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Cone milling of compacted flakes: Process parameter selection by adopting the minimal fines approach

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ABSTRACT

Cone mill was well studied for milling of wet agglomerates. This study evaluated the effects of various process parameters of cone milling roller compacted flakes on the granules produced. Impeller sidearm shapes, screen surface profiles and impeller speeds were studied. Impeller speed was found to play a major role in determining the granule attributes. Besides this, median size, size distribution and percent fines of a milled granule population were mainly determined by the size reduction mechanisms of different impellers and screens. Pre-breaking followed by shearing and slicing of flakes inside the milling chamber was primarily responsible for determining the size, size distribution and percent fines of milled granules. The pre-breaking action could be achieved using teethed round sidearm impeller and lowered the need for screen-based size reduction, thus generating less fines. The shearing and slicing of flakes due to the raised impaction edges of the grater screen also helped to minimize the production of fines. Therefore, the lowest percentage of fines was observed when the teethed round sidearm impeller was used with a grater screen. The results indicated that fines can be reduced considerably with the judicious selection of a suitable impeller and screen combination in the cone mill.

1. Introduction

The main purposes of granulating pharmaceutical powders are to improve flow properties, prevent segregation of components, decrease dust and ensure uniform distribution of ingredients. Roller compaction is a commonly used dry granulation process and is especially useful for heat and moisture sensitive products that do not possess the necessary properties for direct compression into tablets. It is an easily scalable and continuous process in which the material is being densified by compression between two counter rotating rolls to form flakes, ribbons, or briquettes. These roller compacted flakes are then comminuted into granules for tabletting or capsule filling after blending with extra-granular excipients (Inghelbrecht and Remon, 1998; Murray et al., 1998; Vervaet and Remon, 2005).

The granule size, size distribution and amount of fines of the milled flakes are among the most important physical properties which may affect subsequent operations such as flow and compaction, and in turn, content uniformity and dissolution characteristics of final dosage form. Large sized granules improve the flow due to reduced contact surface area with each other. However, large sized granules tend to yield tablets with unacceptable pitted surfaces especially when the granules generally do not have sufficient plasticity. This consideration is specifically important for the roller compaction process as compacted granules are more difficult to deform plastically during tabletting due to their loss of reworkability (He, 2003; Miller, 1997). On the other hand, granule population with large proportion of small granules may suffer from flowability problem due to larger contact surface area. Therefore, a balance between the proportion of large and small sized granules in a granules population is needed to minimize the imperfections on the tablet's surface as well as to improve granules flowability. In general, granule size and size distribution of a final blend are dependent on formulation ingredients and their concentration, as well as the type of equipment and processing conditions employed. One of the most direct ways to control particle size and size distribution of the final blend is milling. Therefore, sizing of granulation becomes a critical unit operation in the manufacture of oral dosage forms (Fonner et al., 1981; Lantz, 1990). In particular, this milling step is crucial in dry granulation process due to relatively poorer binder distribution in roller compacted granules compared to wet and spray dried granules (Seager et al., 1979). Poor binder distribution in granulation may lead to production of granules with wider size distribution and more fines after milling.

In conical screen mill, the rotation of impeller creates a centrifugal acceleration force which pushes the feed material toward the

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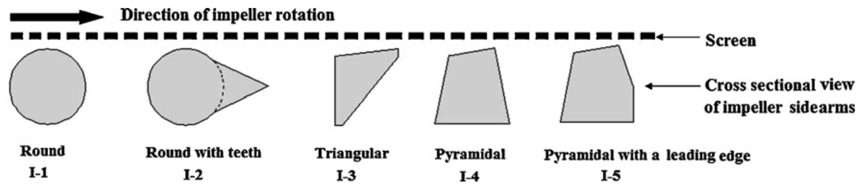

Fig. 1. Cross-sectional view of impeller sidearms along with the position of screen and direction of impeller rotation.

surface of the screen. Particles are trapped between the edge of the impeller and the screen, causing breakage and broken down products are instantaneously discharged through the screen opening diametrically. The discharging action lowers power consumption by the mill as well as excessive fine generation by reducing the retention time of product in the milling chamber. Efficiency of conical screen mill is improved when the milling chamber is kept relatively full (Rekhi and Sidwell, 2005). As the impeller does not touch the rigid screen, there is no danger of contamination from metal abrasion. Moreover, the conical screen mill was reported as producing less noise, narrower particle size distribution of milled products and suitable for both wet and dry materials (Murugesu, 2008).

In conical screen milling, screen aperture size, screen type, shape of impeller sidearm and impeller speed are the various process parameters which can be varied to customize the desired final granule attributes. These process parameters of conical screen mill had already been evaluated for comminution of commercially available granulations (Byers and Peck, 1990; Motzi and Anderson, 1984) and for improving deagglomeration efficiency (Bauerbrandl and Becker, 1996), color uniformity (Fourman et al., 1990) as well as content uniformity (Poska et al., 1993) of tablets produced by direct compression. It was reported that screen aperture size has the largest effect on milling time and work as well as the degree of particle size reduction whereas the impeller side arm shape has the largest effect on overall milling performance (Byers and Peck, 1990). Motzi and Anderson (1984) concluded that effects of screen size, impeller speed and impeller side arm shape on particle size distribution of milled granules must be evaluated in a combination of all three variables and not individually. Screens with grater surface texture were found to produce reduced level of fines compared to smooth screen during dry milling (Schenck and Plank, 2008).

In this study, roller compacted flakes prepared from a placebo dry granulated formulation were selected to evaluate the effect of conical mill process parameters, specifically impeller type and screen type at different impeller speeds. The resulting granulation was evaluated for particle size distribution and fines. Finally, various mill settings were investigated for the minimal fines approach.

2. Materials and methods

2.1. Materials and blending

A simple placebo formulation consisting of α-lactose monohydrate (Pharmatose 200M, DMV, Veghel, Netherlands), microcrystalline cellulose (Avicel PH102, FMC, UK) and magnesium stearate (Sigma-Aldrich, Germany) in the ratio of 49.5:49.5:1 (w/w) was used in this study. Prior to experimentation, all the materials were passed through a 355 μm aperture size sieve in order to break up any loose aggregated lumps in the bulk powders, and stored for at least 48 h at 25 °C and 50% RH. After that, all the materials were blended in a double cone blender (AR 400, Erweka, Germany) rotated at 40 rpm for 50 min.

2.2. Preparation of roller compacted flakes

The powder blend was roller compacted (Pharmapaktor L200/30P, Hosokawa Bepex, Germany) at 50 kN roll force to make flakes at a low roll speed (2.6 rpm). The roller compactor was operated in the automatic mode where the speed of vertical feeding screw was automatically controlled by a feedback system to maintain 50 kN roll force at 2.6 rpm roll speed. The rolls are 20 cm in diameter with 3 cm wide of serrated compaction surface. The flakes produced were then sieved to remove uncompacted material by using a 500 μm aperture size sieve on a sieve shaker (KS 1000, Retsch, Germany) set at 70 shakes per min for 2 min. The sieved flakes were stored for 48 h at 25 °C and 50% RH.

2.3. Milling of flakes

Flakes were milled using conical screen mill (Model 197S, Quadro Comil, Quadro Engineering, Waterloo, Canada) to produce granules. Impellers (Fig. 1) with five different types of sidearm (round [I-1], round with teeth [I-2], triangular [I-3], pyramidal [I-4] and pyramidal with a leading edge [I-5]) and screens (Fig. 2) with two different types of surface profile (grater and smooth) of same aperture size (2388 μm) were evaluated. Each milling run was repeated for three times.

A minimum gap between the impeller and the screen was always maintained using a spacer of suitable thickness to prevent damage done to the machine and metal contaminations entering the final blend (Tables 1 and 2). The mill was operated at five different speeds (1200, 1600, 2000, 2400 and 2800 rpm), which were adjusted while the mill ran empty using a digital tachometer (HT-5500, Ono Sokki, Japan) prior to feeding the flakes into the mill. After validating the mill speed, the mill was set to the desired speed and 200 g of randomly sampled flakes were choke-fed into the mill manually. The total milling time was 3 min. The milling of flakes using different impellers, screens and impeller speed were performed in random order. At the end of each milling run, the amount of un-milled material was determined by weighing the retained material on the screen after milling.

2.4. Characterization of granules

2.4.1. Size and size distribution

Each batch of milled granules was collected and characterized for size and size distribution using a nest of sieves of aperture sizes in $\sqrt{2}$ progression from 180 to 2000 μm. Sieving was carried out using a sieve shaker (VS 1000, Retsch, Germany) vibrated at 1 mm amplitude for 10 min. The fraction of granules collected in each sieve was weighed, and the cumulative percent weight undersize plot was constructed. The d_{10}, d_{50} and d_{90} values were the

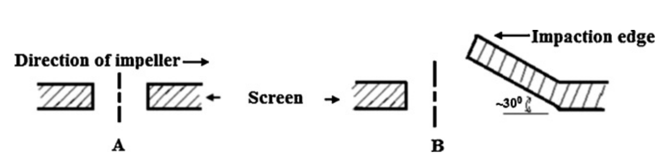

Fig. 2. Surface profile of screens (A) smooth and (B) grater.

Table 1
Screen and spacer bushing specifications of round screen.

Screen number	Screen aperture diameter (μm)	Screen thickness (μm)	Open area (%)	Spacer (μm)
2A045R03137	1143	787.4	37	5080
2A075R05051	1905	1270.0	51	4445
2A094R05041	2388	1270.0	41	4445
2A125R05040	3175	1270.0	40	4445
2A187R03751	4750	939.8	51	6350

Table 2
Screen and spacer bushing specifications of grater screen.

Screen number	Screen aperture diameter (μm)	Screen thickness (μm)	Open area (%)	Spacer (μm)
2A040G03122329	1016	787.4	22	5080
2A079G03123120	2007	787.4	23	3810
2A094G03123121	2388	787.4	23	3175
2A125G03123126	3175	787.4	23	3175
2A187G03123132	4750	787.4	23	6350

diameters of the granules at the 10th, 50th and 90th percentiles, respectively, and were determined from the plot. The size and size distribution of the granules were represented by the mass median diameter (MMD or d_{50}) and the span ($S_{d_{50}}$), respectively. The span was calculated using Eq. (1).

$$S_{d_{50}} = \frac{d_{90} - d_{10}}{d_{50}} \quad (1)$$

2.5. Percentage of fines

In size analysis of granules batches, granules of particle size less than 180 μm were considered as fines. Percentage of fines was determined by Eq. (2).

$$\text{Fines} \quad (\%) = \frac{\text{Amount of granules} \quad (< 180 \quad \mu\text{m})}{\text{Total amount of granules}} \times 100 \quad (2)$$

3. Results and discussion

3.1. Preliminary studies and results

Preliminary studies were conducted on the roller compactor to determine the optimal operating range for producing flakes of acceptable quality using the abovementioned placebo blend. The roller compactor was operated using an automated mode where the desired roll force can be set for a particular roll speed, with roll gap and screw speed varied automatically. The selected roll force for this study was 50 kN. It was observed that the flakes produced at 50 kN roll force could be produced at different roll speeds ranging from 2.6 to 7 rpm. However, flakes produced at higher roll speed tended to laminate more after compaction than the flakes produced at lower roll speed, although both were produced at same roll force (50 kN). Lower roll speeds provided an opportunity for the flakes to bond better due to the longer dwell times. This in turn reduced the lamination tendency of the flakes upon exiting from the compression zone. Therefore, a low roll speed of 2.6 rpm was chosen for this study.

Preliminary studies were also carried out on conical screen mill to select the suitable screen aperture size and impeller speed range for the main study. Flakes produced at 50 kN roll force, smooth screen, grater screen and I-1 impeller were used for the preliminary exercise. The screen aperture size and the impeller speed range for this study were selected based on the percentage of fines (<180 μm) and coarse particles (>1400 μm) produced after milling. Tables 1 and 2 show the specifications of smooth and grater screens, respectively, regarding their aperture diameter, thickness and open area (%) along with the thickness of spacer bushing used to maintain the minimum gap between impeller and screen. Cut off points for percentages of fines and coarse particles in a granule population were arbitrarily selected to be less than 50% and 10%, respectively. From this preliminary study, 2388 μm screen aperture size and impeller speeds ranging from 1200 to 2800 rpm were selected for the subsequent experiments.

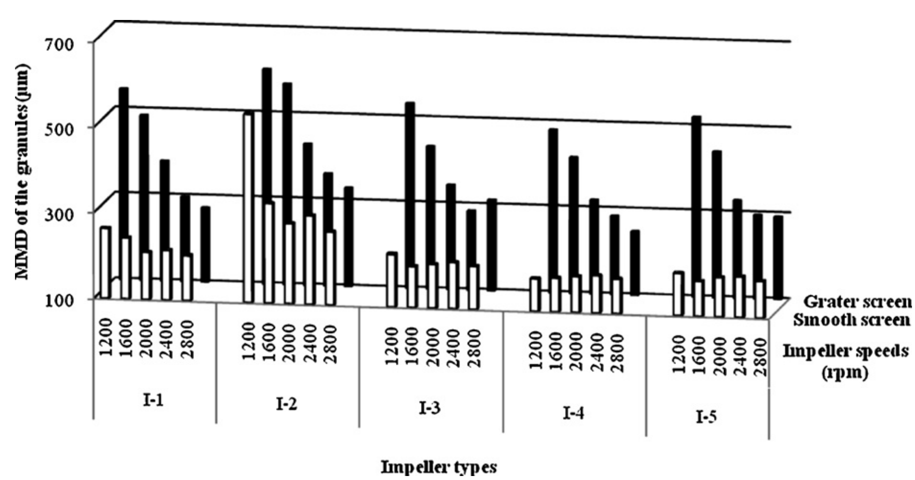

Fig. 3. MMD of granules after milling 200 g of flakes at different milling conditions using 2388 μm aperture size screen.

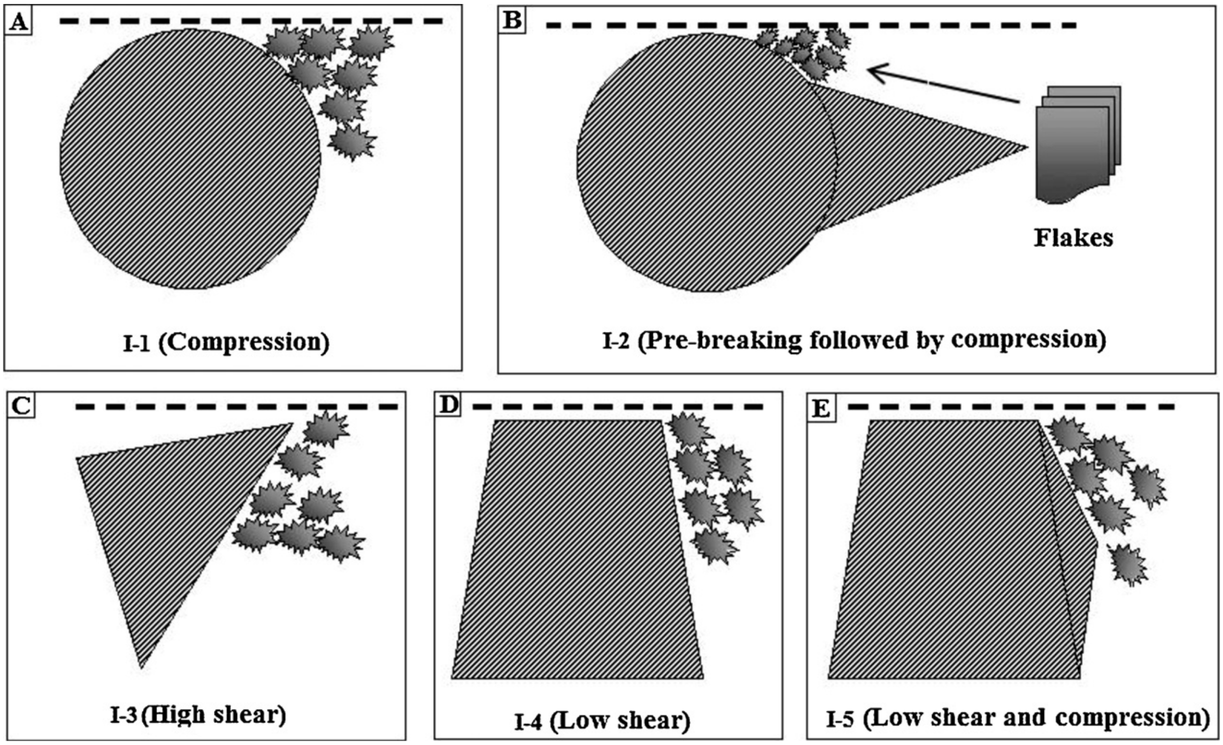

Fig. 4. Size reduction mechanisms of different impellers.

3.2. Effect of impeller sidearm shapes and screen types on the granules size and size distribution at different impeller speeds

Fig. 3 shows the effect of different impeller sidearm shapes and screen types on the MMD of the milled granules at different impeller speeds. It was clear that the grater screen consistently produced granules with significantly larger MMD values (ANOVA, $p < 0.05$) than the smooth screen at different impeller speeds for the same type of impeller. Among the impellers, I-2 impeller tended to produce granules with larger MMD irrespective of screen type. However, the differences in the MMD of granules produced by different impellers were relatively small when grater screen was used. On the contrary, the differences in granule sizes produced by different impellers were marked when the screen was smooth. More specifically, very small granules (~200 μm) were produced by impellers I-3, I-4 and I-5 fitted with a smooth screen at different impeller speeds. No effect of impeller speed on granule size was observed when using the same three impeller types.

The uneven surface of the grater screen due to the raised impaction edges of the holes allowed the flakes to trap more firmly between screen and impeller, which caused the flakes to break more readily by shearing action and faster release of the milled material from the milling chamber. In case of the smooth screen, flakes were not trapped as firmly and this resulted in a slippage of flakes between the impeller and the screen. This led to the longer residence time of flakes inside the milling chamber, causing prolonged total milling time and increased the extent of size reduction and formation of smaller granules or even fines due to greater impact. However, this mechanism was applicable for impellers I-1, I-3, I-4 and I-5 but not I-2 when used with the smooth screen. This observation could be attributed to the pre-breaking action of I-2 impeller. Pre-breaking of flakes by the pointed teeth of I-2 impeller

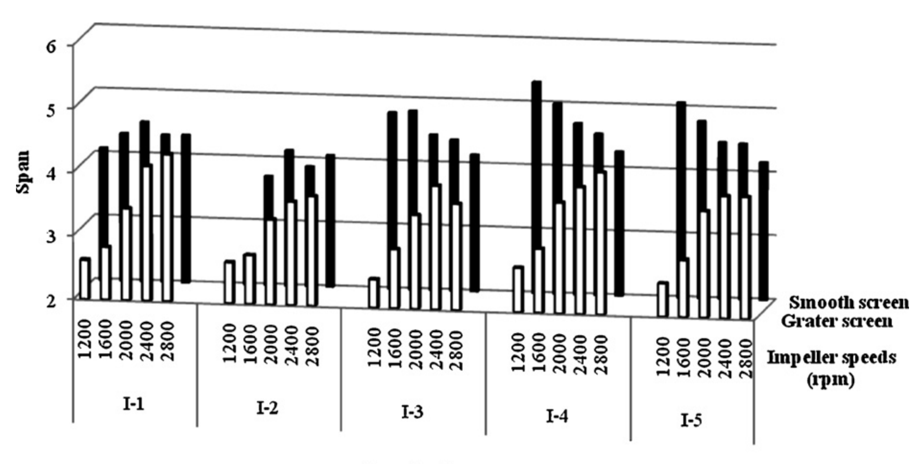

Fig. 5. Span of granules after milling 200 g of flakes at different milling conditions using 2388 μm aperture size screen.

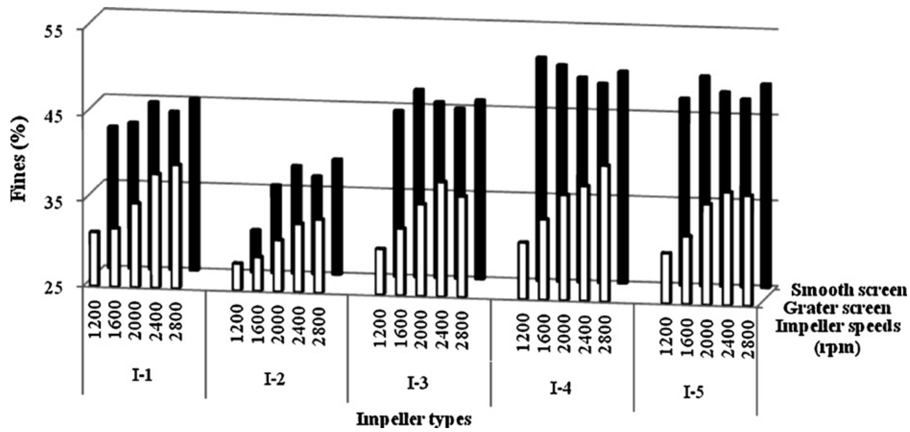

Fig. 6. Percent fines produced after milling 200 g of flakes at different milling conditions using 2388 μm aperture size screen.

led to the production of smaller sized flakes which were easily trapped in between the round sidearm of the I-2 impeller and the smooth screen, thus facilitating the passage of milled flakes from the milling chamber (Fig. 4B). For the impellers I-1, I-3, I-4 and I-5, they lack the geometric teeth-like protrusions of I-2 impeller to assist in the breaking of flakes to sizes suitable for trapping in between the impeller sidearm and screen. To some extent, I-1 impeller demonstrated some capacity to trap the flakes in between impeller sidearm and screen, allowing compressive forces to act on the screen surface to impinge the trapped material more aggressively and to expel comminuted flakes from milling chamber, but it lacked the more efficient pre-breaking of I-2 impeller (Fig. 4A). The size reduction mechanism of I-3 impeller was the high shear force due to the presence of its sharp edge (Fig. 4C), which led to the production of slightly bigger granules than those produced by I-4 or I-5 impeller (Fig. 3). Conversely, the side arms of the I-4 impeller were flat-faced with sharp edges, and because they were parallel to the screen surface, the I-4 impeller produced rather low shear action (Fig. 4D). The I-5 impeller is almost similar to I-4 impeller but with a positive leading edge, which provided some sort of forward compressive action like impeller I-1, but it lacked the ability to efficiently break flakes (Fig. 4E). When used in combination with the smooth screen, I-1 impeller produced slightly larger sized granules than the ones produced by I-3, I-4 or I-5 impellers. This may be attributed to its ability to provide stronger compressive action. No significant differences (ANOVA, $p > 0.05$) in the MMD of the granules were observed when smooth screen was used with I-2 impeller or the grater screen with any of the remaining four types of impeller. Clearly, the pre-breaking of the flakes by I-2 impeller was akin to the action of the grater surface of the screen. Therefore, it was concluded that the MMD values for the granules were the largest when the impeller along with the shearing and trapping of flakes due to the raised impaction edge of the grater screen gave rise to the pre-breaking of flakes. This situation occurred when the I-2 impeller was used with the grater screen that resulted in the production of granules of largest MMD.

Fig. 5 shows the span values of the granules produced after milling of flakes using combinations of the five impeller types and two different screens at various impeller speeds. Smaller span values were observed with the granules produced by the grater screen. It was found that an increase in impeller speed tended to decrease the span values with smooth screen, except that an increase was noted for I-2 impeller, as for when the grater screen was used. It was previously observed that the MMD of the granules was not markedly affected by the impeller speed except for I-2 impeller with the smooth screen. Therefore, decreased span values with increasing impeller speed were mainly attributed to the decrease in d_{90} of the granules and not the d_{10} values, which had remained rather constant (Table 3). On the other hand, the increases of span values at higher impeller speeds with the grater screen were primarily due to the decrease in both d_{50} and d_{90} values of the granule batches with increase in impeller speeds (Table 4). The d_{10} values were rather similar throughout for both screens. Span values of the granules produced using either smooth or grater screen were comparable when I-2 impeller was used.

3.3. Effect of impeller speeds and types with different screens on the percentage of fines generated during milling

The generation of fines during compaction and milling is a major problem in the pharmaceutical industry, especially when potent active ingredients are involved. Fines generation is undesirable as it contributes to material loss and environmental pollution. Selection of suitable formulation ingredients and their concentrations (e.g. binder) as well as proper processing conditions can help to reduce the generation of fines. Because dry granulation does not involve the addition of binding liquid, it causes inefficient distribution of binder particles throughout the blend, which results in many composite particles to be loosely held together. As such, milling step is much more critical in dry granulation process as a culprit for fines generation.

Table 3
d_{10} and d_{90} values of granules resulted from smooth screen at different milling conditions.

Impeller speed (rpm)	I-1 (μm)		I-2 (μm)		I-3 (μm)		I-4 (μm)		I-5 (μm)	
	d_{10}	d_{90}	d_{10}	d_{90}	d_{10}	d_{90}	d_{10}	d_{90}	d_{10}	d_{90}
1200	45.0 (0.0)	1118.3 (5.2)	60.0 (0.0)	1395.0 (5.0)	40.0 (0.0)	1103.3 (6.3)	35.0 (0.0)	973.3 (5.8)	37.5 (0.0)	1049.2 (3.8)
1600	42.5 (0.0)	1088.3 (7.6)	50.0 (0.0)	1287.5 (6.6)	38.3 (1.4)	981.7 (17.6)	35.0 (0.0)	931.7 (23.6)	35.0 (0.0)	905.8 (11.3)
2000	40.0 (0.0)	985.0 (15.0)	47.5 (0.0)	1233.3 (12.6)	40.0 (0.0)	941.7 (2.9)	35.8 (1.4)	901.7 (2.9)	37.5 (0.0)	895.0 (22.9)
2400	40.0 (0.0)	970.0 (8.7)	49.2 (1.4)	1243.3 (7.6)	40.0 (0.0)	953.3 (5.0)	37.5 (0.0)	890.0 (5.0)	38.3 (1.4)	908.3 (2.9)
2800	40.0 (0.0)	927.5 (7.5)	45.8 (1.4)	1146.7 (12.6)	40.0 (0.0)	875.0 (2.9)	35.0 (0.0)	808.3 (2.9)	37.5 (0.0)	813.3 (2.9)

Values in parentheses represent standard deviations.

Table 4
d_{10} and d_{90} values of granules resulted from grater screen at different milling conditions.

Impeller speed (rpm)	I-1 (μm)		I-2 (μm)		I-3 (μm)		I-4 (μm)		I-5 (μm)	
	d_{10}	d_{90}	d_{10}	d_{90}	d_{10}	d_{90}	d_{10}	d_{90}	d_{10}	d_{90}
1200	55.0 (4.3)	1486.7 (12.6)	60.0 (0.0)	1656.7 (8.8)	58.3 (2.9)	1363.3 (13.8)	55.8 (1.4)	1356.7 (11.5)	56.7 (1.4)	1373.3 (2.9)
1600	55.0 (0.0)	1413.3 (17.6)	59.2 (1.4)	1634.2 (11.3)	55.0 (0.0)	1325.8 (5.2)	51.7 (1.4)	1307.5 (17.5)	54.2 (1.4)	1335.0 (6.6)
2000	50.0 (0.0)	1360.8 (5.2)	54.2 (1.4)	1490.8 (26.7)	50.0 (0.0)	1250.0 (5.0)	47.5 (0.0)	1244.2 (10.1)	48.3 (1.4)	1257.5 (17.5)
2400	45.8 (1.4)	1275.0 (22.9)	50.0 (0.0)	1365.0 (13.2)	45.0 (0.0)	1175.0 (7.5)	45.8 (1.4)	1182.5 (7.5)	45.8 (1.4)	1208.3 (15.3)
2800	45.0 (0.0)	1229.2 (5.2)	50.0 (0.0)	1283.3 (14.6)	48.3 (1.4)	1196.7 (7.6)	44.2(1.4)	1101.7 (2.9)	46.7 (1.4)	1195.8 (18.1)

Values in parentheses represent standard deviations.

Table 5
Combinations of impeller and screen in different mill setting.

Screen + impeller	Category I Grater + I-2	Category II Smooth + I-2	Category III Grater + I-1/I-3/I-4/I-5	Category IV Smooth + I-1/I-3/I-4/I-5
Shearing and trapping (screen)	√	–	√	–
Pre-breaking (impeller)	√	√	–	–

The effect of impeller sidearm shapes, screen types and impeller speeds on the amount of fines (%) generated during milling is shown in Fig. 6. Generally, smooth screen produced more fines compared to grater screen in spite of having higher percentage of open area. However, the smooth screen performance was comparable with the grater screen when the I-2 impeller was employed. In addition, it was also found that I-2 impeller produced the lowest amount of fines with both screen types.

In a milling operation, the combination of impeller and screen was considered to be superior if it produces granules with the same MMD as granules produced by another set of mill conditions but with less fines. Hence, for comparison of two batches of granules with respect to the amount of fines, it would be ideal to use granule batches with similar MMD values. Therefore, from the observations of Section 3.3, mill settings were broadly classified into four categories depending on the presence or absence of pre-breaking action from the impeller and shearing action from the screen (Table 5). In Fig. 7, the amount of fines generated is plotted as a function of MMD values of the granules at different mill setting. At a targeted MMD of the granules, minimum amount of fines (%) was generated using Category I mill setting followed by Category II, III and IV. Synergistic actions (pre-breaking, shearing and trapping) brought about by Category I mill setting produced the lowest amount of fines whereas, highest amount of fines was produced in Category IV mill setting which was devoid of all these actions. From Fig. 7, it was also observed that Category II mill setting tended to produce lesser amounts of fines compared to Category III mill setting producing mill particles of equivalent MMD values. Therefore, it was concluded that pre-breaking of flakes was more important than the shearing and trapping of flakes in minimizing fines generation. From these findings, it was found that the pre-breaking action of flakes had mirrored the amount of fines formed. It was previously reported that in wet granulation, the extent of size reduction mainly determined the amount of fines formed and a lower degree of size reduction was associated with less fines (Verheezen et al., 2004). Findings from this study concurred with the concept that pre-breaking action mainly broke the flakes into smaller size before passing through the aperture of screen that resulted in less fines by reducing the of degree of size reduction.

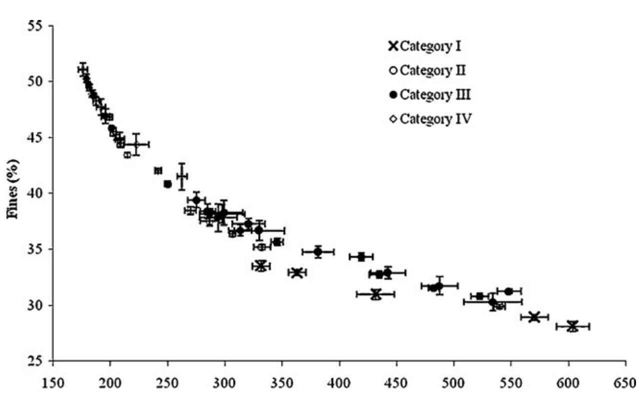

Fig. 7. Relation between fines and MMD of the granules at different mill settings.

Fines formation can also be reduced by the application of multiple step milling. Multiple step milling reduced fines by reducing the degree of size reduction. However, increasing the number of separate milling step would reduce efficiency of the manufacturing process. Therefore, the use of in situ pre-breaking of roller compacted flakes inside the milling chamber would be the better approach at minimizing the fines generated as well as optimizing milling efficiency in manufacturing.

4. Conclusions

Conical screen mill was used to evaluate the effect of various processing parameters on the characteristics of the milled granules from roller compacted flakes. From this study it appears that both the type of impeller and screen play important roles in determining the quality of milled granules. It seems the impeller and screen, which have pre-breaking and shearing action due to their special geometric configuration, are best for the comminution of flakes. I-2 impeller and grater screen were found to have these requisites. Either one of them when present in any mill setting resulted in the production of granules with better quality from flakes, in terms of granules size, size distribution and fines.

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