

Effect of mill types on the properties of granules produced by roller compaction technique

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ABSTRACT

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Mill type, a less explored parameter in roller compaction, may significantly influence granule properties and interact with other process variables due to the diverse mill designs available today. This study aimed to investigate the effects of mill type (bar and knife rotors) and its interactions on granule size distribution and bed density using a full 2^3 factorial design, varying mill speed (250–500 rpm), roll force (4–8 kN/cm), and screen size (1.59–2.36 mm). The results showed that mill speed was the most influential parameter, interacting with mill type to produce opposite effects on granule size and density due to differences in milling mechanisms and rotor-screen gap. Additionally, the bar rotor tended to produce larger granules and a denser bed than the knife rotor. These findings emphasize the importance of mill type selection and its interaction with process parameters in optimizing granule properties, contributing to improved roller compaction performance and final product quality.

Keywords: roller compaction; bar rotor; knife rotor; granule size distribution; bulk density; tap density

1. INTRODUCTION

Active ingredients are often incorporated into drug products prior to being administered to patients. Among these, oral solid dosage forms are commonly preferred due to their stability and ease of administration (Conway, 2008). Their production requires preparation of formulation blends. Although a straightforward approach like direct compression can be used, achieving acceptable content uniformity in the final product may be challenging unless the blends exhibit good flowability (Chan et al., 2016). This issue arises because powders with particle size smaller than 50 μm in diameter generally have poor flow properties, as strong cohesive forces overcome gravitational forces (Lee, 2010). Roller compaction is a dry

granulation technique widely used in the pharmaceutical industry. This process converts drug powders into granules through mechanical compaction, improving their physical properties and aiding in-process issues such as rat holing in hoppers due to poor powder flow and sticking to punches during tableting (Bejugam et al., 2015; Shaikh et al., 2018). Roller compaction offers several advantages over other granulation methods. For instance, it facilitates continuous processing, allowing seamless integration into continuous manufacturing lines. This process does not use a liquid binder or a drying process, avoiding problems related to high temperatures and the presence of water or solvents (Ganesh & Reklaitis, 2020; Shaikh et al., 2018). The process includes compacting drug powders into ribbons (long, thin sheets) using two counter-rotating

rolls, then milled and sieved through a screen to yield granules (Kleinebudde, 2004).

Among roller compaction compartments, the mill part has received relatively low attention although it strongly influences granule quality. For example, mill speed affects granule size distribution. It can be adjusted to change granule size immediately (Wilms et al., 2022). Adjusting the mill speed affects the balance between large granules and fines (Samanta et al., 2012), influencing the flowability. Screen size also has an impact on particle size, which then influences both flow and compactability of the granules (Brubaker & Moghtadernejad, 2024; Rowe et al., 2017). Screen type also affects the residence time of ribbons in the milling chamber, leading to changes in granule properties (Samanta et al., 2012). In some types of mills, the angle of rotation can be adjusted, resulting in affecting granule size (Sakwanichol et al., 2012).

Mill type can affect both process performance and granule quality, but it has received little attention in literature despite the wide range of available designs. Oscillating granulators are commonly used in the pharmaceutical industry for transforming ribbons into granules. They are also used to grind oversized granules, leading to more uniform particles obtained. This can reduce segregation during downstream processing (Alizadeh et al., 2017). Modern roller compactors often integrate the mill, supporting continuous granulation processes. This adjustment can reduce material loss during production. The mill typically consists of one or two rotors and a screen. Selecting an appropriate mill may enhance production efficiency and reduce the proportion of fines. Due to its potential impact, the effect of mill type should be further investigated in both research and pharmaceutical development.

Few studies have systematically investigated the impact of mill type. Perez-Gandarillas et al. (2016) investigated the effect of mill type on granule size using the star and pocket mould-grooved rotors. Mill angle, roll force, mill speed, and the type of sealing system were varied to investigate the interaction effects between mill types. Although no major differences in size distribution was found, differences in throughput between the two rotor designs were observed (Perez-Gandarillas et al., 2016). Haeffler et al. (2019) characterized the granules produced by integrated mills combined with roller compactors from different brands (Hosokawa, Gerteis, and Alexanderwerk), as well as those produced by an oscillating granulator. It was revealed that there were minor differences in granule size between integrated mills and the oscillating granulator after milling granules using the same roller compactor. However, significant variations in granule size were found among granules produced by different integrated mills. These variations were likely caused by differences in ribbon thickness produced by different roller compactor brands, which affected the proportion of fines obtained. Additionally, inconsistencies in parameters such as mill speed across brands further contributed to variability in the experiment (Haeffler et al., 2019). From the outcomes of these studies, it can be inferred that changes in mill type have not shown significant effects on granule attributes, or the observed effects remain inconclusive. This lack of clarity highlights a gap in current knowledge and provides the basis for this study.

This study statistically investigated the effect of mill parameters including mill type, screen size, and mill speed on granule attributes using a design of experiments in the first part. The design corresponded to multivariate mathematical models for assumptions on the probability distributions of the observed variables. Roll force was also selected because it directly affected ribbon tensile strength, porosity and density (Csordas et al., 2018; Selvi et al., 2024; Souihi et al., 2013), which can subsequently govern various granule attributes such as fine fraction, granule size distribution, and granule density (Omar et al., 2015; Weyenberg et al., 2005). The primary objective of this study was to screen for significant main effects and interactions across different mill types. Therefore, two levels of each parameter were evaluated using linear models, which were sufficient for screening purposes. In the second part of the study, a post-analysis of the mathematical models corresponding to a variety of previous responses was performed. The actual results of granules produced with a middle level of parameters were compared with the model predictions as experimental confirmation. This approach enabled the verification of model performance and assessment of correlation patterns. It confirmed strong linear correlations between parameters and responses. The aim of this study was to examine the effect of mill types and their interaction with key process parameters on granule attributes. The effects on granule size distribution, the proportion of large granules and fines, and the density of granule beds were investigated.

2. MATERIALS AND METHODS

2.1 Materials

Microcrystalline cellulose (MCC) (Avicel PH-102, DuPont, Wilmington, Delaware, USA), a common pharmaceutical excipient, was used as blends for all experiments in this study. Before the experiments, the blend was sieved through a 595- μ m screen to remove aggregated powder.

2.2 Roller compaction

The blend was roller compacted into ribbons using a roller compactor (CCS220, Fitzpatrick, Illinois, USA) equipped with serrated-surface rolls and cheek plates. Before compaction, the blend in the hopper was fed into the roll compartment using horizontal and vertical feed augers. The rolls measured 2 cm in width and 20 cm in diameter. Ribbons were produced under controlled conditions of less than 25°C and 50% RH, maintained using a dehumidifier and an air°C conditioner. Two levels of roll force (4 and 8 kN/cm) were applied to produce ribbons with different tensile strengths. The gap between the rolls was automatically adjusted through a gap-controlled mode. Other feed and compaction parameters were kept constant, as detailed in Table 1. Each compacted ribbon was then sequentially fed into the mill compartment for further processing.

2.3 Milling

In pharmaceutical manufacturing, granule size reduction is typically achieved using milling devices such as oscillating granulators and conical mills. Modern roller compactors offer an alternative by incorporating integrated mills. In Fitzpatrick's design, a hammer mill equipped with a screen is positioned beneath the roll compartment (Figure 1), and

the mill rotor is designed to be easily replaceable, allowing quick adaptation to different configurations.

In this experiment, compacted ribbons were milled into granules under varying conditions. The variables included two screen sizes (1.59 and 2.36 mm), two mill speeds (250 and 500 rpm), and two rotor types (bar and knife rotors) (Figure 2), along with additional parameters detailed in Table 1. Different batches of approximately 100 g of granules were produced by adjusting these parameters and mill types. The resulting granules were collected after passing through the screen.

Table 1. Roller compaction and milling parameters

Parameters	Set value
<i>Feed and compaction compartment</i>	
Horizontal feed speed (rpm)	15
Vertical feed speed (rpm)	150
Roll speed (rpm)	5
Roll force (kN/cm)	4, 8
<i>Mill compartment</i>	
Mill type	Bar, knife rotor
Mill speed (rpm)	250, 500
Screen type	Round aperture
Screen size (mm)	1.59, 2.36

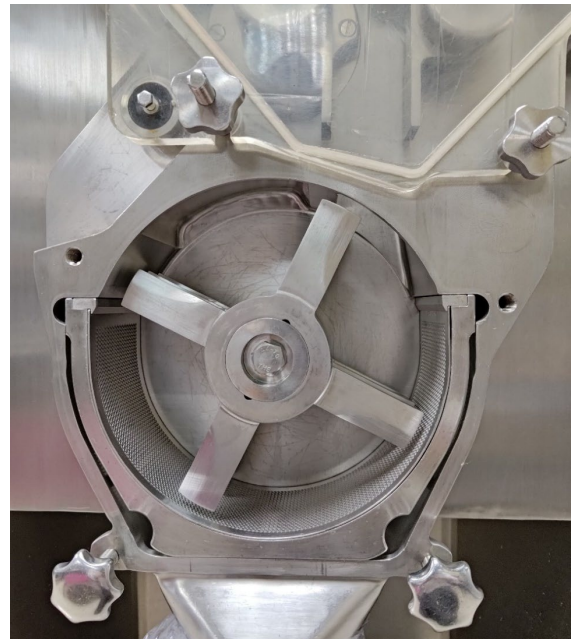


Figure 1. Mill compartment of the Fitzpatrick roller compactor

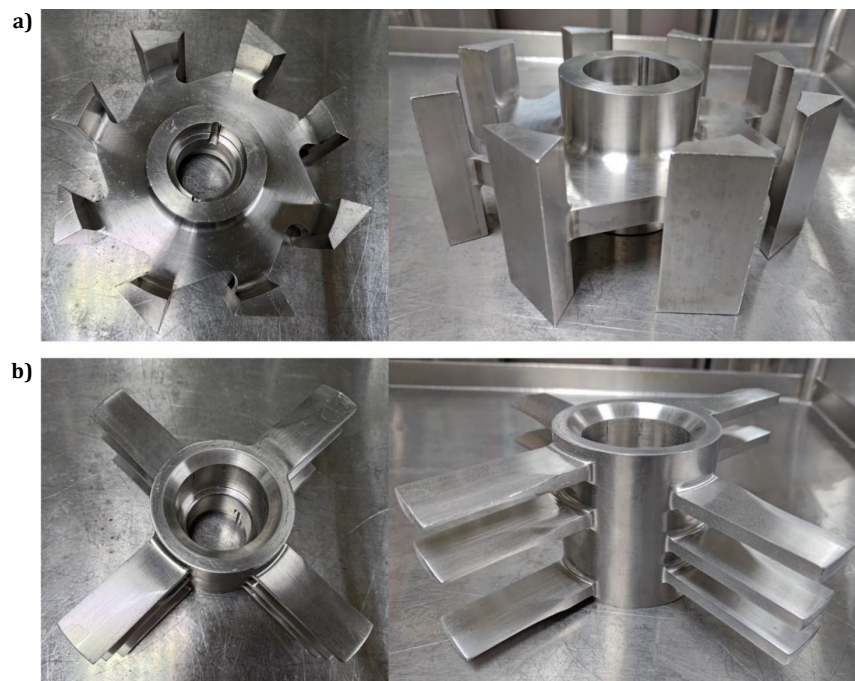


Figure 2. Types of mills including (a) the bar rotor and (b) the knife rotor

2.4 Granule characterization

Sieve analysis of 50 g of granules was conducted in duplicate using a vibrating sieve shaker (Vibro, Retsch GmbH, Haan, Germany) to determine the granule size distribution, including the 35th, 50th, and 65th percentiles (d_{35} , d_{50} , and d_{65}) as well as the proportions of large and fine particles. Sieves with mesh sizes of 74, 149, 177, 250, 400, and 841 μm and a pan were arranged and vibrated for 5 minutes during the analysis. The percentage of large

granules was calculated as the proportion of granules 841 microns or larger using Equation 1, while the percentage of fine powders was calculated as the proportion of particles smaller than 149 microns using Equation 2.

$$\% \text{ Large granule} = \frac{\text{Mass of granules } (\geq 841 \text{ microns})}{\text{Total mass of granules}} \times 100 \quad (1)$$

$$\% \text{ Fine} = \frac{\text{Mass of granules } (< 149 \text{ microns})}{\text{Total mass of granules}} \times 100 \quad (2)$$

The bulk and tap densities of 50 to 100 g of granule beds were determined in duplicate using 250-mL measuring cylinders and a tap density analyzer (PT-TD300, Pharma Test, Hainburg, Germany). During the analysis, the granules were tapped 10, 490, and 750 times, respectively, with the corresponding volume recorded at each stage. If the volume difference between the last two measurements exceeded 2 mL, an additional 1,250 taps were applied until the criterion was met. The fixed drop height of 3 mm and a tap rate of 250 taps per minute were used, following the second method (low drop) for analyzing tapped bulk density outlined in the United States Pharmacopeia general chapter <616> (United States Pharmacopeial Convention, 2025).

2.5 Statistical analysis

The experiments were designed and analyzed using a design of experiment software (Design Expert version 13, Stat-Ease, Minneapolis, USA). A full 2^3 factorial design with 8 experiments was applied to each mill type. Sixteen runs were performed in this study. Mathematical models and Pareto charts were generated to evaluate and compare the correlations of each factor across both mill types. Only significant factors were included in the models. Coefficients of determination (R^2) and p -value were computed to evaluate the fit of the models. The Pareto charts display effect values, quantifying the impact of each factor. Statistical significance was assessed using ANOVA, with a threshold of $p < 0.05$ indicating a significant effect.

2.6 Experimental confirmation

A post-analysis of the mathematical equations corresponding to various responses—namely d_{35} , d_{50} , d_{65} , % large granules, % fines, bulk density, and tap density—was conducted to verify the model's validity. MCC, sieved through a 595- μm screen, was used in this test. The granule production approach remained consistent, using mid-level settings for each factor (375 rpm mill speed, 1.905 mm screen size, and 6 kN/cm roll force). These settings, considered the worst-case scenario for validation, were applied to both mill types. Granules in each condition were produced in triplicate and characterized using the same approaches described earlier. Actual results for each response were compared with the predicted values computed using the design of experiment software (Design Expert version 13, Stat-Ease, Minneapolis, USA). Each mathematical model was considered accurate if the average result fell within the 95% prediction interval (PI).

3. RESULTS AND DISCUSSION

3.1 The effect on the percentiles of granule size

The results of sieve analysis for granules in the range of 74–841 μm were determined and calculated as d_{35} , d_{50} , and d_{65} . The analysis revealed differences in granule size between the bar and knife rotors. Specifically, the d_{35} , d_{50} , and d_{65} values for granules produced by the bar rotor were generally larger than those obtained by the knife rotor under the same conditions, as shown in Figure 3.

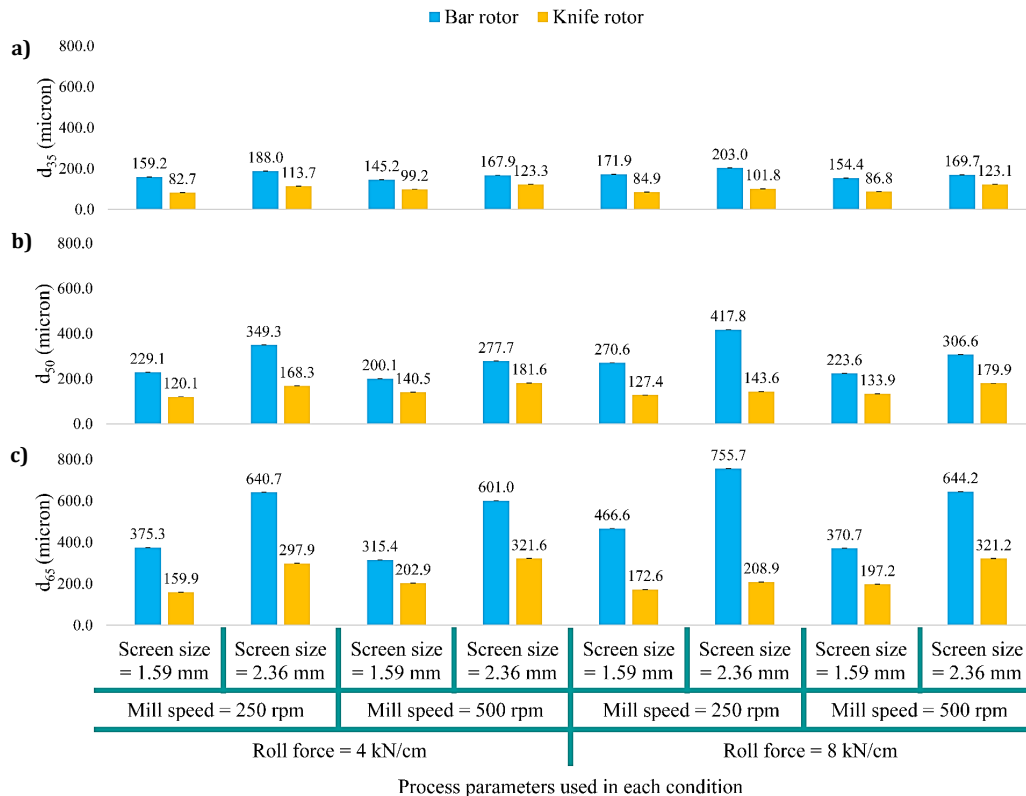


Figure 3. (a) d_{35} , (b) d_{50} , (c) d_{65} values of MCC granules prepared using different mill types under various parameters

Linear equations for prediction of d_{35} , d_{50} , and d_{65} were constructed. The equations for granules produced by the bar rotor are presented below:

$$d_{35} = 139.40236 - (0.085203 \times \text{Mill speed}) + (31.66200 \times \text{Screen size})$$

$$d_{50} = 107.03637 - (0.258910 \times \text{Mill speed}) + (138.94328 \times \text{Screen size})$$

$$d_{65} = -198.47015 + (363.91247 \times \text{Screen size})$$

The equations for granules produced by the knife rotor are as follows:

$$d_{35} = 14.17667 + (0.049154 \times \text{Mill speed}) + (35.10316 \times \text{Screen size})$$

$$d_{50} = 25.03238 + (0.074896 \times \text{Mill speed}) + (48.66292 \times \text{Screen size})$$

$$d_{65} = -31.89552 + (135.28271 \times \text{Screen size})$$

The coefficients of each parameter in the equations reflect their quantitative impact on granule size percentiles. Significant models ($p < 0.05$) regarding percentile responses were identified, as shown in Table 2, regardless of whether a bar or knife rotor was used during the milling process. The table also reveals that the effect of mill speed on responses representing smaller granule sizes is more significant compared to larger granules. The p -value of d_{35} , d_{50} , and d_{65} were 0.0120, 0.0380, and > 0.0500 , respectively, when using the bar rotor, and 0.0306, 0.0328, and > 0.0500 , respectively, when using the knife rotor. Additionally, the correlation between the parameters and the granule size percentiles is further discussed using the Pareto chart for d_{35} , d_{50} , and d_{65} , as illustrated in Figure 4.

Table 2. Statistical results of parameters in models predicting granule responses for bar and knife rotors

Response	Source	Bar rotor			Knife rotor		
		p -value	R^2	Model summary	p -value	R^2	Model summary
d_{35}	Model	0.0058	0.8728	significant	0.0023	0.9124	significant
	Mill speed	0.0120			0.0306		
	Screen size	0.0070			0.0012		
	Roll force	*			*		
d_{50}	Model	0.0081	0.8540	significant	0.0035	0.8955	significant
	Mill speed	0.0380			0.0328		
	Screen size	0.0057			0.0021		
	Roll force	*			*		
d_{65}	Model	0.0008	0.8683	significant	0.0108	0.6885	significant
	Mill speed	*			*		
	Screen size	0.0008			0.0108		
	Roll force	*			*		
% Large granule	Model	<0.0001	0.9413	significant	0.0011	0.8514	significant
	Mill speed	*			*		
	Screen size	<0.0001			0.0011		
	Roll force	*			*		
% Fine	Model	0.0195	0.7931	significant	0.0024	0.9112	significant
	Mill speed	0.0348			0.0206		
	Screen size	0.0214			0.0014		
	Roll force	*			*		
Bulk density	Model	0.0020	0.9668	significant	N/A	N/A	not significant
	Mill speed	0.0344			*		
	Screen size	0.0009			*		
	Roll force	0.0070			*		
Tap density	Model	0.0018	0.9689	significant	0.0099	0.6975	significant
	Mill speed	0.0101			0.0099		
	Screen size	0.0011			*		
	Roll force	0.0043			*		

* Excluded from the model as the parameter had no significant impact ($p \geq 0.05$) on the response

According to the Pareto charts, screen size was the most critical factor affecting all percentiles of granule size regardless of the mill types. This result aligned with findings by Rambali et al. (2001), where increasing the screen size facilitated the passage of larger granules. Additionally, mill speed demonstrated a significant effect on granule size, particularly on the d_{35} and d_{50} . However, the effects varied depending on the rotor type. With the bar rotor, increasing mill speed negatively affected granule size, consistent with results from multiple studies (Perez-Gandarillas et al., 2016; Rekhi & Sidwell, 2016; Sakwanichol et al., 2012). This reduction in granule size

was attributed to the increased frequency of abrasive and mechanical stress at higher rotor speed, resulting in finer granules. In contrast, the knife rotor exhibited a positive relationship between mill speed and granule size. The opposing effect observed with different mill types can be explained by differences in throughput and their effects on milling time. A higher rotor speed could accelerate the milling process, reducing the time granules spent inside the mill chamber. Shorter milling time resulted in a higher proportion of large granules, similar to Samanta et al. (2012). For the knife rotor, slower throughput and longer milling time were observed, as evidenced by the

higher amount of residual ribbons remaining in the chamber after the process compared to the bar rotor configuration (Figure 5). The residual mass for the knife rotor was approximately 30–40 g, whereas the mass by the bar rotor was consistently below 5 g. This accumulation by knife rotor suggested the presence of a bottleneck of the milling process, where the reduction in milling time became the dominant factor influencing granule size. Conversely, with the bar rotor, the absence of this bottleneck allowed higher mill speed to increase

granule collisions, rather than efficiently delivering granules through the screen. The difference in throughput between the two rotor types can be attributed to their distinct mechanisms. The bar rotor's wide tip can compress the material against the screen, and the smaller rotor–screen gap facilitated more efficient granule delivery. In addition, roll force, which influenced ribbon tensile strength and density (Omar et al., 2015; Souihi et al., 2013), had a minor effect on granule size regardless of the mill type used.

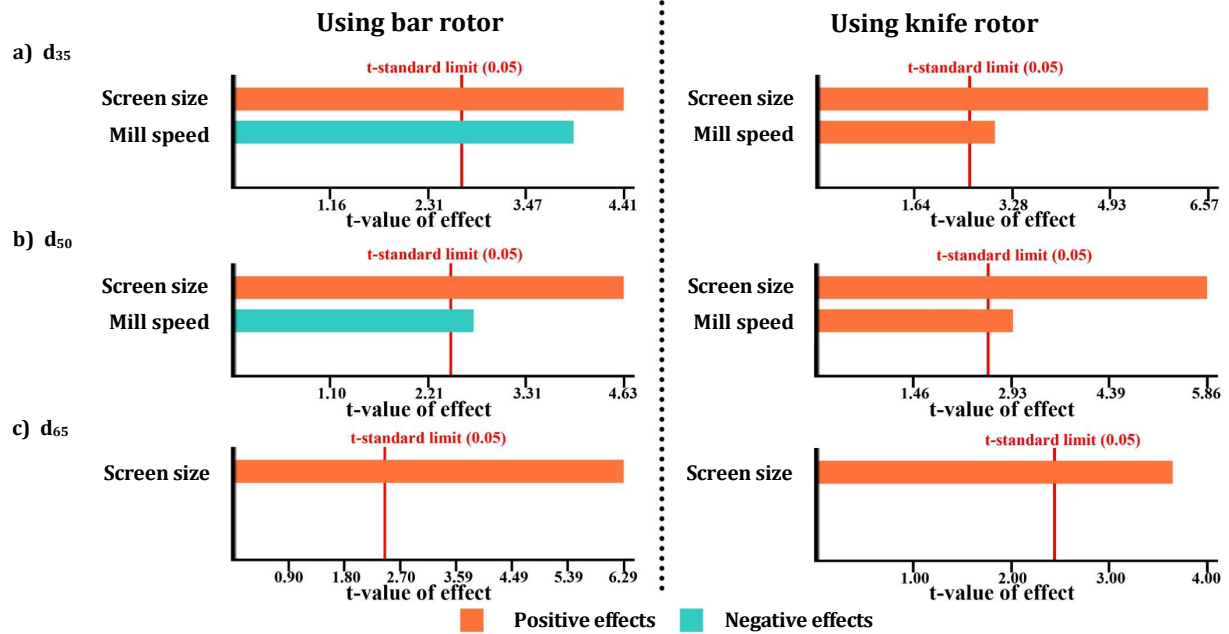


Figure 4. Pareto charts showing the standardized effects of process parameters on (a) d_{35} , (b) d_{50} , (c) d_{65} of MCC granules prepared using different mill types under various parameters.

Note: The red vertical line indicates the t-value threshold ($\alpha = 0.05$); parameters with t-values exceeding this limit are considered to have a statistically significant effect.

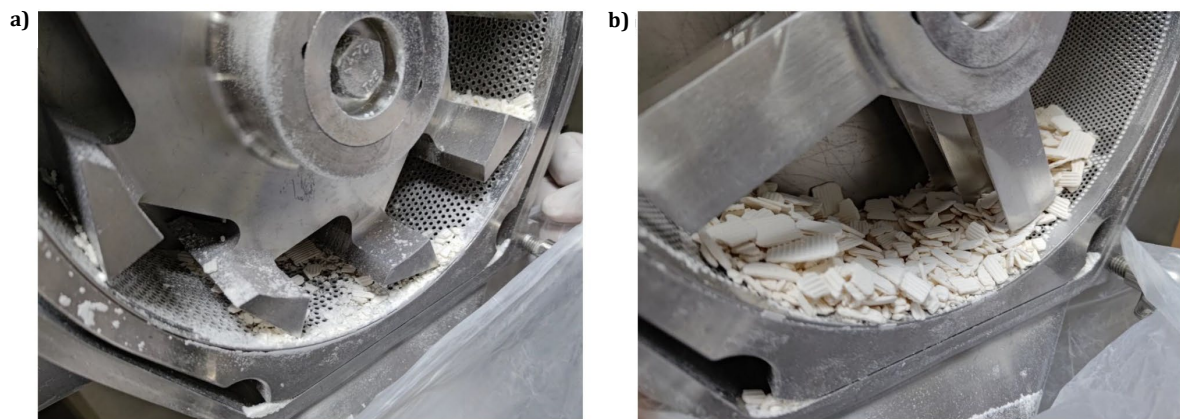


Figure 5. Residual ribbons remaining in the mill chamber after being milled by (a) the bar rotor and (b) the knife rotor

3.2 The effect on % large granules and % fine granules

The percentages of the granules with a diameter of 841 μm or larger, referred to as % large granules, and the granules with a diameter smaller than 149 μm , referred to as % fines, were calculated based on the sieve analysis, as shown

in Figure 6. Noticeable differences were observed in both responses when using different mill types under the same conditions. Specifically, granules produced by the bar rotor tended to have a higher % large granules and a lower % fines compared to those produced by the knife rotor.

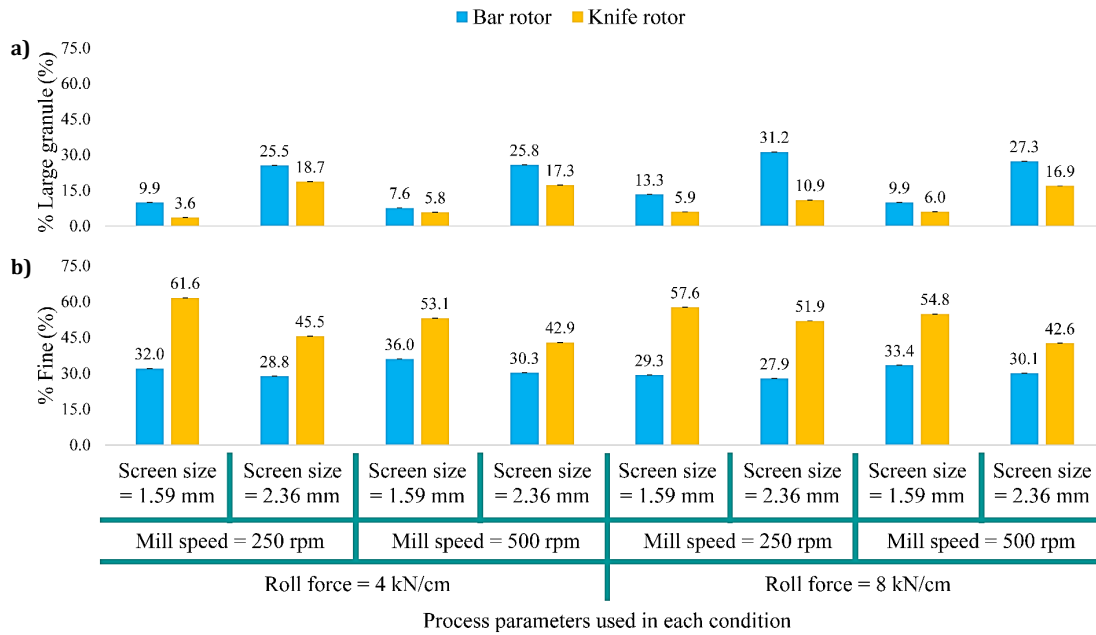


Figure 6. (a) % Large granules and (b) % fines of MCC granules prepared using different mill types under various parameters

Linear models predicting % large granules and % fines were developed. The equations below represent the case where a bar rotor is used:

$$\% \text{ Large granules} = -25.46578 + (22.41558 \times \text{Screen size})$$

$$\% \text{ Fines} = 35.21187 + (0.011830 \times \text{Mill speed}) - (4.41234 \times \text{Screen size})$$

For granules produced using a knife rotor, the corresponding equations are as follows:

$$\% \text{ Large granules} = -16.57662 + (13.78247 \times \text{Screen size})$$

$$\% \text{ Fines} = 88.25873 - (0.023240 \times \text{Mill speed}) - (14.32468 \times \text{Screen size})$$

The significance of the models ($p < 0.05$) for % large granules and % fines, regardless of whether a bar or knife rotor was used in the milling process, is presented in Table 2.

After converting the % large granules and % fine results into Pareto chart as shown in Figure 7, screen size was identified as the most significant parameter, regardless of whether the bar or knife rotor was used. It showed a positive correlation with % large granules and a negative correlation with % fines. This means that using a larger screen size increased the % large granules while decreasing the % fines. This effect occurs because a larger screen aperture allowed more large granules to pass through, resulting in a higher proportion of large granules and fewer fines. Mill speed had a significant impact on % fine but only a slight effect on % large granules, regardless of the mill types. Interestingly, the opposite effect depending on the rotor type was still observed. With a bar rotor, a higher mill speed increased % fines and decreased % large granules. In contrast, with the knife rotor, a higher mill speed reduced % fines and increased % large granules. This can be explained by the same reasoning as the effect on granule size percentiles. It was attributed to the interplay between milling force and milling time. A higher rotor speed generated greater force and more frequent

milling, which enhanced size reduction. However, the milling process occurred more rapidly, reducing the overall milling time. This shorter milling duration resulted in a higher proportion of larger granules. For the knife rotor, a bottleneck effect caused by longer milling times played a crucial role. The reduced milling time became the dominant factor at higher mill speeds, allowing granules to pass through the screen more quickly, resulting in a higher proportion of larger granules. In contrast, the bar rotor, which lacked this bottleneck effect, primarily caused the rupture of larger granules at higher mill speeds, rather than facilitating their faster passage through the screen. Furthermore, roll force did not have a significant impact on % large granules or % fines, regardless of the rotor type used. This indicates that roll force within the range of 4–8 kN/cm did not noticeably affect granule size distribution responses.

3.3 The effect on the density of granule beds

The evaluation of packed granule density revealed that different mill types influenced the results, as shown in Figure 8. Overall, the bulk and tap densities of the granules produced by the bar rotor were higher than those obtained using the knife rotor under identical conditions. However, when the rotor speed increased to 500 rpm and the screen aperture size decreased to 1.59 mm, the tap density of granules produced by the knife rotor surpassed that of the bar rotor.

Linear equations were developed for bulk and tap densities. For granules produced using the bar rotor, the equations are:

$$\text{Bulk density} = 0.338247 - (0.000065 \times \text{Mill speed}) + (0.060065 \times \text{Screen size}) + (0.006563 \times \text{Roll force})$$

$$\text{Tap density} = 0.490503 - (0.000110 \times \text{Mill speed}) + (0.064935 \times \text{Screen size}) + (0.008750 \times \text{Roll force})$$

For granules produced using the knife rotor, the bulk density model showed no statistically significant results. Therefore, only the equation for predicting tap density was generated as follows:

$$\text{Tap density} = 0.538750 + (0.000160 \times \text{Mill speed})$$

As presented in Table 2, the models for predicting tap density were statistically significant ($p < 0.05$) for both mill types. However, for bulk density, only the model using the

bar rotor demonstrated statistical significance. According to Figure 8, the bulk density of granules produced by the knife rotor exhibited minimal variation across different parameters. This limited variation may be attributed to the relatively small changes in granule size observed when altering the milling parameters with the knife rotor, as shown in Figure 3, since granule size is known to influence the bulk density of granule beds (Saw et al., 2013).

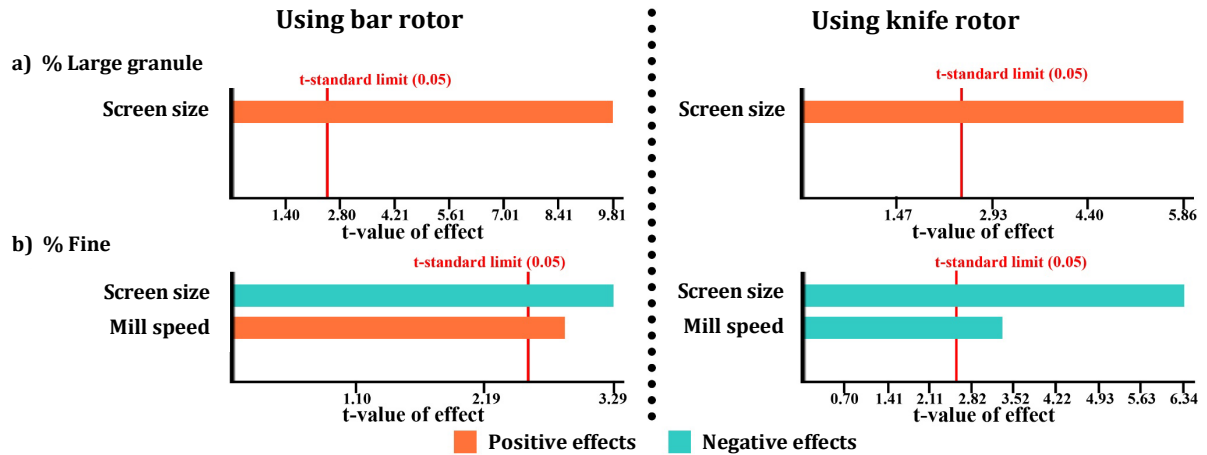


Figure 7. Pareto charts showing the standardized effects of process parameters on (a) % large granules and (b) % fines of MCC granules prepared using different mill types under various parameters.

Note: The red vertical line indicates the t-value threshold ($\alpha = 0.05$); parameters with t-values exceeding this limit are considered to have a statistically significant effect.

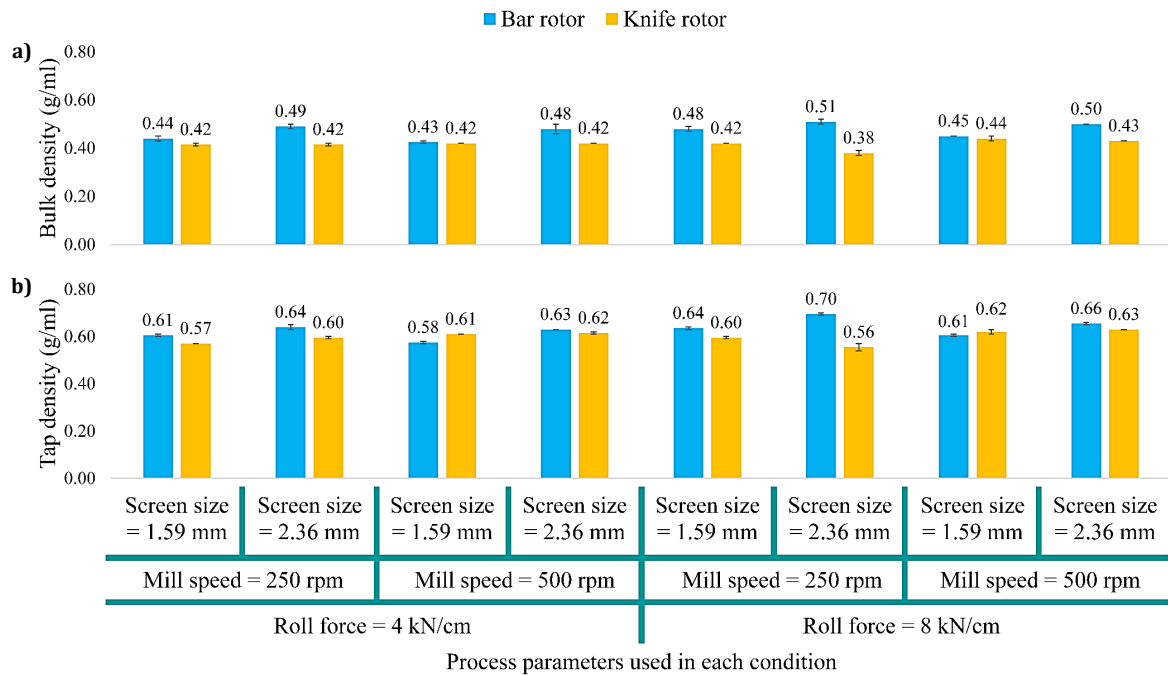


Figure 8. (a) Bulk and (b) tap densities of MCC granules prepared using different mill types under various parameters

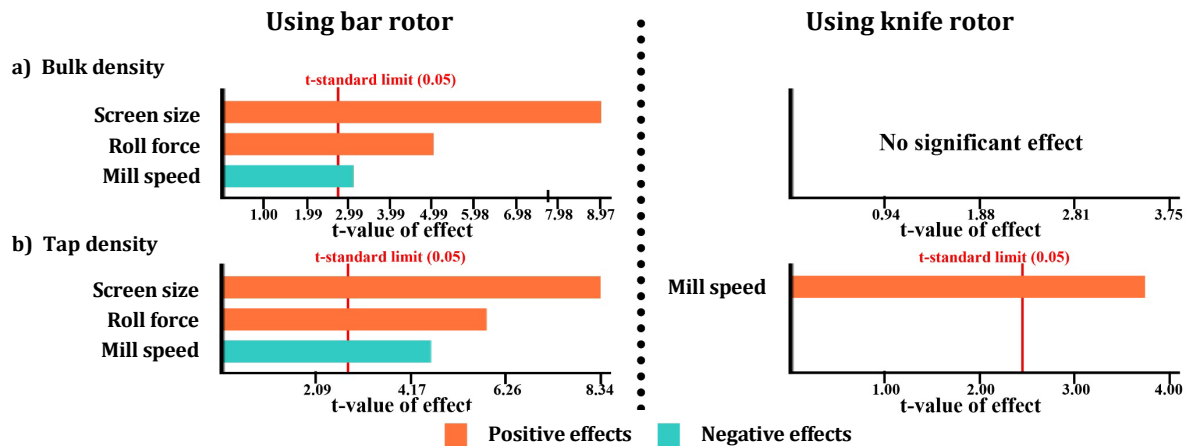


Figure 9. Pareto charts showing the standardized effects of process parameters on (a) bulk and (b) tap densities of MCC granules prepared using different mill types under various parameters.

Note: The red vertical line indicates the t-value threshold ($\alpha = 0.05$); parameters with t-values exceeding this limit are considered to have a statistically significant effect.

The Pareto chart comparing bulk density, as shown in Figure 9a, revealed no significant effect when using the knife rotor. This aligns with the lack of statistical significance observed in the bulk density model for the knife rotor. In contrast, for the bar rotor, screen size was the most critical factor. A positive correlation was observed – larger screen sizes resulted in higher bulk density of the granules, consistent with the findings of Souihi et al. (2013). This effect occurs because larger screen apertures allow larger granules to pass through, reducing their specific surface area. With a lower surface area, cohesion forces between granules are reduced, making the granule less bulkiness, and increasing their bulk density. Moreover, roll force was identified as a significant parameter with a positive effect on bulk density, also aligning with Souihi et al. (2013). Increasing roll force produced harder and denser ribbons, which led to denser granules and, consequently, higher bulk density of packed granules. In contrast, mill speed showed a significant negative effect on bulk density when using bar rotor. As shown in Figure 3, higher mill speeds produced smaller granules, increasing their specific surface area. This heightened surface area strengthened cohesion forces between particles, counteracting gravitational setting. As a result, the granules became bulkier, leading to a decrease in bulk density (Janssen et al., 2022; Mohammadi & Harnby, 1997).

The comparative effect values for tap density, shown in Figure 9b, indicated that mill speed was a significant parameter for both mill types. With the bar rotor, mill speed had a negative effect, while with the knife rotor, it had a positive effect. This difference is consistent with the previously observed interplay between mill stress and milling time as mill speed increased. In addition, screen size and roll force had significant positive effects on tap density when using the bar rotor, with screen size emerging as the most critical parameter. These positive effects can be attributed to the formation of larger granules as screen size and roll force increased. Larger granules, due to their lower specific surface area, reduced cohesion force between particles, allowing them to flow more easily under gravity (Shah et al., 2023). Improved flowability enabled the powder to compact more effectively during tapping,

resulting in an increased tap density. This behavior aligns with the findings of Jonat et al. (2004), where the addition of a glidant, such as colloidal silicon dioxide, improved the tap density of MCC. Practically, larger granules are less efficient at rearranging and packing densely, leading to a looser packing structure, while smaller particles can fill the voids between larger granules, thereby enhancing tap density (Santl et al., 2012). However, as shown in Figure 6, all experimental conditions in this study produced more than 25% fines, exceeding the amount required to fill voids. This excess of fines may obscure the expected filling effect, reducing its impact on tap density. Interestingly, screen size and roll force did not have a significant impact on tap density when using the knife, suggesting that the mechanical differences between the two rotor types influence how these parameters affect granule compaction.

3.4 Experimental confirmation

The actual results for each response were compared with the predicted values calculated using the established equations to validate the mathematical models. The outcomes of this comparison are presented in Table 3. Although most models demonstrated moderate to high coefficients of determination ($R^2 = 0.6885\text{--}0.9689$) and statistically significant p -values ($p < 0.05$) as shown in Table 2, nearly all actual results, with the single exception of tap density for the knife rotor, fell outside the 95% prediction interval. While a high R^2 value generally indicates that the model explains the variability at the design boundaries, the failure to predict mid-level responses strongly indicates the presence of significant curvature in the design space. This suggests that the linear models cannot fully capture the complex, non-linear quantitative effects of these parameters. Consequently, the predictive capacity of the current models is limited. Despite these limitations, these linear models remain effective for their primary purpose of identifying the significant parameters, examining two-factor interactions, and exploring the direction and strength of effects. Because this study was designed for initial parameter screening rather than predicting optimization, exploring quadratic designs remain a subject for future work.

Table 3. Experimental confirmation comparing the actual results with the 95% prediction interval at the mid-level settings of mill speed, screen size, and roll force for both bar and knife rotors

Response	Using bar rotor					Using knife rotor				
	Predicted mean	n	95% PI low	Actual mean	95% PI high	Predicted mean	n	95% PI low	Actual mean	95% PI high
d ₃₅	167.767	3	154.102	264.291	181.433	99.3055	3	89.1242	123.091	109.487
d ₅₀	274.632	3	217.464	465.096	331.8	145.578	3	129.748	204.158	161.407
d ₆₅	494.783	3	457.335	747.211	532.231	225.142	3	157.784	377.059	292.499
% Large granule	17.2359	3	13.0965	30.0204	21.3754	9.61006	3	5.34839	20.0622	13.8717
% Fine	31.2426	3	28.6989	22.7875	33.7864	52.3269	3	48.0199	41.2477	56.6338
Bulk density	0.46767	3	0.453909	0.491833	0.481432	*	*	*	*	*
Tap density	0.625455	3	0.609447	0.656467	0.641462	0.59875	3	0.573559	0.595541	0.623941

4. CONCLUSION

A 2³ full factorial design was applied for each mill type to analyze the correlations between milling parameters and granule attributes using linear models. The research provided invaluable insights into how mill types interact with other parameters, significantly affecting granule properties. Among the examined parameters, mill speed exhibited the most significant interaction effects between the two mill configurations. Opposite trends were observed. With a bar rotor, increasing mill speed resulted in fewer large granules and more fines obtained. In contrast, with a knife rotor, higher mill speeds led to fewer fines and a higher amount of larger granules. These opposing effects were also reflected in bulk and tap densities. Additionally, granules produced with a bar rotor were generally larger and more densely packed than those obtained by a knife rotor under identical conditions. These findings highlight the critical influence of mill type on key granule attributes using linear models to identify significant factors and interaction trends. However, experimental confirmation results revealed that the linear models could not fully capture the complex relationships between process parameters and granule attributes. Consequently, this study provides preliminary evidence of the influence of mill type and its interactions with key process parameters, but the predictive capacity of the current models remains limited. In addition, it is important to emphasize the material limitations of this study. As only MCC was evaluated, the results may not be directly generalizable to brittle active pharmaceutical ingredients and excipients. Future research should extend the range of parameter levels to three or more levels to capture non-linear behavior and improve predictive accuracy and support process prediction and optimization frameworks. Some approaches such as fractional factorial, central composite, and Box–Behnken designs may be selected to reduce the experimental burden, determine response surfaces, and identifying design spaces for optimization. Furthermore, additional responses such as granule flowability could be investigated to provide a more holistic understanding of the roller compaction process and further refine pharmaceutical manufacturing practices.

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AUTHOR CONTRIBUTIONS

T.T. Writing – original draft, Software, Investigation, Methodology, Formal analysis; C.P. Formal analysis, Visualization, Supervision, Writing – review & editing; P.O. Supervision, Resources; P.C. Methodology, Conceptualization, Visualization, Supervision, Writing – review & editing; P.P. Methodology, Conceptualization, Visualization, Supervision, Writing – review & editing.

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