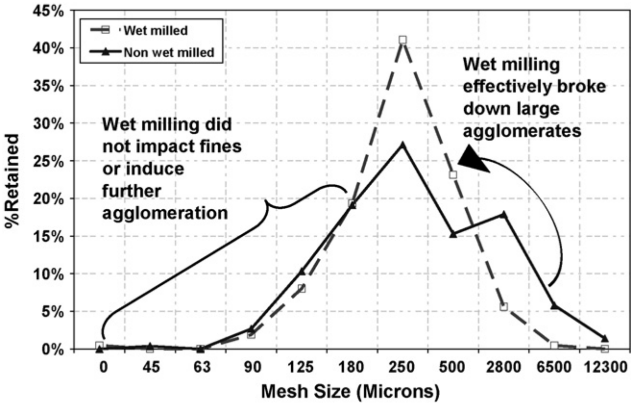

Fig. 2. Histogram showing the impact of wet milling on the particle size of PVP-based granulation at 65% fluid level (wet milled samples (□), and non-wet milled (▲)).

As seen in Figs. 1 and 2, wet milling at both 55 and 65% fluid levels broke down large agglomerates without impacting the material in the particle size range below 125 μm. This suggests that wet milling in this study exclusively involved breakage events with no additional granulation occurring. Mercury porosimetry measurements were used to determine if any granule consolidation had occurred during wet milling. For the non-wet milled samples, the pore size distributions demonstrated a mode at ∼25 μm, with a shoulder out to ∼0.5 μm. With increasing fluid levels the magnitude of the mode decreased as the shoulder grew slightly in the range of 0.5–5 μm. Total porosity values were 48% for the 55% fluid level material and 40% for the 65% fluid level material. Both the shape of the pore size distributions and the total porosity were nearly identical between wet milled and non-wet milled samples. This suggests no densification of the granules occurred during wet milling.

Studies were conducted without a mill screen in an attempt to ascertain the role of the screen. Note that these studies involved the formulation using HPC as a binder. Additional wet milling experience (data not shown here) has confirmed qualitative similarity in wet milling responses for the PVP and HPC granulations. Wet material was passed through a screen-less mill multiple times with the impeller operating at 2000 rpm. Samples were then tray dried, with particle size of dried samples measured as a function of the number of passes through the mill. As shown in Fig. 3, these studies revealed that by eight passes, the resulting particle size distribution closely approximated milling with the nominal 375Q (9.5 mm aperture) screen. Note that there was a slight reduction in the level of material less than 90 μm after eight passes through the mill. This is likely a result of excessive material handling associated with passing the same material through the mill multiple times. Excessive handling is believed to have caused some agglomeration of fine particles whereas single pass milling, with or without a screen, did not show any evidence of such agglomeration.

Wet milling experiments using different impeller speeds were also performed. Fig. 4 shows that a change in impeller speed from 1000 to 2500 rpm minimally influenced the resulting wet milled particle size data. Use of both 1000 and 2500 rpm eliminated all agglomerates greater than 6.3 mm and neither speed

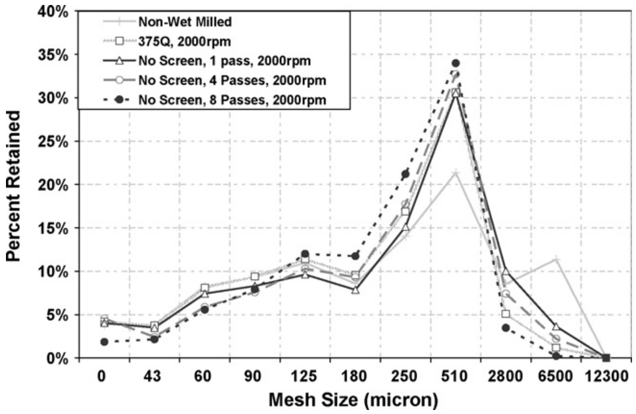

Fig. 3. Histogram showing the impact wet milling on the particle size of HPC-based granulation at 40% fluid level. Data is shown for single pass milling with a 375Q screen, single pass milling without a screen, and multi-pass milling without a screen.

impacted the size region below 90 um. The use of 2500 rpm did result in slightly more breakdown of agglomerates between 2.8 and 6.3 mm but, all in all, impeller speed had relatively little effect on wet milling performance.

3.2. Dry milling trials

Figs. 5 and 6 show particle size data before and after dry milling for the 55 and 65% fluid level samples, respectively. Dry milling of each sample effectively eliminated all agglomerates larger than the mill screen aperture (1.0 mm). In the case of the 55% fluid level material, the largest agglomerates appeared to primarily break down into particles less than 125 μm. For the 65% fluid level sample, the largest agglomerates appeared to break down into particles less than 180 μm. Compared to wet milling, dry milling broke down large agglomerates into much finer particles.

Dry milling trials across a range of impeller speeds were carried out for the 65% fluid level granulation. Fig. 7 shows that dry milling broke down the largest agglomerates predominantly into fine particles for all impeller speeds investigated and that changes to impeller speed primarily impacted the extreme regions of the particle size distribution. Increases to impeller speed reduced the level of particles >500 μm at the direct expense of raising the level of particles <45 μm.

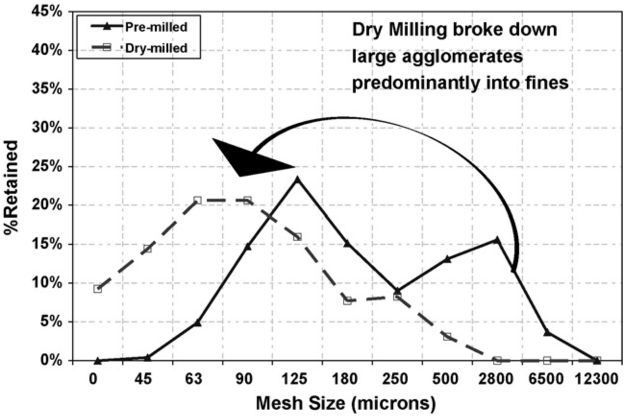

Fig. 5. Histogram showing the impact of dry milling on the particle size of PVP-based granulation at 55% fluid level.

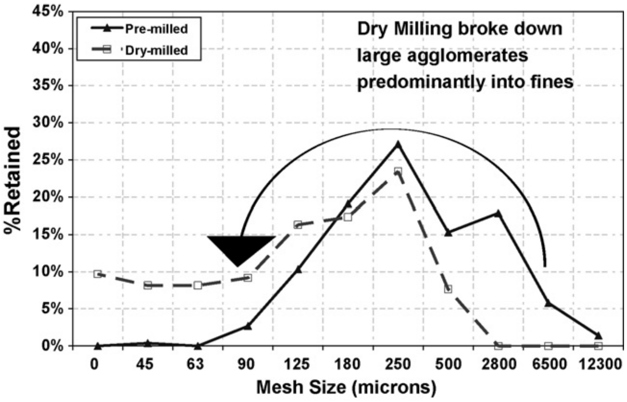

Fig. 6. Histogram showing the impact of dry milling on the particle size of PVP-based granulation at 65% fluid level.

Additional dry milling experiments were conducted with feed granules of varying size. To support these trials, tray dried gran-

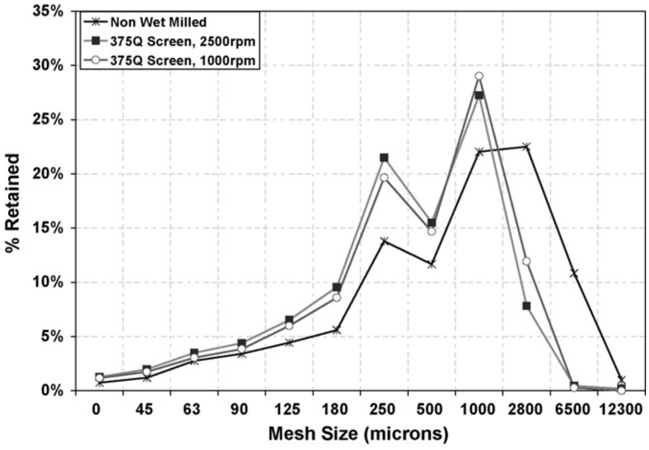

Fig. 4. Histogram showing the impact of impeller speed on the particle size of HPC-based granulation at 45% fluid level.

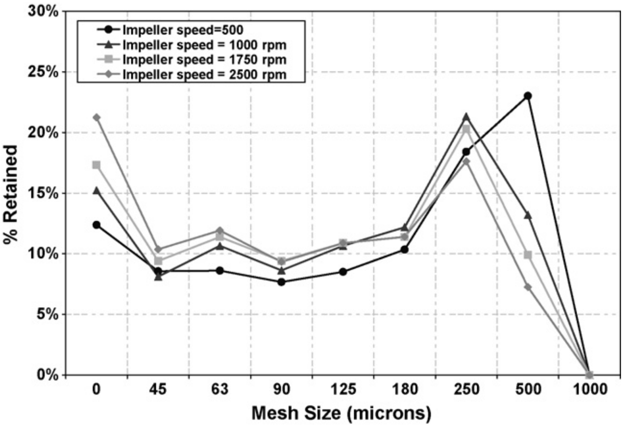

Fig. 7. Histogram showing the impact of impeller speed during dry milling on the particle size of PVP-based granulation at 65% fluid level. See Fig. 6 for the corresponding un-milled particle size data.

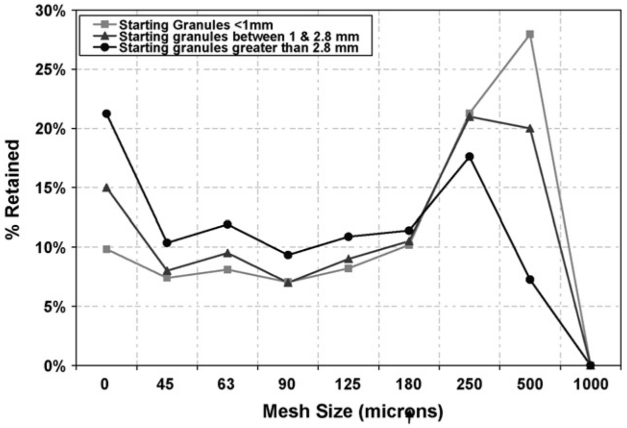

Fig. 8. Histogram showing the impact of feed size on dry milled particle size for PVP-based granulation at 65% fluid level.

ulation at 65% fluid level was sieved into three size fractions: >2.8, 1–2.8 and <1 mm. The particle size results from independent milling trials with each of these size fractions are plotted in Fig. 8. Interestingly, the coarser starting material led to a higher level of fines generation during dry milling.

Additional dry milling studies involved an evaluation of different mill screen surfaces. Data presented thus far utilized mill screens with grated surfaces (vendor G type screens). These cheese-grater types of screens are claimed by the vendor to reduce fines generation during dry milling. As a means of comparison, dry milling trials with the 65% fluid level granulation were also performed using screens with smooth, non-grated surfaces (vendor R type screens). Two different smooth-surface screens were evaluated: a 1.0 mm aperture screen (39R) and a 1.9 mm aperture screen (75R). Fig. 9 compares the particle size data obtained from milling with the two different smooth-surface screens to milling with the grated-surface screen having a 1.0 mm aperture. This data shows that the smooth and grated screens having comparable apertures of 1.0 mm yielded material with significantly different particle size characteristics. The smooth screen resulted in less material >180 μm and elevated levels of material <90 μm. In order to begin to approximate levels of particles less than 180 μm obtained from milling with the grated screen, a smooth screen with nearly double the aperture size was required (75R). Thus, while it still appears in all the scenarios investigated that the largest particles break down predominantly into fines during the dry milling process, surface texture of the mill screens did exhibit some degree of influence on the resulting particle size data.

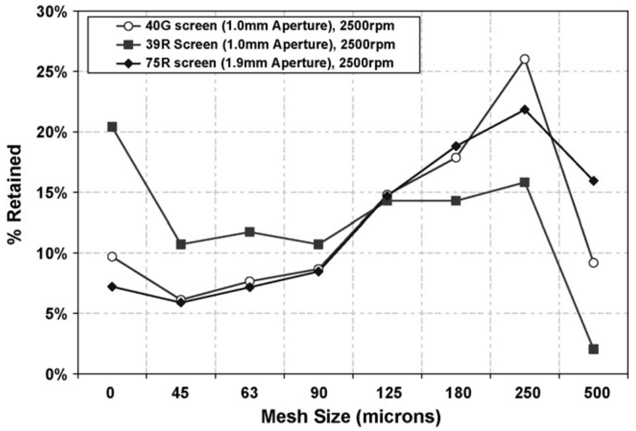

Fig. 9. Histogram showing the impact of dry milling screen aperture and surface texture on particle size of PVP-based granulation at 65% fluid level. Refer to Fig. 6 for the corresponding particle size of the starting material.

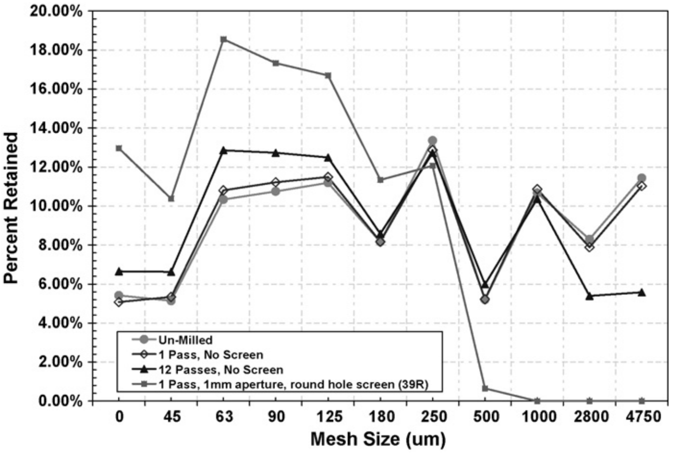

Fig. 10. Histogram showing the impact of dry milling on particle size of HPC-based granulation at 40% fluid level. Data is shown for single-pass milling with a 1.0 mm aperture screen (39R) and multiple passes through the mill without a screen.

The final round of dry milling studies sought to ascertain the role of the mill screen in agglomerate breakage. Note that these studies involved the formulation using HPC as a binder. Additional dry milling experience (data not shown here) has confirmed qualitative similarity in dry milling responses for the PVP and HPC granulations. A sample of 40% fluid level granulation was passed through the mill multiple times without a screen in place. Particle size was measured as a function of the number of passes through the mill. Fig. 10 plots particle size data for 1 and 12 passes without a screen along side data obtained from milling the same material with a 1.0 mm aperture screen (39R). After one pass through the mill without a screen, the resulting material was virtually indistinguishable from the un-milled material. However, after 12 passes without a screen, the resulting particle size data began to seemingly approach the results from single-pass milling with a screen. A linear extrapolation of the sieve results beyond 12 passes suggests that by 60–70 passes of milling without a screen, the sieve data would roughly approximate one pass through the mill with a screen.

3.3. *Effect of wet milling on dry milling*

After studying the wet milling and dry milling operations separately, the next set of experiments sought to investigate any interdependencies between the two milling steps. These experiments evaluated the impact of wet milling on the dry milling process. Wet milled and non-wet milled samples at 65% fluid level were tray dried and then dry milled. Fig. 11 shows that the inclusion of a wet milling step reduced the level of fines

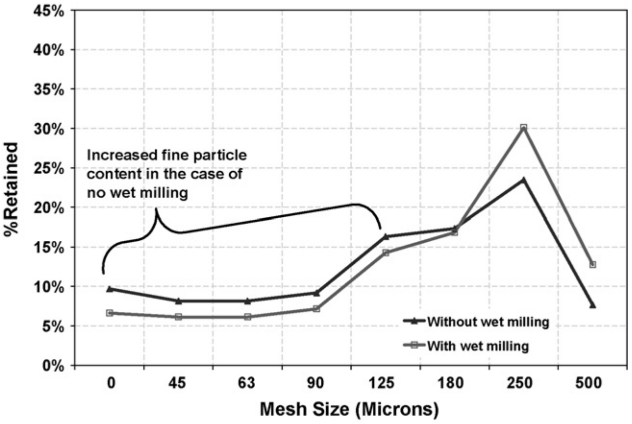

Fig. 11. Histogram showing the impact of wet milling on the dry milling particle size of PVP-based granulation at 65% fluid level.

generated during dry milling. These data highlight a relationship between the two milling steps, which will be addressed in greater detail in the next section.

4. Discussion

Fig. 11 demonstrated how inclusion of a wet milling step in a high-shear process train could result in the generation of fewer fine particles during dry milling. Potential benefits of reduced fines content for a pharmaceutical granulation include enhanced flow properties and reduced risk of size-based segregation. To this end, a more fundamental understanding of the milling operations was sought with the ultimate goal of applying this knowledge to optimize particle size control in the manufacture of oral solid dosage forms. The remainder of this section is dedicated to discussion of the breakdown mechanisms of granules in both the wet and dry states.

4.1. Wet milling analysis

Contrary to some previous reports on wet milling (Propst, 1988; Quadro Bulletin, 1990; Kadam, 1991; Parikh et al., 1997), granules in this study did not appear to undergo size reduction through any sort of extrusion phenomena. Comparing size data from milling with and without a screen suggests that the mill screen did not influence the breakdown mechanism. The multi-pass data in Fig. 3 suggests that the wet agglomerates broke down due to collisions with the impeller, not extrusion through the mill screen. It appears that the screen served primarily as a classifier, increasing residence time of the largest particles in the milling zone until impact events broke them down into size fractions below the screen aperture.

Wet milling data in Figs. 1–4 showed breakage of large agglomerates without detectable granule growth as evident by the unaltered fines content. Mercury porosimetry data indicated the absence of granule consolidation during wet milling. The breakage of agglomerates and the absence of growth and consolidation suggests that wet milling in this study occurred primarily in what Iveson and Litster refer to as the ‘crumb’ region of their granule regime map (Iveson and Litster, 1998; Iveson et al., 2001). The crumb region is defined as occurring where impact kinetic energy is high relative to the plastic energy absorbed by the agglomerates per unit strain. As a result, destructive forces dominate in the crumb region with no granule growth occurring (Iveson et al., 2003; Iveson and Page, 2004).

Wet milling data presented in the results section indicated relatively little sensitivity to the process conditions explored in this work. Fig. 3 demonstrates that the mill screen was serving only as a classifier during wet milling and Fig. 4 shows that changes to impeller speed from 1000 to 2500 rpm had a negligible influence on the resulting particle size data. The only parameter in this study that exhibited some degree of wet milling sensitivity was fluid level of the granulated material. The 65% fluid level material broke down into coarser size fractions relative to the 55% fluid level material (see Figs. 1 and 2). This is thought to be a consequence of higher granule strength associated with the 65% fluid level sample. Researchers have linked increased granule consolidation to increased granule strength (Kristensen et al., 1985; Iveson et al., 2001; Simons and Pepin, 2003). Therefore, the increase in granule strength with increasing fluid level in this study would be consistent with the porosity data presented earlier.

The wet milling findings in this study can also be utilized to infer what material properties might be most significantly contributing to strength of the agglomerates, particularly those in the 1–10 mm range that were impacted during wet milling. The strength of wet agglomerates is reported to depend on a balance between capillary, frictional and viscous forces (Kristensen et al., 1985; Bika et al., 2001; Iveson et al., 2001; Verkoeijen et al., 2002; Simons and Pepin, 2003; van den Dries et al., 2003; Fu et al., 2004; Kohonen et al., 2004; Fournier et al., 2005; Herminghaus, 2005). The lack of impeller speed dependency in Fig. 4 suggests that viscous forces are not dominant here. Viscous forces contribute to agglomerate strength via dissipated energy of liquid bridges during their rupture under dynamic load (Iveson et al., 2001; Kohonen et al., 2004). Had viscous forces largely contributed to agglomerate strength in this work, impeller speed would have been expected to impact breakage since viscous forces are highly strain rate dependent (Iveson et al., 2003; Herminghaus, 2005). Frictional forces are also believed to not have dominated in this study since an increase in granulating fluid level led to break down into larger, as opposed to smaller, size fractions (see Figs. 1 and 2). Had frictional forces been dominant, the opposite behavior would have been expected due to an increase in lubricating effects associated with the higher fluid level (Iveson et al., 2003; Simons and Pepin, 2003). Thus, by the process of elimination, capillary forces are thought to have dominated granule strength in this work. The binder fluid located between solid particles in wet granulated material results in capillary forces that are thought to be directly proportional to the binder fluid’s surface tension (Iveson et al., 2001; Verheezen et al., 2004). Wet granulation studies conducted by Fournier et al. (2005) with spherical glass particles also concluded that capillary forces dominated wet granule strength.

4.2. Dry milling analysis

A comparison of data from the wet milling and dry milling trials in this investigation would lead one to easily conclude that wet and dry agglomerates follow different routes of breakage in a conical screen mill. Breakage during wet milling appears to be dominated by fragmentation-like events, whereby large agglomerates break down into moderately sized agglomerates. On the other hand, dry milling is seemingly dominated by some other mechanism as evident by the breakdown into mostly fine particles. As a matter of fact, Fig. 8 indicates how coarser starting material broke down into finer material after dry milling. A more in depth analysis of dry milling follows.

Breakage of dry agglomerates is reported to generally proceed via wear, also commonly referred to as attrition or erosion (Kadam, 1991; Parikh et al., 1997; Subero and Ghadiri, 2001). This route of breakage is attributed to pore structures within the agglomerates that serve as defects and stress concentrators (Kadam, 1991; Bika et al., 2001; Iveson and Page, 2004). Subero and Ghadiri (2001) further qualified that stresses from impacts do not propagate readily throughout porous agglomerates, resulting in what they refer to as localized disintegration, particularly at low impact velocities. A similar theory of limited crack propagation was proposed by Hogg et al. (2002), who stated explosive fracture would occur at the contact point for agglomerates. Subero and Ghadiri (2001) showed that at high velocities, some level of fragmentation could occur as agglomerates began to propagate stresses to a point where resulting crack lengths approached the agglomerate diameters. Salman et al. (2003) showed similar results with single particle impact trials using fertilizer granules. Their studies showed damage limited to the contact area at low velocities resulting in localized disintegration, then a transition to larger scale cracking at higher velocities, and nearly complete disintegration of the granules at the highest velocities (Salman et al., 2003). Additionally, Samimi et al. (2003) showed a similar transition during single particle impact tests with two granules processed by different routes, where localized chipping occurred at low velocities and larger scale fragmentation at higher velocities.

Attempts to quantify the breakage mechanism(s) of dry agglomerates in this study were performed using breakage models available in the literature. Numerous empirical models have been proposed for the breakage of single component systems (Austin, 2002; Tavares and King, 2002; Vogel and Peukert, 2003; Hill, 2004; Bilgili and Scarlett, 2005), while a more limited set of empirical models have been reported on agglomerates that correspondingly involve complex pore structures (Neil and Bridgewater, 1999; Utsumi et al., 2002). The limited number of predictive models that address the breakage properties of agglomerates (Subero and Ghadiri, 2001) are accompanied by even fewer experimental studies to substantiate these theories (Iveson and Page, 2004; Subero and Ghadiri, 2001; Verheezen et al., 2004). The lack of applicable models and experimental data for agglomerate systems is likely due to the difficulty of measuring intrinsic mechanical properties of agglomerates (Bika et al., 2001; Vogel and Peukert, 2003; Liu et al., 2003; Pitchumani et al., 2003). One model that has been successfully applied to both single component systems (Han et al., 2003) and agglomerated systems (Salman et al., 2003) is the impact attrition model, proposed by Ghadiri and Zhang (Ghadiri and Zang, 2002; Zang and Ghadiri, 2002). The following equation for impact attrition predicts how the volumetric wear rate, V, depends on granule size and impeller speed:

$$V \propto \frac{\rho_{\mathrm{p}} U^2 d_{\mathrm{g}} H}{K_{\mathrm{c}}^2}$$

where ρ is the particle density, U the impact velocity, d_{g} the granule diameter, H the hardness and K_{c} is the fracture toughness. Breakage or volumetric wear rate, V, was defined in this study as the amount of material after dry milling that passed through a 90 μm sieve. The applicability of this equation was investigated here through examining responses in wear rate due to variations in granule feed size and impeller velocity. This evaluation proceeded with the assumption that density, hardness and fracture toughness were roughly equivalent across the range of granule feed sizes tested. This was considered a reasonable approximation given that compositional consistency across granule size had been experimentally demonstrated for this and similar systems. Compositional consistency is believed to maintain material property consistency well enough for the purposes of this investigation.

Fig. 12 shows wear rate as a function of starting granule size for five different sieve cuts collected from the 65% fluid level material. The figure shows a linear relationship between fines generation and starting size of the granules. In Fig. 13, wear rate for the 65% fluid level material is plotted against mill speed with the assumption that impact velocity is directly proportional to rotational speed of the impeller. The plot shows a strong relationship between fines generation and impeller speed squared. The facts that wear rate is linearly dependent on the diameter of the feed material and shows a second-order dependence on impact velocity suggests that the dry agglomerates in this study broke down in the conical screen mill by impact attrition. Verheezen et al. (2004) reached similar conclusions, where large agglomerates broke down into fines regardless of mill settings during conical screen milling trials with a formulation comprised of hydroxypropylcellulose, lactose and corn starch. Additionally,

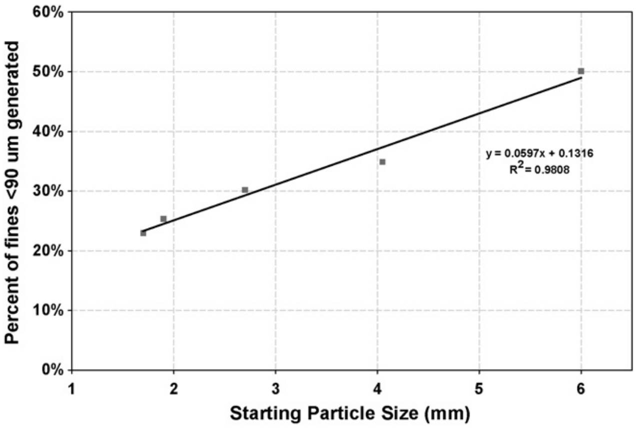

Fig. 12. Effect of feed granule size on fines generation during dry milling.

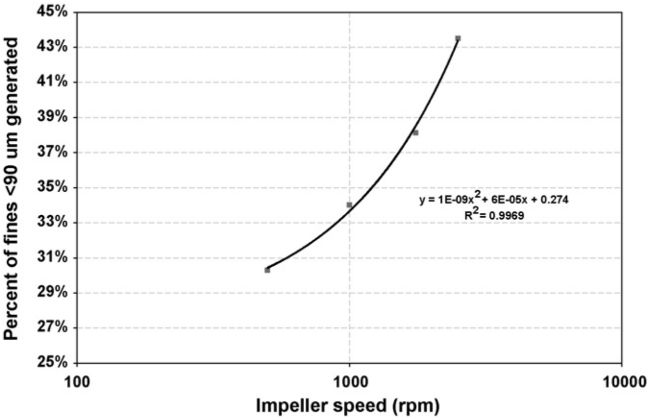

Fig. 13. Effect of impeller speed on fines generation during dry milling.

Hogg et al. (2002) concluded for ball milling of sintered alumina aggregates that the route of breakage appeared to be fixed regardless of mill speed or aggregate density, with breakage generating significant fines.

Similar to the conclusion reached for wet milling, the dry milling data in this work suggests that the mill screen acted only to increase residence time in the impact zone, and did not play a significant role in the mode of breakage. Fig. 10 shows that by 12 passes through a mill without a screen, the resulting particle size began to approach single-pass milling with a 1.0 mm aperture, non-grated screen. It was speculated that 60–70 passes through the mill would have yielded results on par with single-pass milling with a screen. This implies that impact of granules with the impeller determines the route of breakage and that the screen serves merely as a classifier. However, in Fig. 9, the use of a grated screen was demonstrated to result in fewer fines compared to non-grated screens of similar aperture. Verheezen et al. proposed that grated screens reduce residence time in a conical screen mill due to the grates acting to channel material through the screen apertures, essentially improving the classifying efficiency of the mill screen. Lower residence times would result in fewer impacts, and therefore less breakage (Verheezen et al., 2004). The findings in our work seem to support his hypothesis. An alternative theory, though, is that the grated surface texture does influence the route of breakage and perhaps acts to chip off fragments from the large agglomerates. The introduction of a second mode of breakage could, in turn, lessen the contributions from impact attrition. Regardless of which theory is more accurate, the data in Figs. 12 and 13 were generated with a grated mill screen and so it appears that impact attrition remains the dominant mechanism irrespective of which type of conical mill screen is employed.

5. Conclusions

The route of breakage during milling in a conical screen mill was found to be significantly different for pharmaceutical agglomerates in the wet and dry states. Wet agglomerates larger than 1.0 mm broke down primarily into moderately sized fragments larger than 125 μm. In contrast, when milled after drying, these same large agglomerates broke down predominantly into particles under 125 μm. By varying the size of feed material and impeller speed during milling trials, impact attrition was identified as the primary mechanism governing dry granule breakage. The results in this study also suggest that, for both wet and dry milling, the mill screen did not play a dominant role in determining the mode of agglomerate breakage. In the case of dry milling, screens with grated surfaces did lead to a reduced level of fines compared to non-grated screens of similar aperture. However, it is not clear at this point whether this result is related to residence time effects in the mill or due to the grated surface contributing to a secondary mode of breakage. Regardless, impact attrition is thought to remain the primary route of breakage for dry granules in a conical screen mill. The findings in this study provide fundamental insight into the breakdown of agglomerated pharmaceutical materials and practically demonstrate that inclusion of a de-lumping step prior to drying can lead to a reduced level of fine particle generation during dry milling.

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