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Analysis of Pin Milling of Pharmaceutical Materials

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Abstract

Milling is an important process for tailoring the particle size distribution for enhanced dissolution, content uniformity, tableting, etc., specially for active pharmaceutical ingredients and excipient in pharmaceutical industries. Milling performance of particulate solids depends on the equipment operating conditions (geometry, process conditions and input energy etc.) as well as material properties (particle size, shape, and mechanical properties, such as Young's modulus, hardness and fracture toughness). In this work, a newly developed approach to assess the breakability of pharmaceutical materials using an aerodynamic dispersion method has been combined with the Discrete Element Method (DEM) to simulate the dynamic behaviour of a number of pharmaceutical materials in a pin mill. A sensitivity analysis is carried out addressing the effect of the milling conditions (rotational speed of the mill and feed particle flow rate) and feed properties on the milled products in terms of the shift in the specific surface area of the milled particles. The outcome of the work is used as a method to predict the breakage of the particles for the milling conditions where chipping takes place.

KEYWORDS: milling; breakage; impact; Picoline; pin mill

1 Introduction

Particle size reduction is a common and crucial process in food, chemical and pharmaceutical industries (Patel et al, 2008) to tailor the particle size distribution to meet the process and product requirements, such as dissolution of a drug (Khadka et al., 2014) or content uniformity of the dosage forms (Poska et al., 1993; Rohrs et al., 2006). It also influences the product flowability and packing properties and, in the case of pharmaceutical ingredients, tablet strength and pharmacological effects of the drug (Neikov, 2009). Milling is as a critical unit operation, as it changes the width and cut-off of the particle size distribution as well as particle shape and surface properties, which all contribute to defining the product quality (Nakach et al., 2004). Mills are classified depending on the way in which the forces are applied (e.g. impact, shear and compression) (Naik and Chaudhuri, 2015 and Loreti. 2017). The choice of a mill depends on the feed material properties, such as feed particle size and hardness, as well as the properties of the end product. Milling can be done in dry state (dry milling) or using a liquid medium, which is referred as wet milling. The process has a number of disadvantages, depending on the mill type. It could cause poor product flowability, solid state transformation and agglomeration as the particle size is reduced to a range where adhesive forces dominate the inertial and gravitational forces. It is also a very energy intensive and inefficient process (Canilha et al., 2012). Amongst various mill types, the focus of this study is on the pin mill. It is a mechanically driven machine, having a rotor-stator system, comprising two disks; one rotating and one stationary with pins mounted on them. The rotational speed can be varied depending on particle properties and size reduction extent. The maximum speed depends on the size and type of the mill. The particles are

fed and introduced to the centre of the mill. Impact is the main breakage mechanism in this mill, where the product particle size range of 10 - 100 μm is normally achieved (Saravacos and Kotaropoulos, 2002; Nakach et al., 2004; Lan and Mahaparta, 2007). There is no control over the milled particle size distribution and so a combination of a pin mill and integrated classifier would be needed to provide the desired particle size distribution (Stein et al., 2010). Nakach et al. (2004) studied the effect of rotational speed, number of passes (by feeding back the milled product), particle size and feed rate in a pin mill using vitamin C particles. The specific surface area of the milled powder was found to vary linearly with the square of the rotational speed up to 150 m/s peripheral speed, beyond which the slope changed. They also reported that after two passes the product particle size distribution no longer reduced further. The effect of the feed rate on the product size distribution was found to be negligible. Nowakowski et al. (1986) used two different types of pin mill and an attrition mill (the latter not addressed here) to investigate the damage on starch particles as a result of milling of flour. They used an Alpine 63 laboratory counter-rotating pin mill, operating at 27000 rpm (equivalent to 37 m/s peripheral speed), and a commercial-sized Alpine Contraplex 250 CW counter-rotating pin mill, operating at 6000 and 11500 rpm (equivalent to 240 m/s peripheral speed). It was found that pin milling of flour resulted in chipping and splitting of starch granules as opposed to attrition-milled flours which was by surface abrasion. The milled particles were then analysed using X-ray diffraction. It was shown that the effect of heat generated in a pin mill adversely affected the quality of starch particles. Fisher's work (2006) on milling of active pharmaceutical ingredients also showed that due to generation of heat the operating temperature could rise to 40-60 °C.

Despite the above-mentioned extensive studies, the dynamic behaviour and breakage mechanisms of the particles in the pin mill, and in fact for most mill types are poorly understood.

A number of test methods have been developed to analyse and assess the breakability of materials, ranging from quasi-static to dynamic stressing for both single and assemblages of particles in an attempt to describe the processes prevailing in a mill (Ghadiri et al., 2007; Olusanmi et al, 2011; Bonakdar et al., 2016a). The choice of technique and device depends on the dominant breakage mechanism of the mill (e.g. impact, shear or compression, surface abrasion). For instance, dynamic impact breakage techniques, such as the single particle impact testing, are best suited to analyse and evaluate the particle breakage in pin mills. The works of Salman et al. (1995, 2003) on the breakage of alumina agglomerates and fertiliser granules, Lecoq et al. (2003) on sand, Kwan et al. (2003) on microscrytalline cellulose, Samimi et al. (2004) on detergent granules, Khanal et al. (2004) on large concrete balls and Bonakdar et al. (2016a) on spray-dried burkeite particles are examples of application of this technique for evaluation of particle breakage. However, availability of the device, time taken for measurement and minimum sample quantity are some of the limitations of the single particle impact testing. Recently, Bonakdar et al. (2016a) developed a novel breakability assessment technique using aerodynamic dispersion by the Scirocco disperser of the Malvern Mastersizer 2000. The analysis of Ali et al. (2016) was used for calculating the particle impact velocity as a function of the applied pressure to the dispersion nozzle. Using this approach, the breakage of particles as a result of impact in the disperser was evaluated at different air pressures and expressed as a shift in the specific surface area of the particles. This was then related to different parameters such as size and envelop density of feed particles, impact velocity and size of debris produced as a result of breakage. This method provided a fast and simple method to evaluate the breakability of different materials using a very low quantity of them. The breakability of sucrose, aspirin, α-

lactose monohydrate and spray-dried burkeite particles was assessed using this technique (Bonakdar et al. 2016 a, b).

Size distribution of the broken/ milled particles provides information on particle breakability and the role of material properties (Aulton, 2002 and Backhurst et al., 2002) . For particles with low fracture toughness, Heywood (1950-2) showed that in the initial stages of size reduction, fragmentation takes place. As milling progresses (or as the rotational speed is increased), the large fragments break into smaller pieces. By the last stage of milling very fine particles are produced. This pattern does not apply to tough particles, where size reduction is effected by surface chipping, as in attrition milling (Ghadiri et al. 2007). So clues could be obtained on the mechanism of size reduction by studying the temporal variations of particle size distribution.

The extent of particle breakage as a result of milling can of course be easily quantified. However, the interpretation of the trend and its dependence on the mill dynamics and feed properties require an analysis of particle dynamics within the mill. This can best be done by numerical simulations based on Discrete Element Method (DEM). However, simulation of milling and particle breakage poses serious challenges. Generation of fine particles, resulting in a substantial increase in the number of particles with smaller sizes and differing shapes, is an issue which cannot easily be tackled by DEM alone with the current computer power and memory. Therefore, different approaches have been used to handle this problem and predict closer results to reality (Capece et al. 2018). Nevertheless, DEM still provides a significant insight into the dynamics of the milling process and particle behaviour, where obtaining similar information by experimental work can be difficult in the case of particle velocity and impossible for prevailing stresses in the mill.

In this study, DEM simulation has been used to analyse the particles dynamics in a pin mill. The information obtained on velocity and number of impacts is combined with single particle breakage kernels to predict the milling behaviour in terms of the relative shift in the specific surface area. PicoPlex (the pin mill of Picoline) has been chosen as a mill of interest. Picoline (Hosokawa Alpine AG, Augsburg, Germany) is a modular miniature process system, comprising eight different machines, specially designed for small quantity of material (from <1 g to several grams). PicoPlex is one of the modules and works similarly to a pin mill. The unit is composed of two disks on which pins are mounted, as shown in Figure 1; one rotating and one stationary.

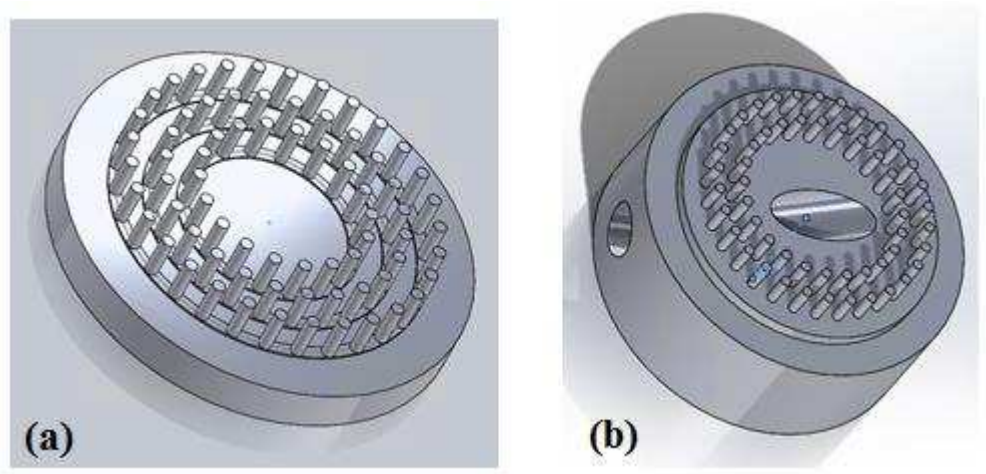

Figure 1. PicoPlex geometry; (a) rotating disk and (b) stationary disk

The feed is introduced to the centre of the mill, the particles impact onto the pins, break and leave the unit. The experimental part of the work here has been carried out by milling aspirin, paracetamol and α-lactose monohydrate. The breakage kernels of the materials have been developed using the approach of Bonakdar et al. (2016a). EDEM simulation software package (DEM Solutions, Edinburgh, UK) is then used to analyse the particle dynamics in the mill. The

impact velocity and collision frequency, obtained from simulations, are then used in conjunction with the breakage kernels to describe the process of size reduction in the mill. The outcomes of the simulations are compared with results of experiments carried out on the mill.

2 Methodology

The materials used for milling are crystals of aspirin, paracetamol and α-lactose monohydrate (DMV, the Netherlands). Based on the specification of PicoPlex unit, the maximum particle feed size to be used for milling is 500 μm due to the geometry and gap size between the pins. Therefore each material is sieved to provide a narrow size distribution of feed particles. Sieve cuts of 300-355 μm, 355-425 μm and 425-500 μm are used for aspirin and paracetamol, and 212-250 μm, 300-355 μm, 355-425 μm and 425-500 μm for α-lactose monohydrate (α-LM), based on the quantity available. Each sieve cut is then fed into the mill using a very low flow rate to ensure single particle collisions with the pins and avoid interparticle interactions, so as to provide a sound interpretation with the aid of the breakage kernels established by Scirocco testing. Three rotational speeds are used: 3000, 6000 and 10000 rpm. The milled products after each test are collected and their size distribution is analysed using the wet module of the Malvern Mastersizer 2000 (Malvern Instruments, Malvern, UK). The breakage function of each material is then developed using the breakability assessment technique, based on aerodynamic dispersion proposed by Bonakdar et al. (2016a). The choice of materials has also been in line with their work. The Malvern Mastersizer 2000 particle size analyser is used to quantify the shift in the specific surface area of the particles as they break due to impact. The breakage kernel is expressed in terms of the relative shift in the specific surface area as a function of different parameters, such as the feed particle size and envelope density, impact velocity, average size of

the debris produced and material properties. The EDEM software package is used to simulate the dynamic behaviour of the particles in the mill and obtain information, such as distribution of number of impacts as well as impact velocity. The combination of the EDEM simulation and breakage kernels enables the prediction of the shift in the specific surface area of the particles as a function of rotational speed in the range in which the dominant breakage mechanism is chipping. The predicted results are then compared to those of experiments.

3 Results and Discussion

3.1 Experimental

Particles of each material were sieved using American Standard Test Sieve Series (ASTM) to provide narrow size distributions. Each sieve cut was then fed into the PicoPlex mill using a vibratory feeder at a very low flow rate. Tests were carried out at 3000, 6000, 10000 and 30000 rpm rotational speeds - the only controllable variable of the mill. The size distribution of the milled particles was then analysed using the wet module of the Malvern Mastersizer 2000. 2,2,4-trimethylpentane, on its own and also with 0.1 w/w % lecithin and propanol-2-ol were used as the liquid medium for dispersion of aspirin, paracetamol and α-lactose monohydrate, respectively. The particle concentration was adjusted so that an obscuration of 5-10 % of the laser light was obtained for all the measurements. As an example the particle size distributions of each material after milling at different speeds of the rotor are shown in Figures 2-4 for the smallest sieve cut of each feed materials. The results for other sieve sizes are shown in Appendix. The shift in the specific surface area of the milled products was calculated based on the particle size distribution data reported by Malvern Mastersizer 2000 measurements, which will be used in the next sections.

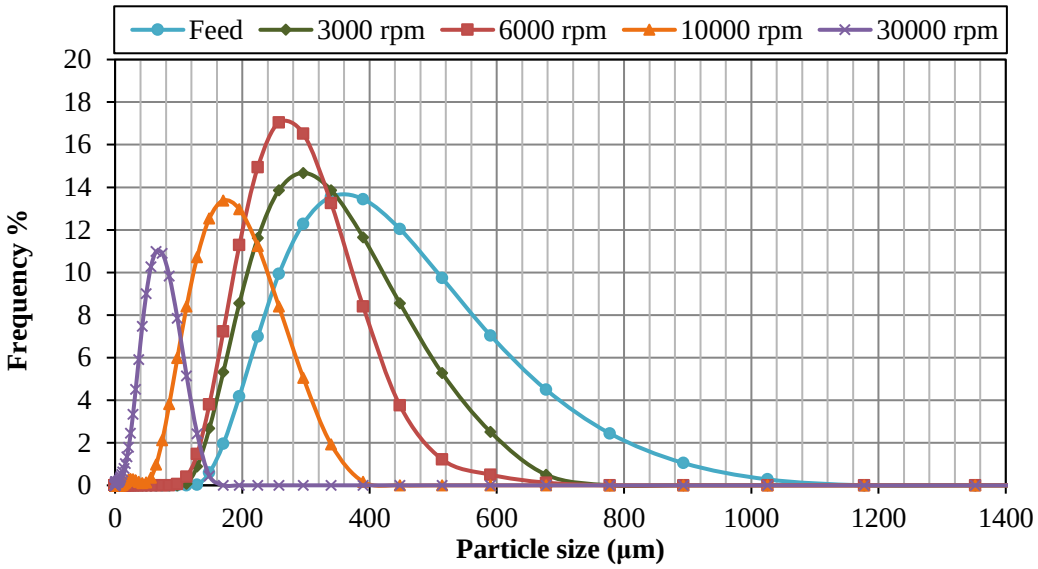

Figure 2. Particle size distribution of the milled product of aspirin (300-355 µm feed size) at different rotor speeds

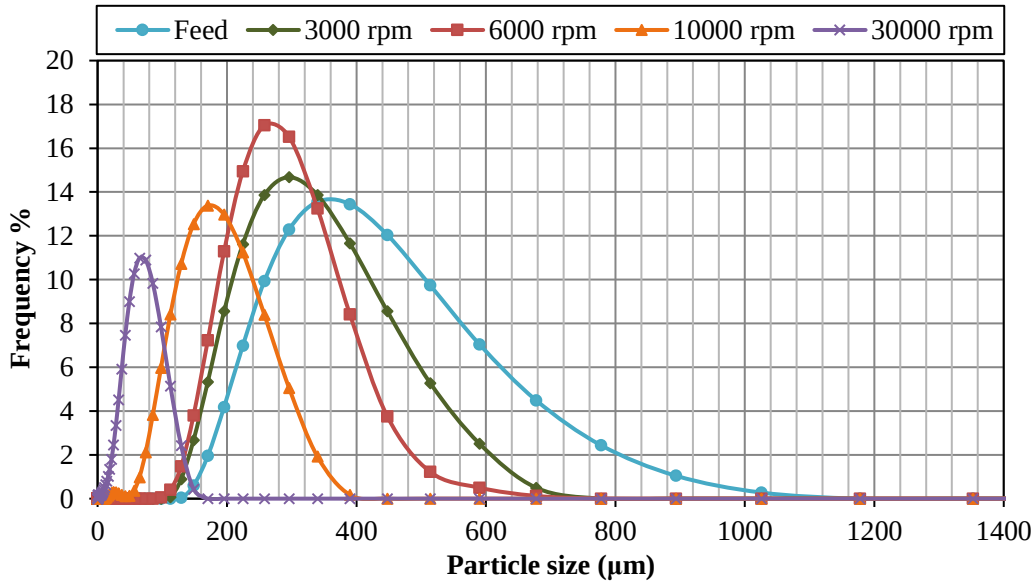

Figure 3**. Particle size distribution of the milled product of paracetamol (300-355 µm feed size) at different rotor speeds**

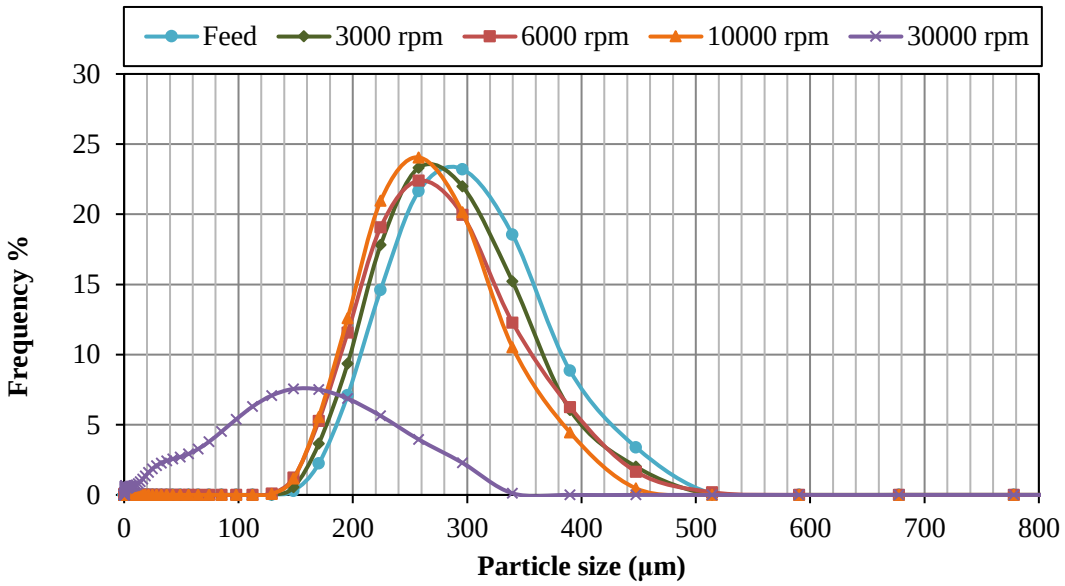

Figure 4. Particle size distribution of the milled product of α-lactose monohydrate (212-250 µm feed size) at different rotor speeds

Despite sieving the feed particles to narrow size cuts, particle size analysis by laser diffraction tends to show a wide size distribution, but with the mode representing the size well. As it can be seen, increasing the rotational speed results in a shift in the particle size distribution (PSD) curves towards finer particle sizes. For aspirin and paracetamol (Figures 2 and 3) the shift is clearly observed. However for α-lactose monohydrate, the trend is very different, as the shift is slight for rotational speeds up to 10000 rpm. However, when the rotational speed is increased to 30000 rpm, a drastic change in the particle size distribution to fine particles is noted. Observations of the milled α-lactose monohydrate particles by Scanning Electron Microscopy (SEM) clearly confirm the change in the breakage pattern, as shown in Figure 5.

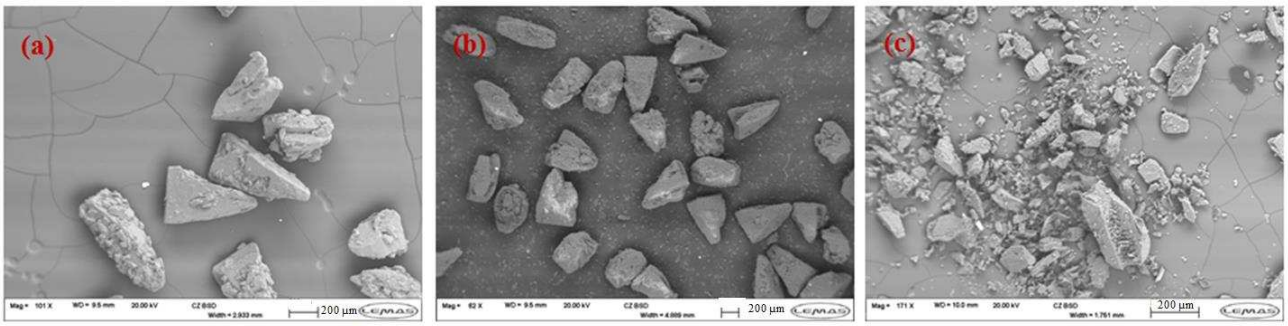

Figure 5. SEM images of (a) 212-250 µm feed particles of α-lactose monohydrate; (b) milled at 3000 rpm and (c) milled at 30000 rpm

No clear difference between the feed and milled particles is observed when α-LM particles are milled at 3000 rpm, showing that particles go through chipping and surface abrasion. However as the rotational speed is increased to 30000 rpm, particles experience a significant breakage by fragmentation and disintegration. This behaviour can further be explored by investigating the transition velocities of different patterns of breakage. However, as the focus of this study is on the chipping regime, it has not been investigated.

In order to analyse the milling results, the approach of Bonakdar et al. (2016a) is used, i.e. particle breakage is expressed in terms of the relative shift in specific surface area of the particles. In the cases where the envelope density of the particles does not change as a result of breakage, this is given by Eq. (1):

$$\frac{\Delta SSA}{SSA_\circ} = \beta \frac{\rho_f \bar{d}_{f,v} V^2 H}{K_c^2} \times \frac{\bar{d}_{f,v}}{\bar{d}_{d,v}} \qquad \text{Eq. (1)}$$

where $\bar{d}_{f,v}$ is the average feed particle size (on a volumetric basis), $\bar{d}_{d,v}$ is the average size of the debris, ρ_f is the envelope density of feed particles and V is their impact velocity. The group

($\beta\, H/K_c^2$) is regarded as a lumped parameter, called the breakability index of the material, in which β, H and K_c represent the proportionality factor, hardness and fracture toughness of the material, respectively.

The breakability assessment test was previously carried out on aspirin and α-lactose monohydrate by Bonakdar et al. (2016a). The same approach is applied here to paracetamol. Sieve cuts of 355-425 μm, 425-500 μm and 500-600 μm were used to carry out the tests using the Scirocco disperser of the Malvern Mastersizer 2000 for nozzle air pressures 0.5 barg to 4 barg with 0.5 barg interval. The feed particles size distribution was taken as that obtained at 0.1 barg, assuming no breakage at this pressure. The relative shift in the specific surface area, $\Delta SSA/SSA_0$, of the particles is then plotted as a function of $\rho_f \bar{d}_{f,v} V^2 \frac{\bar{d}_{f,v}}{\bar{d}_{d,v}}$. The paracetamol results are plotted together with those of aspirin and α-lactose monohydrate as shown in Figure 6.

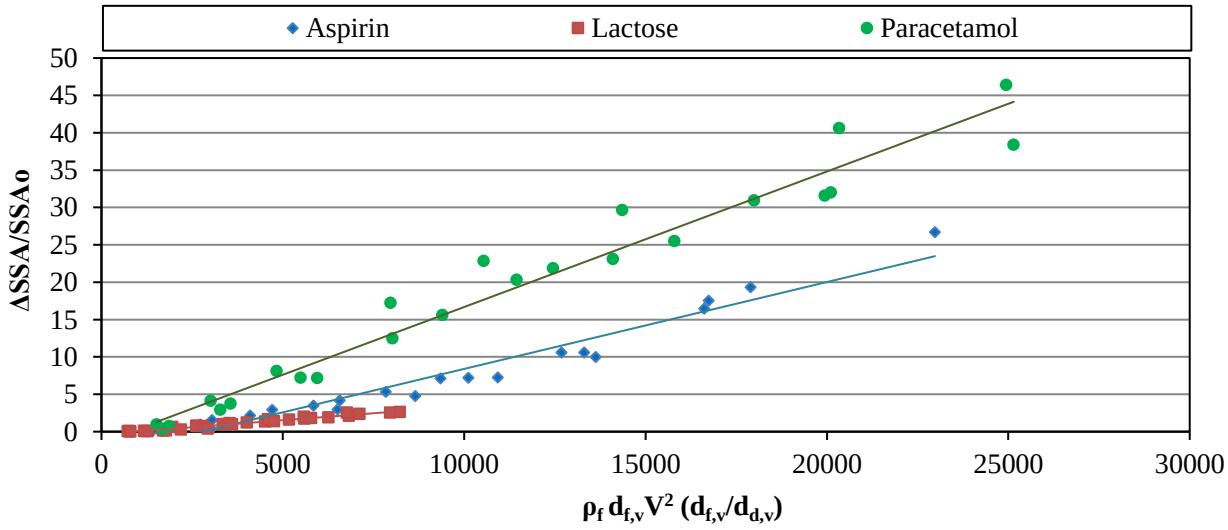

Figure 6. $\Delta SSA/SSA_0$ as a function of $\rho_f \bar{d}_{f,v} V^2 \frac{\bar{d}_{f,v}}{\bar{d}_{d,v}}$ for aspirin, paracetamol and α-lactose monohydrate obtained by breakability assessment test

The breakage kernels of the materials are obtained by linear regression of the data of Figure 6 and are given by Eqs (2), (3) and (4) for aspirin, paracetamol and α-lactose monohydrate, respectively.

$$\frac{\Delta SSA}{SSA_o} = 0.0012\rho_f \bar{d}_{f,v} V^2 \frac{\bar{d}_{f,v}}{\bar{d}_{d,v}} - 3.19 \quad \text{Eq. (2)}$$

$$\frac{\Delta SSA}{SSA_o} = 0.0019\rho_f \bar{d}_{f,v} V^2 \frac{\bar{d}_{f,v}}{\bar{d}_{d,v}} - 1.45 \quad \text{Eq. (3)}$$

$$\frac{\Delta SSA}{SSA_o} = 0.0004\rho_f \bar{d}_{f,v} V^2 \frac{\bar{d}_{f,v}}{\bar{d}_{d,v}} - 0.34 \quad \text{Eq. (4)}$$

Another outcome of the breakability test using the Scirocco disperser of the Malvern Mastersizer 2000 is the relationship between the average size of the debris (the chippings) as a function of the feed particle size and impact velocity for each individual material. Using the size distribution curves of feed particles and broken particles, $\bar{d}_{d,v}$ is calculated based on the procedure reported by Bonakdar et al. (2016a). Therefore, the relationship between $\bar{d}_{f,v}/\bar{d}_{d,v}$ as a function of impact velocity and average size of the feed particles can be established for a given pressure. Plotting all the data shows a linear relationship between $\bar{d}_{f,v}/\bar{d}_{d,v}$ and $\bar{d}_{f,v}V^2$. As an example such a relationship has been established and shown in Figure 7 for paracetamol particles.

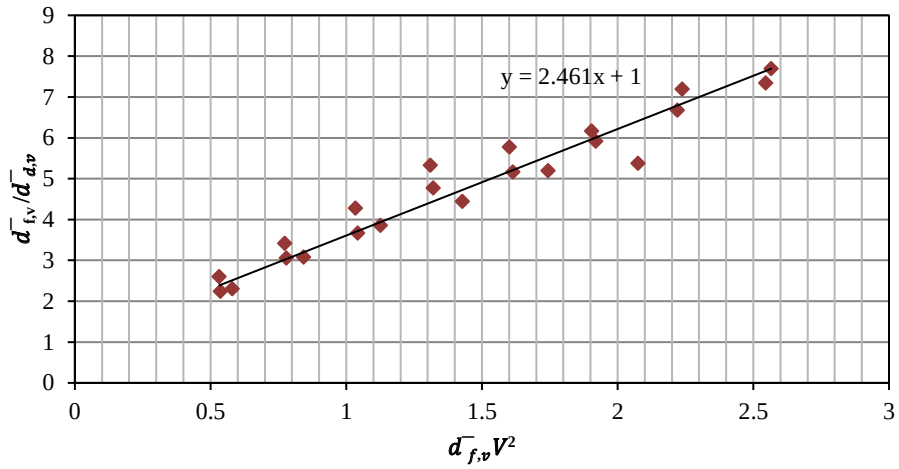

Figure 7. Relationship between $\bar{d}_{f,v}/\bar{d}_{d,v}$ and $\bar{d}_{f,v}V^2$ for paracetamol particles based on Scirocco breakability test data

The same approach has been used for other materials. Equations (5) to (7), expressing these relationships for aspirin, paracetamol and α-lactose monohydrate, respectively, are listed below.

$$\frac{\bar{d}_{f,v}}{\bar{d}_{d,v}} = 1.81\bar{d}_{f,v}V^2 + 1 \qquad \text{Eq. (5)}$$

$$\frac{\bar{d}_{f,v}}{\bar{d}_{d,v}} = 2.46\bar{d}_{f,v}V^2 + 1 \qquad \text{Eq. (6)}$$

$$\frac{\bar{d}_{f,v}}{\bar{d}_{d,v}} = \bar{d}_{f,v}V^2 + 1 \qquad \text{Eq. (7)}$$

By inserting Eqs (5 – 7) into Eqs (2 – 4), the breakage kernels become independent of the size of debris produced. Therefore the feed particle size and envelope density and the impact velocity in the mill are the only input parameters needed to quantify the relative shift in the specific surface area of the particles, and therefore to predict the particle breakage in the mill.

3.2 DEM Simulations

To apply the above breakage kernels to predict particle breakage in the pin mill, information on particle collision velocity and frequency is needed. This is done by numerical simulation using the EDEM software package. The focus of this study is on the chipping process, and therefore the mill dynamics at the low rotational speed of 3000 rpm has been simulated. The 3D geometry of the PicoPlex mill was first prepared using SolidWorks (Figure 1) and then imported into EDEM software package. Material properties used as input specification are given in Table 1. Spherical particle shape was used in the simulations (using the average size of the sieve cut) and a number of particles corresponding to about 0.5 g of material were then fed into the mill at 0.2 g/s feed rate. The simulation was stopped after all the particles left the mill. It should be noted that the shear moduli values for both material and target have been reduced, by keeping the ratio between them constant in order to speed up the simulations. Scaling down the shear moduli will not affect the impact data as long as there is no adhesion/ cohesion involved (Moreno et al., 2005). Hertz-Mindlin contact model (Nan et al. 2017) has been used for all the simulations.

Table 1. Material and geometry properties used in EDEM simulations

Parameter	Particle	Steel (pins of the mill)
Static friction coefficient	0.5	0.5
Coefficient of restitution	0.35	0.35
Density (kg/m^3)	1397 (aspirin), 1290 (paracetamol), 1520 (α-LM)	7800
Poisson's ratio	0.25	0.25
Shear modulus (MPa)	1	40

Although, the tip speed of each ring is known, particles are impacting at different impact velocities at each ring. To provide a comprehensive image on particle impact in the mill, each

particle was tracked and its information was recorded. The data of all the particles were then used to obtain the distribution of impact velocities and number of impacts in the mill. These were obtained for all the rings in the mill. As an example, the distributions of the number of impacts and impact velocities for 327.5 μm spheres, corresponding to the arithmetic mean value of 300-355 μm aspirin, for the rotating inner ring are shown in Figures 8 and 9, respectively.

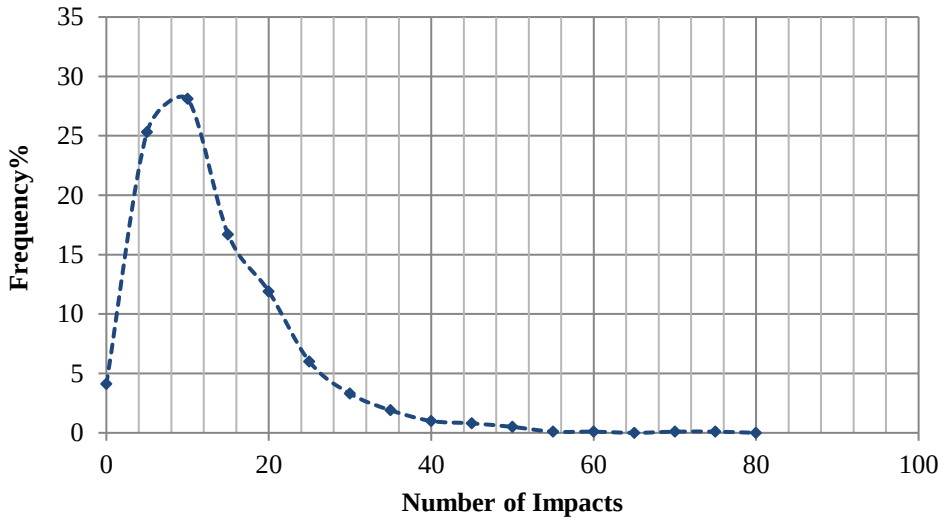

Figure 8. Distribution of number of impacts for 300-355 μm spheres representing aspirin at the rotating inner ring of PicoPlex mill at 3000 rpm

As it can be seen in Figure 8, particles experience a wide range of number of impacts during their journey in the mill. About 4% of the particles exit the mill without impacting on any of the pins. The simulation observation also shows that some of the particles experience a large number of impacts between two pins, similar to table tennis ball, before they move out of the region. Looking at the distribution of impact velocities (Figure 9), it can be seen that particles experience a range of impact velocities. The majority of the particles impact at around 2.3 m/s. Maximum

impact velocity of 5 m/s was observed for 327 µm particles. The tip speed of the rotating inner ring is 3.1 m/s.

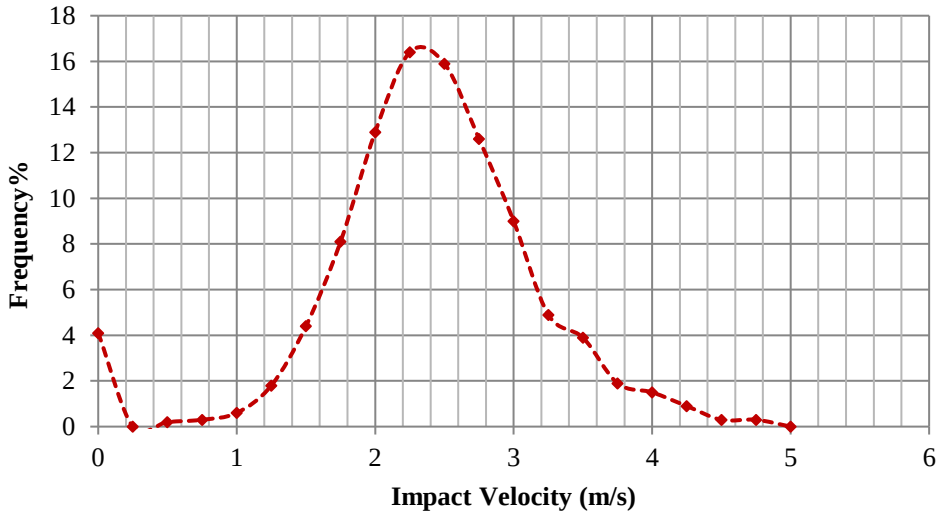

Figure 9. Distribution of impact velocities for 300-355 µm spheres representing aspirin at the rotating inner ring of PicoPlex mill at 3000 rpm

These sets of data provide useful information of journey of the particles in the mill. It should be noted that no breakage mechanism is included in the simulations. Nevertheless, the data are still representative of the situation in the mill, as the breakage mechanism under consideration is chipping.

In addition to determining the distribution of impact data for a population of particles in the mill, it is interesting to explore the trajectory of each single particle. Therefore, 10 simulations were run, and the particle velocity for each impact was recorded. As an example, the data obtained for 300-355 µm particles, representing aspirin, are shown in Figure 10 (the data for 355-425 µm and 425-500 µm are shown in Figures S7 and S8 of the supplementary document).

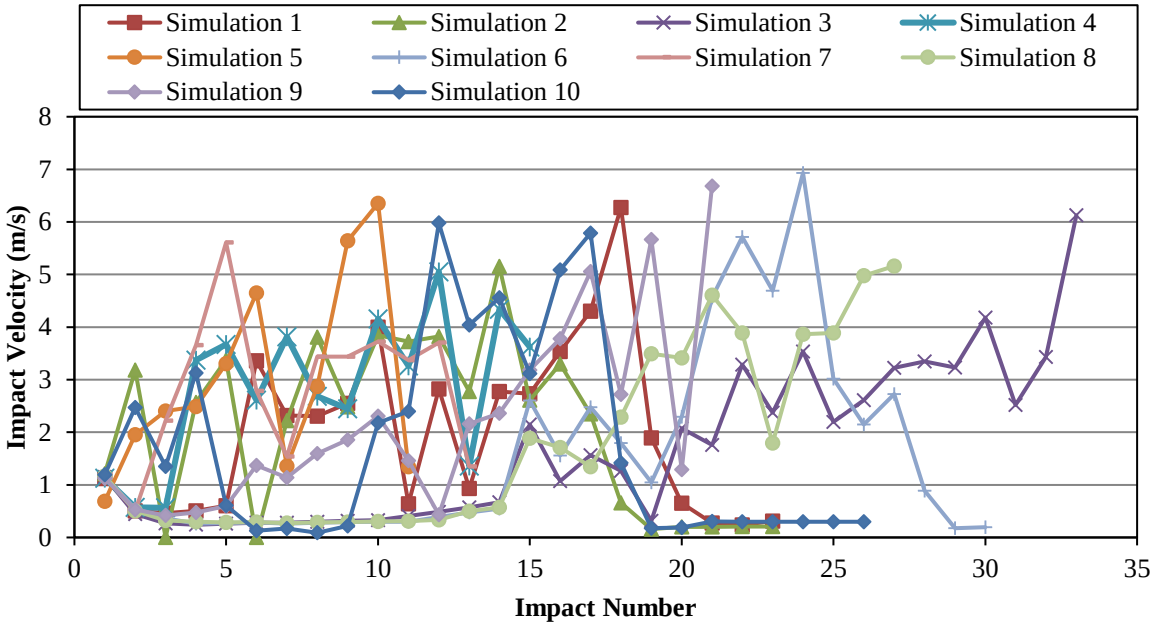

Figure 10. Impact data obtained by ten different simulations of a single 300-355 µm particle (aspirin) at 3000 rpm

Simulation results show particles experience different impact numbers and velocities. For instance, simulation 8 shows that a single particle, from start until it exits the mill, experiences 27 impacts with the minimum and maximum impact velocities of 0.2 m/s and 5.1 m/s, whilst another particle in simulation 5 just experiences 11 impacts with a minimum and maximum impact velocities of 0.7 m/s and 6.3 m/s. Clearly, there is a wide range of impact numbers and velocities that the particles experience as they go through different pins/ rings.

At 3000 rpm, which in PicoPlex is classified as a fairly low rotational speed, chipping/ surface abrasion is the dominant breakage mechanism. The breakage kernel of each material is then used to calculate the progressive change in the specific surface area of the particles as they go through the mill. As an example, the procedure to calculate the change in the specific surface area of particles representing aspirin is described below.

The breakage kernel of aspirin, shown in Eq. (2), is used to calculate the breakage of the particles in the mill, for which the relationship between $\bar{d}_{f,v}/\bar{d}_{d,v}$, impact velocity and size of the feed particles is given in Eq. (5). Therefore, for each simulation shown in Figure 8, the relative shift in the specific surface area of the milled particles, $\Delta SSA/SSA_0$, for each impact is calculated. The calculation is repeated as the particles progress through the collisions, leading to the final shift in the specific surface area of the particle, as shown in Table 2. Using ten particles a reasonably small value of the Coefficient of Variation (13.7%) is obtained.

Table 2. Calculation of the shift in the specific surface area of the particles for simulations of 300-355 μm aspirin particles at 3000 rpm

Simulation Number	Total Number of Impacts	$\Delta SSA/SSA_0$
1	23	0.086
2	23	0.093
3	33	0.076
4	15	0.080
5	11	0.078
6	30	0.103
7	13	0.073
8	27	0.0808
9	21	0.071
10	26	0.103
Average		0.084
Coefficient of Variation (%)		13.7

The same approach is then applied to paracetamol and α–lactose monohydrate. Particle-wall (pin) collision is the main mechanism for particle breakage in this work, as the particle population in the mill is deliberately kept low so that inter-particle interactions are insignificant and make no contribution to the breakage. Therefore considering that a very low feed rate was used experimentally, the single particle simulations are representative of the real behaviour of the particles in the mill. The predicted $\Delta SSA/SSA_0$ obtained by the combined results of simulation and breakability tests are then compared to the measured ones obtained by particle size distribution analysis of the milled materials. The comparison of the results for 300-355 µm, 355-425 µm and 425-500 µm of all the materials at 3000 rpm are shown in Figures 11-13, respectively. Each bar of the simulation results is an average of ten simulations, with a typical coefficient of variation within the range of 5-14%. The experiments were repeated three times and the bars present an average value with a spread of maximum 3%.

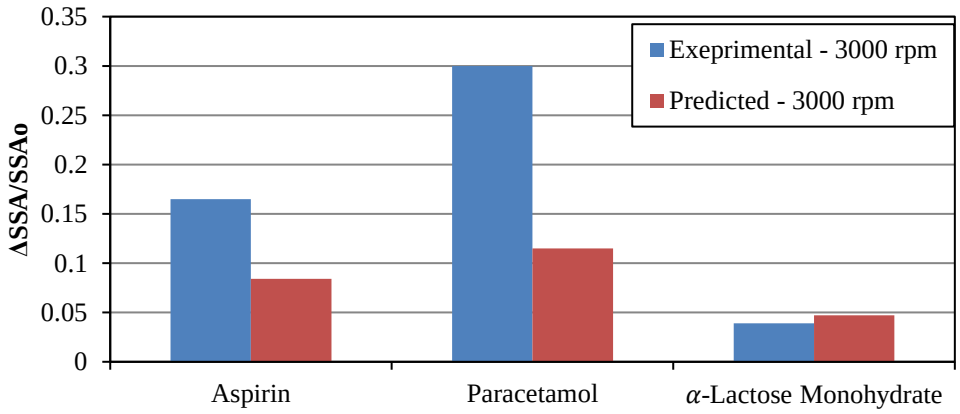

Figure 11. Comparison of the predicted shift in the specific surface area of the particles with the measured valued for 300-355 µm feed particles after milling at 3000 rpm

For 300-355 μm feed particles, the comparison of the predicted and measured values of the relative shift in the specific surface area of the particles (see Figure 11) shows underestimation of the results by simulation for aspirin and paracetamol. However, there is a fairly good match for α–lactose monohydrate. For the larger feed particles (355-425 μm), the same behaviour is observed. Predicted values underestimate the relative shift in the specific surface area of aspirin and paracetamol (see Figure 12). The opposite trend is shown for α–lactose monohydrate. The data reported for the largest feed particle size (425-500 μm) in Figure 13, show under-prediction for aspirin and over-prediction for α–lactose monohydrate and a good match for paracetamol. Therefore no clear trend is discernible. Considering the trend of the relative shift in the specific surface area with particle size, the simulation results clearly show an increase, based on the single particle breakage kernels obtained by the Scirocco testing method. The experimental results show the same trend consistently for aspirin particles, but not for the other two materials. Paracetamol particles do not show a notable dependence of breakage on particle size, whilst α–lactose monohydrate particles appear to show the opposite trend, albeit not breaking to any appreciable extent. α–lactose monohydrate has shown to be a challenging material for characterisation of its breakage, whether in the single particle impact test (Bentham et al., 1996 and Dogbe 2016), or Scirocco test (Bonakdar et al., 2016a) or milling work as carried out here. Crystals of α–lactose monohydrate tend to gather fine dust of the same material on their surfaces due to high adhesion, and the dust is shed on impact, complicating the gravimetric and particle size analyses at low impact velocities. Bentham et al (1996) washed the crystals before testing, and this produced a clearer trend. However this procedure was not attempted here.

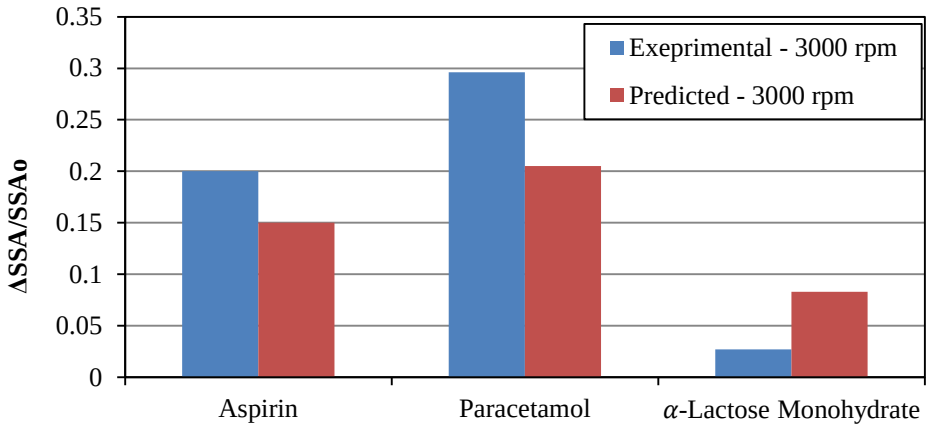

Figure 12. Comparison of the predicted shift in the specific surface area of the particles with the measured valued for 355-425 µm feed particles after milling at 3000 rpm

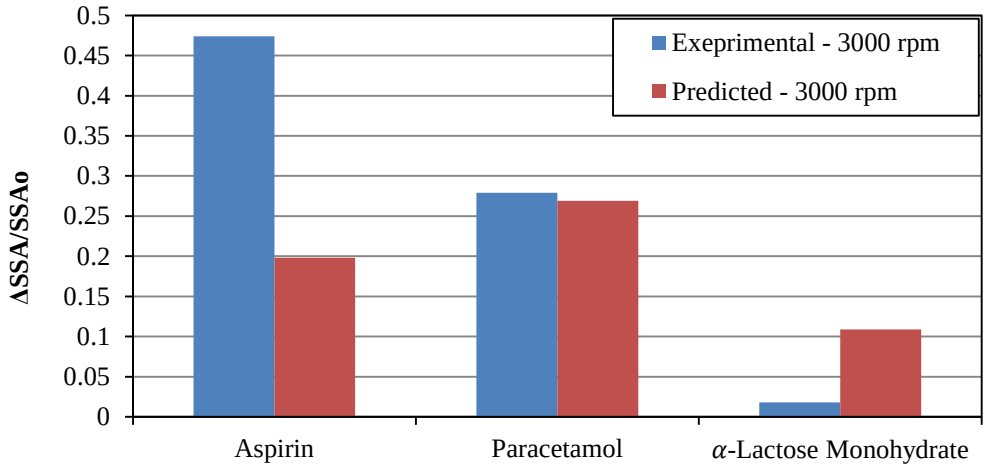

Figure 13. Comparison of the predicted shift in the specific surface area of the particles with the measured valued for 425-500 µm feed particles after milling at 3000 rpm

Based on the results shown in Figures 11-13 the trend of predicted values match the expected trend from breakability testing; for a given particle size paracetamol particles break more than aspirin, and aspirin particles break more than α–lactose monohydrate. The same trend is observed for experimental values. However, this is not the case for the largest feed particle size

(425-500 μm) for which aspirin breaks more than paracetamol and α–lactose monohydrate. Despite differences in the predicted and measured values of $\Delta SSA/SSA_0$, the approach has the potential to predict the behaviour of the particles in the mill. The breakability test method provides a fast and simple approach to develop the breakage kernel of the materials. Using DEM simulation gives an opportunity to better understand the dynamic behaviour of the particles in the mill. The differences between the predicted and measured values of $\Delta SSA/SSA_0$ are attributed to the underlying assumptions in DEM simulation method used here, i.e. the use of spherical particles and not accounting for the breakage mechanism. Of course material properties such as the shear modulus and particle density are accounted for in the simulations, but the structural features of the crystalline materials used here such as the failure plane (e.g. cleavage plane and slip plane) are not still taken into account. Therefore, analysing the real behaviour of the particles in the mill is still a great challenge. Nevertheless, the combination of breakability test and DEM simulation provides a powerful tool for predicting the breakage of the particles in the PicoPlex, where the breakage is by chipping mechanism.

4 Conclusions

A combination of experimental and computational approaches has been used to study the particles behaviour in PicoPlex mill. The breakage of three crystalline materials, i.e. aspirin, paracetamol and α-lactose monohydrate, has been evaluated for the case in which particle breakage is through the chipping mechanism. The breakability assessment technique, using the Scirocco disperser of the Malvern Mastersizer 2000, has been used to develop the breakage kernel for the test materials. This is presented in the form of the relative shift in the specific surface area of the particles as a function of particle properties and impact velocity. The latter

has been quantified by numerical simulations based on DEM. The outcome of the simulations has been used to calculate the progressive change in the specific surface area of the particles after each impact, leading to the estimation of the total $\Delta SSA/SSA_0$.

The method provides a reasonable approach to predict $\Delta SSA/SSA_0$ for the chipping regime. The simulation results are based on single particle breakage kernels and indicate that $\Delta SSA/SSA_0$ increases with particle size consistently for all the three test materials. This is also the case for the experimental results of aspirin, but the results of paracetamol and α-lactose monohydrate do not show such a trend. So there is some discrepancy between the predicted and measured values of $\Delta SSA/SSA_0$ and this is attributed to using spherical particles in the simulations and not accounting for particle breakage to calculate the particle dynamics. Further work is required to account for particle shape and breakage mechanisms.

5 Acknowledgements

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Supplementary Figures:

Particle Size Analyses

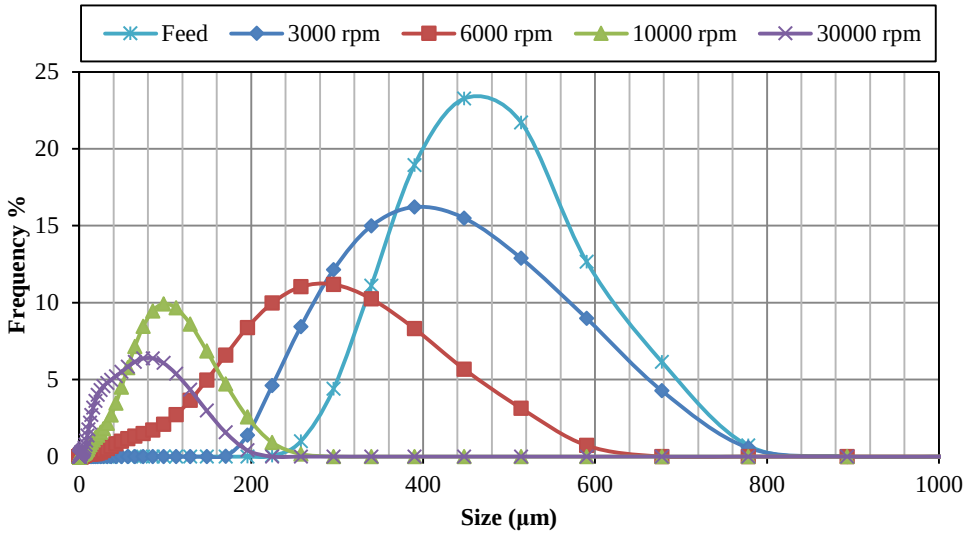

Figure S1. Particle size distribution of the milled product of paracetamol (355-425 µm feed size) at different milling conditions

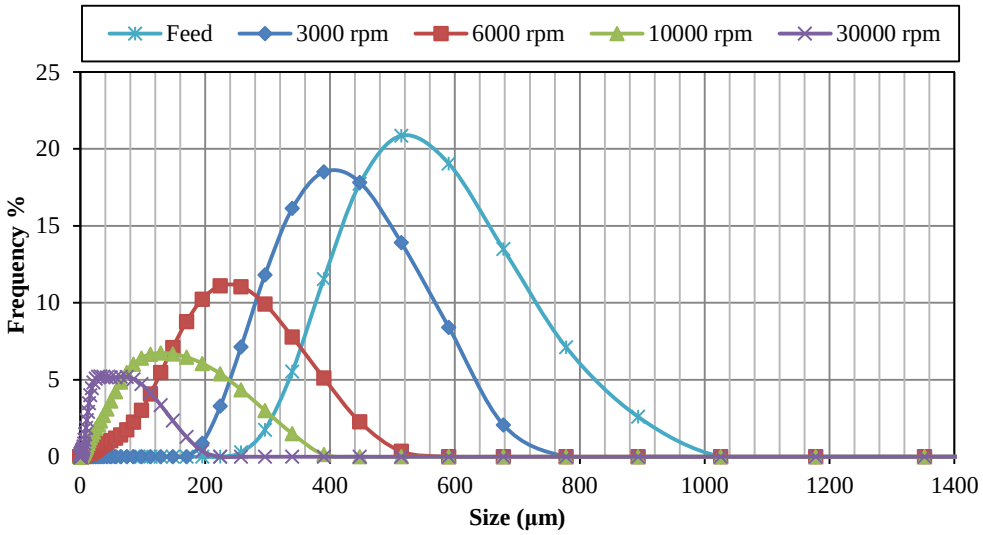

Figure S2. Particle size distribution of the milled product of paracetamol (425-500 µm feed size) at different milling conditions

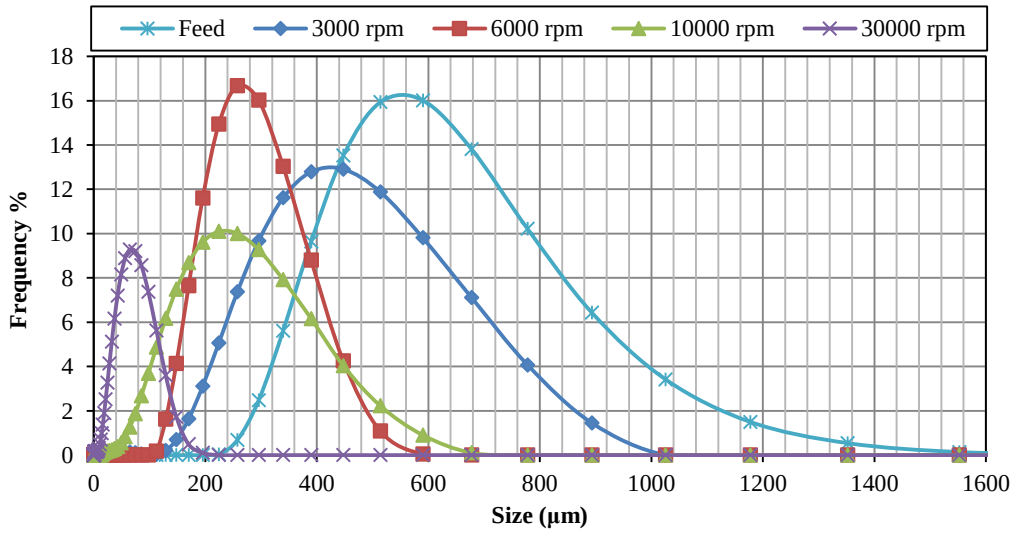

Figure S3. Particle size distribution of the milled product of aspirin (355-425 µm feed size) at different milling conditions

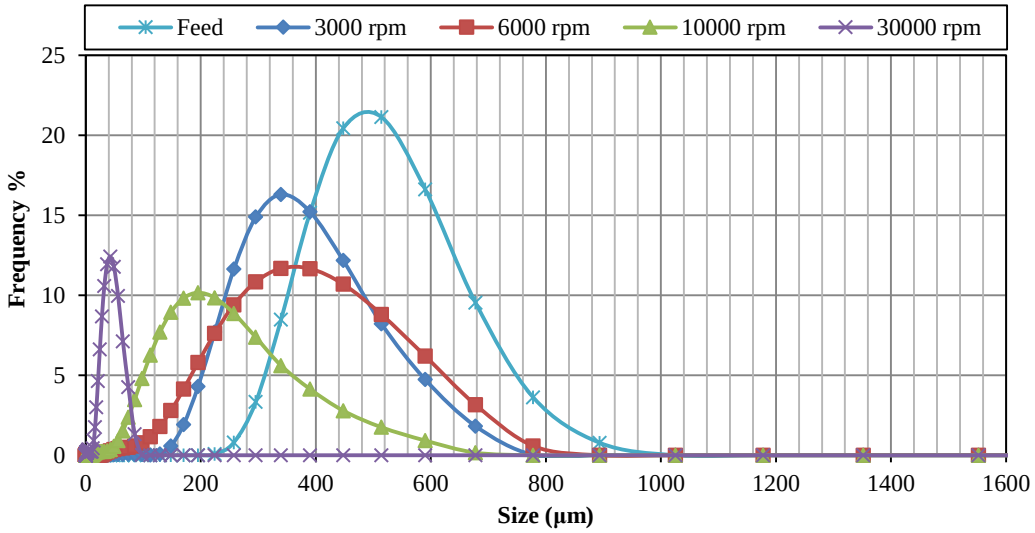

Figure S4. Particle size distribution of the milled product of aspirin (425-500 µm feed size) at different milling conditions

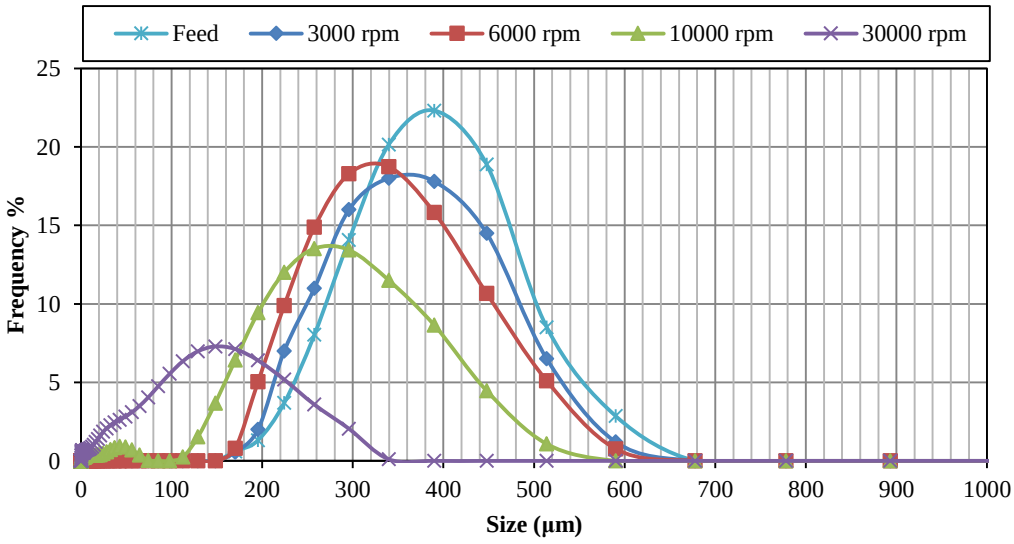

Figure S5. Particle size distribution of the milled product of *α*–lactose monohydrate (300-355µm feed size) at different milling conditions

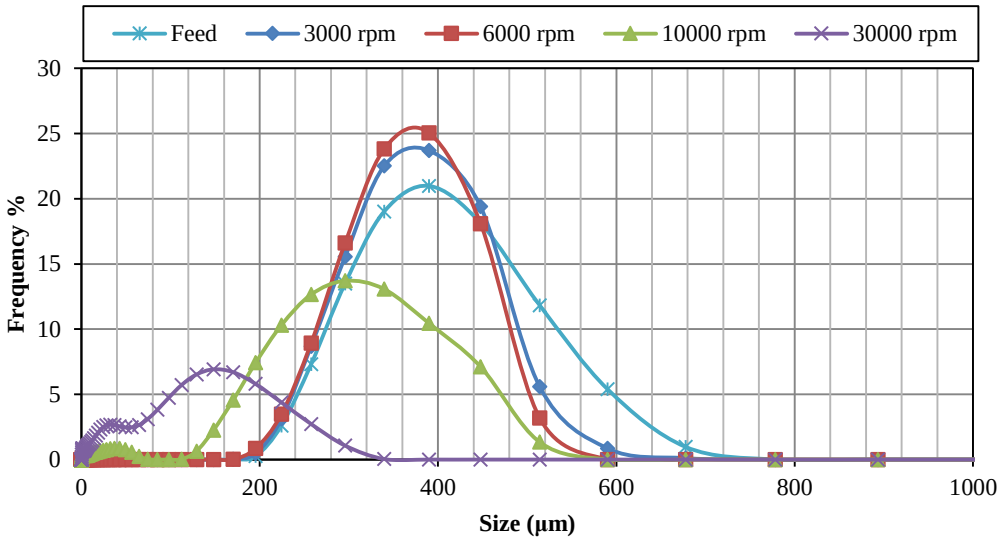

Figure S6. Particle size distribution of the milled product of α–lactose monohydrate (355-425 µm feed size) at different milling conditions