powders

Article

Understanding Powder Behavior in Continuous Feeding: Powder Densification and Screw Layering

Sara Fathollahi [1,*], Pauline H. M. Janssen [1,2], Bram Bekaert [3], Dirk Vanderroost [4], Valerie Vanhoorne [3] and Bastiaan H. J. Dickhoff [1]

[1] DFE Pharma, Klever Strasse 187, 47568 Goch, Germany; pauline.janssen@dfepharma.com (P.H.M.J.); bastiaan.dickhoff@dfepharma.com (B.H.J.D.)
[2] Department of Pharmaceutical Technology and Biopharmacy, University of Groningen, Antonius Deusinglaan 1, 9713 AV Groningen, The Netherlands
[3] Laboratory of Pharmaceutical Technology, Department of Pharmaceutics, Ghent University, Ottergemsesteenweg 460, B-9000 Ghent, Belgium
[4] GEA Process Engineering, Keerbaan 70, B-2160 Wommelgem, Belgium
* Correspondence: sara.fathollahi@dfepharma.com; Tel.: +49-151-5805-7488

Abstract: Background: Precise continuous feeding of active pharmaceutical ingredients (APIs) and excipients is crucial in a continuous powder-to-tablet manufacturing setup, as any inconsistency can affect the final tablet quality. Method: This study investigated the impact of various materials on the performance of a continuous twin-screw loss-in-weight (LIW) feeder. The materials tested included spray-dried lactose, anhydrous lactose, granulated lactose, microcrystalline cellulose (MCC), an MCC–lactose preblend (50%:50% w/w ratio), and a co-processed excipient (lactose–lactitol at a 95%:5% w/w ratio). The feeding performance of these excipients was systematically assessed, focusing on powder densification and screw layering within the LIW feeder. Results: The results demonstrated densification for the spray-dried lactose and preblend. Densification was more pronounced during the initial feeding cycles for spray-dried lactose, but decreased gradually over time. In contrast, the densification remained relatively constant throughout the feeding process for the preblend. Notably, minor screw layering was observed for both spray-dried lactose and anhydrous lactose, with the extent of this issue reducing over time for the spray-dried lactose. Interestingly, granulated lactose grades did not show screw layering, making them preferable for blending with APIs prone to severe screw layering. The LIW feeder control system successfully managed powder densification and minor screw layering, maintaining the mass flow rate at the set point for all investigated materials. Conclusions: These findings inform the selection of optimal excipients, appropriate tooling for LIW feeders, and the enhancement of control strategies to shorten startup times. By addressing these factors, the precision and reliability of continuous feeding processes can be improved.

Keywords: continuous feeding; loss-in-weight (LIW) feeder; screw layering; densification; feed factor variation; API; excipient; lactose; preblend; co-processed

check for updates

Citation: Fathollahi, S.; Janssen, P.H.M.; Bekaert, B.; Vanderroost, D.; Vanhoorne, V.; Dickhoff, B.H.J. Understanding Powder Behavior in Continuous Feeding: Powder Densification and Screw Layering. *Powders* **2024**, *3*, 482–499. https://doi.org/10.3390/powders3040026

Academic Editor: Ecevit Bilgili

Received: 19 August 2024
Revised: 25 September 2024
Accepted: 27 September 2024
Published: 30 September 2024

1. Introduction

Throughout history, continuous production has revolutionized industries, making goods quickly and efficiently. While initially embraced slowly, continuous manufacturing (CM) is steadily gaining momentum in the pharmaceutical industry, aided by FDA and other regulatory support and guidelines [1–3]. CM enables faster production with lower operating cost, modular manufacturing, and better monitoring and control over individual processes, and therefore more consistent product quality [4–7].

One significant advantage lies in CM's integration with process analytical technology (PAT), enabling real-time release testing (RTRT) [8–11]. This allows products to be swiftly released on the market after production, a critical necessity to avoid drug product shortages [5], especially in catastrophic situations (i.e., the COVID-19 pandemic in 2020).

Furthermore, CM provides enhanced scalability [5,12,13]. In view of these advantages, it is crucial to recognize that embracing CM technology is vital for maintaining competitiveness and efficiency in pharmaceutical manufacturing.

Adopting CM requires a comprehensive understanding of the critical material attributes (CMAs) or function-related characteristics (FRCs) of both the active pharmaceutical ingredient (API) and excipients at every unit operation. Knowledge and predictive capability regarding the scalability of materials, whether individual or in combination [14], tailored to the specific unit operation, are essential for establishing a robust production process.

In CM, the production is uninterrupted, with unit operations such as feeding, blending, granulation, and tableting or capsule filling all connected. Feeders play a critical role in continuous manufacturing lines, as they deliver the formulation components to the downstream process and finally to the final drug products. It is therefore important to maintain a steady state in the feeding process, as any variation or inconsistency in feeding can impact the quality of final drug products [15–18].

In continuous processes, blending unit operations are typically designed to reduce variability and create a uniform blend. However, if the feeders fail to provide a consistent flow, particularly with APIs, the blender may not be able to manage sudden fluctuations effectively. Several studies have indicated that variability and disruptions during the feeding operation can impact the performance of downstream unit operations and the quality of the final product [19,20]. The success of the feeder in regulating powder flow relies on the optimal setup of the feeder (type and tooling) and material properties such as particle size, shape, and flow characteristics [21–25].

Loss-in-weight (LIW) feeders are commonly used to feed pharmaceutical powders [18, 26–30]. LIW feeders can operate in either volumetric or gravimetric mode [31,32]. In volumetric mode, material is fed based on a fixed volume by running the feeder at a constant screw speed. This mode is sensitive to changes in material density, which can lead to variations in mass flow rate at constant screw speed. In gravimetric mode, however, the feeder adjusts the screw speed to feed a constant mass of material, minimizing the impact of density changes. The control system continuously measures the material weight in the feeder over time during feeding in gravimetric mode. LIW feeders consist of a hopper for the powder, a weighing platform with a load cell to measure the loss of powder in the hopper for gravimetric control of the mass flow rate, and screws to transport the material out of the hopper to the next unit operation. In a continuous feeder, the hopper is regularly refilled with powder to maintain a suitable fill level for uninterrupted operation. The periodic refilling can lead to densification of the powder at the hopper–screw interface, increasing interparticle stress and causing overfeeding by forcing the powder into the screw flights [22,33,34].

Particle size distribution (PSD) significantly influences the precision of feeding processes. In materials with a wide PSD, smaller particles can fill the voids between larger ones, resulting in increased bulk density (referred to as densification) [14]. This packing effect alters flowability and mass flow rates, potentially leading to variations in material discharge from the LIW feeder, particularly in volumetric mode (where flowability plays a critical role in maintaining precise mass flow rates).

Powder densification in the hopper–screw zone poses challenges by altering material flowability [35] and consistency in the continuous feeding process [22]. As powders compact, their bulk density increases, disrupting uniform material feeding and causing fluctuations in mass flow rates. This necessitates frequent screw speed adjustments to maintain accuracy and can extend startup times, reducing overall process efficiency. Densification is typically not a concern in gravimetric mode feeding, as the control system adjusts screw speed to maintain the target mass flow rate. However, in volumetric mode feeding, such as during refills, the screws operate at a constant speed, so changes in bulk density lead to changes in mass flow rate.

Hopper and screw design [36–39] can significantly influence the solids stress profile within a feeder, affecting bulk density due to powder compressibility [40]. To ensure smooth feeding operation, it is crucial to use tooling, including optimal screw design and size, and appropriate hopper design to mitigate densification effects, facilitating consistent material flow and minimizing disruptions in the feeding process.

Another challenge in LIW feeders is screw layering, when layers of powder accumulate along the length of the screw conveyor in an LIW feeder [30,31]. This can occur when the mass flow rate is too low and/or when the powder has poor flow properties with high affinity to the feeder's screws, e.g., cohesive powder and/or a powder with a high degree of electrostatic charge [41]. Over time, as the screws rotate, the layers of powder can become thicker and more compact, which can lead to disruptions in the feeding process. Screw layering can also cause blockages in the screw zone of the feeder, which can lead to disruptions in the feeding process and therefore potentially impact the quality of the final drug product. Additionally, even a thin layer forming on the screws can reduce the interaction and friction between the screws and powder, altering surface friction and influencing how effectively the screws can transport the powder compared to the friction between the powder and the feeder walls. This in turn can diminish the conveying potential of the feeder. If more and more material sticks to the screw, the desired mass flow rate might not be achieved due to the feeder's motor speed limit. Understanding this feeding challenge is crucial for predicting the CM runtime without interruptions for cleaning material adhered to the screws and halting the feeding unit operation.

To prevent or delay screw layering, it is essential to optimize the mass flow rate and select appropriate tooling, such as screws and screens, tailored to the specific properties of the powder being fed. Additionally, the choice of excipient should be considered. While the API is usually fixed in the formulation, the excipient, such as the type of lactose, can be selected. In the case of preblending of APIs and excipients or excipients alone, choosing an excipient that helps prevent or delay screw layering can improve feeding process.

In this study, we explored powder behavior in continuous feeding, specifically focusing on the degree of powder densification and screw layering among various excipients. While previous research has delved into screw layering within feeders [31], it is noteworthy that (to our knowledge) this study represents the first comprehensive investigation into densification and screw layering with such a diverse collection of excipient types. Additionally, this study introduces a methodology to quantify these effects.

The excipients investigated, spray-dried lactose, anhydrous lactose, granulated lactose, and microcrystalline cellulose, are widely used in the pharmaceutical industry as fillers and binders. Additionally, a preblend and a co-processed excipient were investigated to assess their feeding performance. Traditionally, blends are created to minimize the number of feeders, thereby simplifying the CM process. Recently, co-processed excipients have been introduced by suppliers as an innovative solution for reducing the number of feeders in CM. This rationale underlies the investigation of both an MCC–lactose preblend and a co-processed excipient (lactose–lactitol) feeding in this study.

It is recognized that controlling LIW feeder performance necessitates aligning feeder tooling with material properties and implementing tailored feeder control strategies [15] to minimize variability in fed material concentration. The findings from this study offer valuable insights into the feeding performance of various excipients. Given that excipients are inactive ingredients (that can be present in high volume in the formulation or tablet), they can be selected based on the manufacturing process to optimize API performance. The results of this study support selecting the most suitable excipients to ensure solid CM and scalability. The significance of this study lies in its potential to provide guidance to practitioners in the pharmaceutical manufacturing sector.

2. Materials and Methods

2.1. Materials

An overview of the materials used during this investigation, including their suppliers, is provided in Table 1.

Table 1. Overview of the investigated materials: excipient name, manufacturer, material type, and abbreviation.

Excipient Name	Manufacturer	Material Type	Abbreviation
SuperTab® 11SD	DFE Pharma (Germany)	Spray-dried lactose	11SD
SuperTab® 22AN	DFE Pharma (Germany)	Anhydrous lactose	22AN
SuperTab® 24AN	DFE Pharma (Germany)	Granulated anhydrous lactose	24AN
SuperTab® 30GR	DFE Pharma (Germany)	Granulated lactose monohydrate	30GR
SuperTab® 40LL	DFE Pharma (Germany)	Co-processed lactose-lactitol	40LL
Pharmacel® 102	DFE Pharma (Germany)	Microcrystalline cellulose	PH102

2.2. Material Characteristics

2.2.1. Particle Size Distribution Measurements

Particle size distribution was measured (n = 3) via dry laser diffraction (Sympatec, HELOS/KR, Clausthal-Zellerfeld, Germany). The powder was fed at 0.5 bar and 50% feed rate using a dry dispersion system.

2.2.2. Bulk and Tapped Density Measurements

The bulk and tapped densities were measured (n = 2) according to Ph. Eur. Method 1 using an automatic tapping device (STAV 2003 stampvolumeter, Engelsmann, Ludwigshafen am Rhein, Germany). The Hausner ratio (HR) was calculated as HR = TD/BD.

2.2.3. Ring Shear Testing

The flow function coefficient (ffc) was measured (n = 2) using a ring shear tester (RST-XS, Dietmar Schulze, Wolfenbüttel, Germany). Powders were tested at preconsolidation of 4 kPa, and normal stresses of 1, 2, and 3 kPa were applied until shear failure.

2.3. Blend Preparation

A preblend of PH102:24AN (50:50% w/w) was created by blending the components for 15 min at 25 rpm using a 60 L intermediate bulk container (IBC) blender (GEA®, Wommelgem, Belgium) with a fill volume of approximately 60% v/v.

2.4. Equipment

Trials were conducted using the CDC-50 (GEA®, Wommelgem, Belgium), which encompasses a series of material handling processes, including pneumatic transfer, loss-in-weight twin-screw feeders, a two-stage continuous blender, and tableting. A schematic of the line is shown in Figure 1. In this fully automated tableting line, the handling of materials begins with the transfer of each component from its commercial packaging to the top-up system, which is situated on the feeder hopper. Manual top-up filling was employed as a preventive measure against the risk of material segregation for the investigated preblend.

The vacuum top-up system used in this process comprises a conical hopper with a capacity of 3.2 L, connected to a rotating bowl valve responsible for refilling the twin screw feeder's hopper. To maintain precise control over the material supply, a level sensor is integrated into the conical hopper of the top-up system. This sensor detects the presence or absence of powder by being positioned at a fixed height within the hopper.

A more detailed description of the CDC-50 and the feasibility of processing over an extended period with this line is provided by Holman et al. [42].

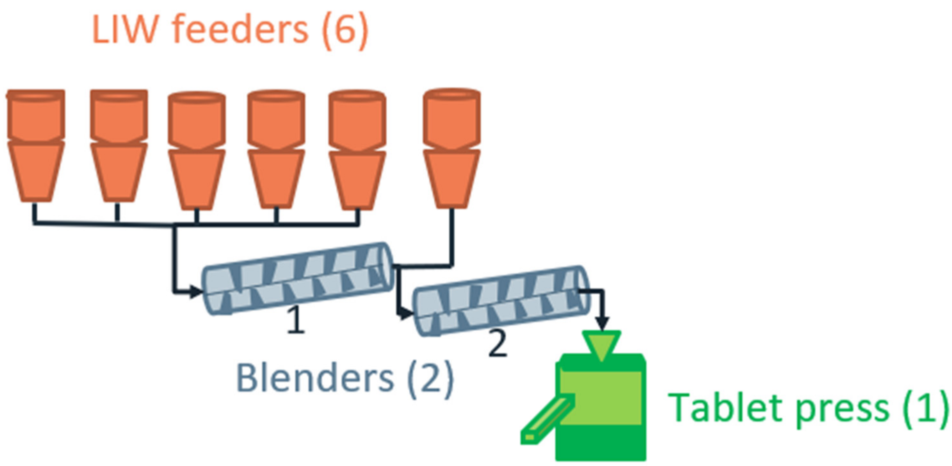

Figure 1. Schematic of the continuous direct compression line investigated in this study.

2.5. Loss-in-Weight Feeder: GEA® Twin Screw Feeder

Twin-screw loss-in-weight feeders (GEA®, Wommelgem, Belgium) were used in this study, which are integral components of the above fully automated tablet production line (see Section 2.4). The feeder consists of a 2 L hopper connected with a horizontally rotating impeller above the screws. Yadav et al. [43] and Furqan et al. [44] provide detailed descriptions of the components of the feeders and their associated top-up systems. The speed of the feeder screws was optimized to ensure a total system flow rate of 20 kg/h.

2.6. Experimental Plan, Data Collection and Processing

A comprehensive analysis of the feeding performance of the investigated materials (see Table 1), as well as a preblend of PH102:24AN at a 50:50% *w*/*w* ratio, was conducted (henceforth, this mixture will be referred to as "preblend"). The mass flow rate for each excipient in Table 1, as well as the preblend, was set to 18.8 kg/h, representing 94% *w*/*w* of the total formulation, with a total system flow rate of 20 kg/h.

The feeder data were collected at a 1 Hz frequency (one value per second) using the ConsiGma® data acquisition system (GEA®, Wommelgem, Belgium). This software enables time-aligned data collection from the feeder, capturing parameters such as net weight, screw speed, mass flow rate, feed factor, and feeding mode. The feed factor is defined as the grams of powder transported per revolution of the feeder screw (g/rev) and offers insights into the material properties within the hopper [44]. The feed factor profile was analyzed to understand the densification and screw layering behavior of different materials.

Data preprocessing, statistical analysis, and graphical visualization were performed in Phyton 3.10.11 (Python Software Foundation, Wilmington, DE, USA). The collected data were filtered within a specified tolerance range (10% of the mass flow rate set point) using a Boolean mask [45] to exclude external disturbances. The initial 300 s were excluded for all investigated materials to exclude the data from the screw priming phase (initial screw filling process).

This study incorporates the concept of "feeding cycles" for data analysis, where these cycles represent the intervals between hopper refills. The feeding cycles are precisely defined and maintained consistently for all investigated materials: a feeding cycle initiates 60 s after the gravimetric mode of the feeder is activated and continues until 20 s prior to the next transition to the feeder's volumetric mode. Figure 2 illustrates a schematic of feeding cycles as defined in this study.

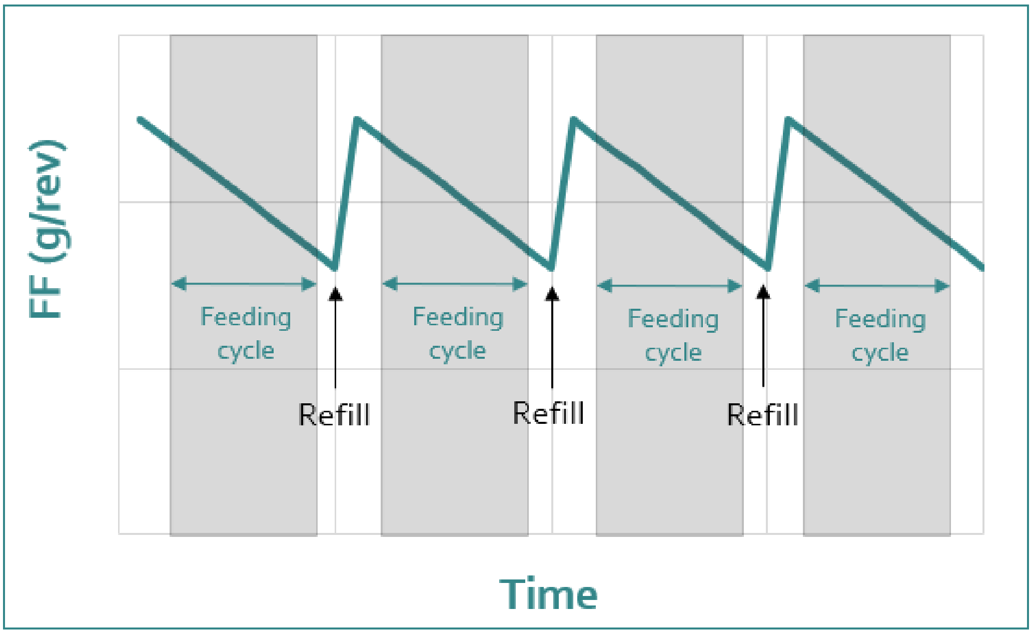

Figure 2. Schematic illustrating the feeding cycles between two consecutive refills (highlighted in gray), and refills in continuous feeding.

For each of these feeding cycles, various analytical metrics were computed, including slopes, statistical data, and linear regression fits. For quantitative comparison of investigated materials, the feeder's average mass flow rate (MF), average feed factor (FF), as well as standard deviation (SD) and the relative standard deviation (RSD) of the MF and FF, were calculated. This comprehensive analysis allowed for a detailed examination of the performance within each feeding cycle.

2.6.1. Quantifying Densification and Screw Layering

The FF slope within one feeding cycle was used as a measure of powder densification in the feeder's hopper. The overall FF slope was used as an indicator of screw layering. Figure 3 provides a schematic overview of the FF profiles that show densification and/or screw layering.

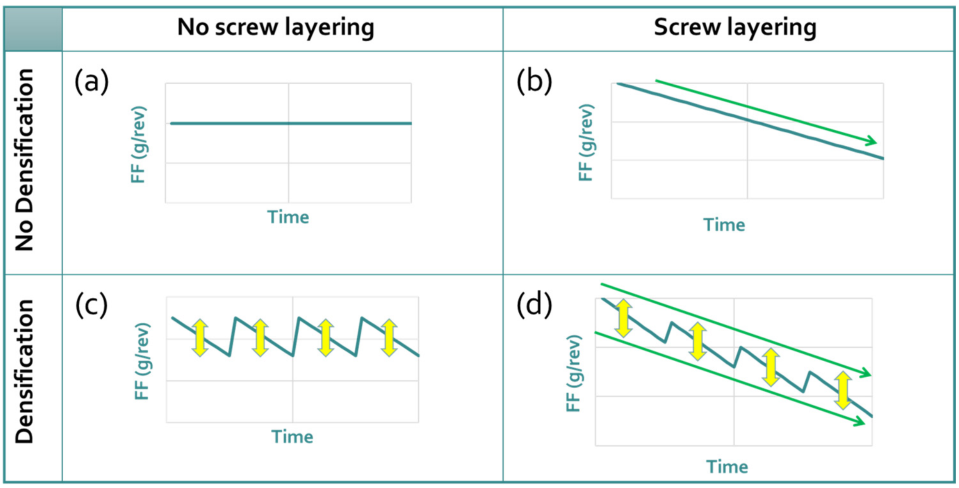

Figure 3. Schematic illustrating the phenomena of densification and screw layering in continuous feeding. The light green lines indicate screw layering, and the yellow arrows show densification. (**a**) No densification, no screw layering, (**b**) no densification, but screw layering, (**c**) densification, no screw layering, (**d**) densification and screw layering.

The data presented in this study relate to the continuous tableting process of Janssen et al. and Bekaert et al. [19,20]. As the feeding duration varied for the materials investigated, a standardized process time of 1500 s was used to ensure uniform processing duration for all materials. This standardized process time was used for calculating the overall linear regression slopes for the FF, a parameter that indicates screw layering, enabling a fair comparison of the investigated materials. This descriptor is subsequently referred to as the overall slope.

Furthermore, to ensure a fair comparison between different materials, a standardized process time of 1500 s was used in the calculation of the overall average mass flow rate (overall average MF) and its RSD (overall average MF RSD), as well as the overall average feed factor (overall average FF) and its RSD (overall average FF RSD).

The feeding performance evaluation of the investigated materials was compared in terms of average mass flow rate ($MF_{avg.}$), its relative standard deviation ($RSD_{MF}\%$), average feed factor ($FF_{avg.}$), and its standard deviation (SD_{MF}) and relative standard deviation ($RSD_{FF}\%$), calculated for each feeding cycle during the standardized process time of 1500 s, given by Equations (1), (2) and (3), respectively.

$$MF_{avg.} = \frac{1}{N}\sum_{1}^{N} MF \qquad FF_{avg.} = \frac{1}{N}\sum_{1}^{N} FF \tag{1}$$

$$SD_{MF} = \sqrt{\frac{\sum_{1}^{N}\left(MF - MF_{avg.}\right)^2}{N}} \qquad SD_{FF} = \sqrt{\frac{\sum_{1}^{N}\left(FF - FF_{avg.}\right)^2}{N}} \tag{2}$$

$$RSD_{MF}\,\% = \frac{SD}{MF_{avg.}} \cdot 100 \qquad RSD_{FF}\% = \frac{SD}{FF_{avg.}} \cdot 100 \tag{3}$$

3. Results and Discussion

3.1. Material Properties

The material properties of the investigated materials are summarized in Table 2. The ffc of lactose and co-processed materials was above 10, indicating free-flowing properties. The powder flow of the investigated MCC, PH102, was categorized as easy-flowing.

Table 2. Summary of the properties of the investigated materials.

Material	d10 (µm)	d50 (µm)	d90 (µm)	Bulk (Poured) Density (g/cm^3)	Tapped Density (g/cm^3)	Hausner Ratio (-)	ffc @4 kPa (-)	Moisture Content (% *w*/*w*) *
11SD	44	119	223	0.63	0.75	1.19	17	0.2
22AN	47	203	395	0.68	0.80	1.17	15	0.1
24AN	37	121	298	0.54	0.68	1.25	13	0.1
30GR	38	126	297	0.63	0.78	1.24	17	0.1
40LL	80	180	350	0.54	0.65	1.20	16	0.0
PH102	30	87	200	0.33	0.46	1.39	7	4.0

* Data from the supplier certificate of analysis (CoA) for the batches used in this study.

3.2. Feeding Performance

The feeding performance of the different materials is summarized in Table 3. The overall average MF remained at the set point (18.8 kg/h) with low variation (RSD < 1.3%), indicating that the feeder's control system operated with high precision and encountered no significant issues like blockage, ratholing, bridging, or caking.

Table 3. Summary of the overall MF and overall FF with their RSD.

Material	Overall Average MF (kg/h)	Overall Average MF RSD (%)	Overall Average FF (g/rev)	Overall Average FFRSD (%)
11SD	18.8	1.1	2.3	1.9
22AN	18.8	1.2	2.4	1.6
24AN	18.8	0.9	1.9	0.6
30GR	18.8	0.3	2.1	0.4
40LL	18.8	0.9	1.9	0.9
PH102	18.8	1.0	1.3	0.7
Preblend	18.8	1.3	1.5	1.3

The variation in overall average FF RSD (even though slight, RSD < 2%) indicated adjustments in screw speed by the feeder to maintain the set MF. This variation suggested occurrences of slight densification and/or screw layering in the hopper–screw zone. To precisely quantify these phenomena, a more detailed analysis of the FF data was required, as described in Section 2.6.1.

3.3. Detection of Screw Layering and Densification

The FF data of all investigated materials were evaluated according to the method described in Section 2.6. The FF axis scalar remains constant across all graphs in this section (1.2–2.5 g/rev) to ensure a fair comparison of the investigated phenomena. The feeding cycles are visually represented in the figures of this section using shaded light-gray regions. The local FF linear regression, shown with dotted black lines, serves as an indicator of the extent of powder densification in the feeder hopper (hopper–screw zone). The overall FF linear regression, shown with a solid black line, reflects screw layering (the degree of screw layer formation).

The feeding results for the spray-dried lactose, 11SD, and anhydrous lactose, 22AN, are shown in Figure 4. The results of feeding 11SD (Figure 4, top graph) indicated both densification during each feeding cycle and screw layering. Densification (indicated by the local FF linear regression, shown with dotted black lines) was higher in the initial feeding cycles of 11SD. One reason for this could have been the impact of screw filling on feeding performance during these initial cycles. As the screw speed increases more strongly to reach the desired MF, it leads to a greater reduction in the FF.

In general, the control system of the feeder divides the hopper into ten sections, assigning a corresponding screw speed for feeding each specific region. When the recorded mass loss of the feeder deviates from the set point, the control strategy adjusts the screw speed to maintain the MF set point. This adjustment reduces the FF (as MF is maintained at the set point but the screw speed increased). Stronger adjustments of screw speed occur during the initial cycles, improving over time as the screws are fully filled with the powder and the control system's assumption becomes more accurate.

Another reason for the higher densification (steeper slope) in the initial cycles could have been the initial system assumption being less accurate. Consequently, the screw speed increases (stronger adjustment) over time to maintain the MF at the set point, resulting in a greater reduction in FF. This effect disappears once the feeder reaches a state of control. As the screws become fully filled and the feeder stabilizes (reaches its state of control), the slope of the local FF linear regression decreases, indicating reduced densification. Although this starting phase is typically excluded in commercial production, it provides valuable insights into the impact of material properties on feeding during the startup phase. These insights support improvements in the feeding process and help shorten startup times.

Furthermore, feeding 11SD showed evidence of screw layering, indicated by the negative slope of the overall FF linear regression, which gradually flattened over time. Screw layering occurs when a thin layer of material adheres to the feeder screws, resulting in less material being conveyed per screw revolution. To maintain the MF set point, the screw speed is increased. This effect becomes apparent when the starting FF of a feeding cycle is lower than that of the previous feeding cycle. Therefore, the slope of the overall FF linear regression (over multiple feeding cycles) was used as a measure of screw layering in this study.

The feeding results of 11SD showed that screw layering was more pronounced initially, characterized by a steeper slope, which gradually reduced. This indicated that a thin layer of powder formed on the screws without further accumulation.

While the extent of screw layering for 11SD is minimal and not visibly apparent on the screws during feeder cleaning, it is essential to note that excessive screw layering, particularly with materials like micronized APIs, can potentially disrupt the feeding process and cause operational stoppages. Hence, it is crucial to systematically quantify screw layering for API feeding or API–excipient preblend to estimate the continuous feeding duration accurately. As briefly discussed by Janssen et al. [19], feeding micronized model API (paracetamol) introduced significant challenges during the continuous tableting process. After five days of experimentation, screw layering of the API became a severe issue, necessitating a halt in the process for screw cleaning before continuation.

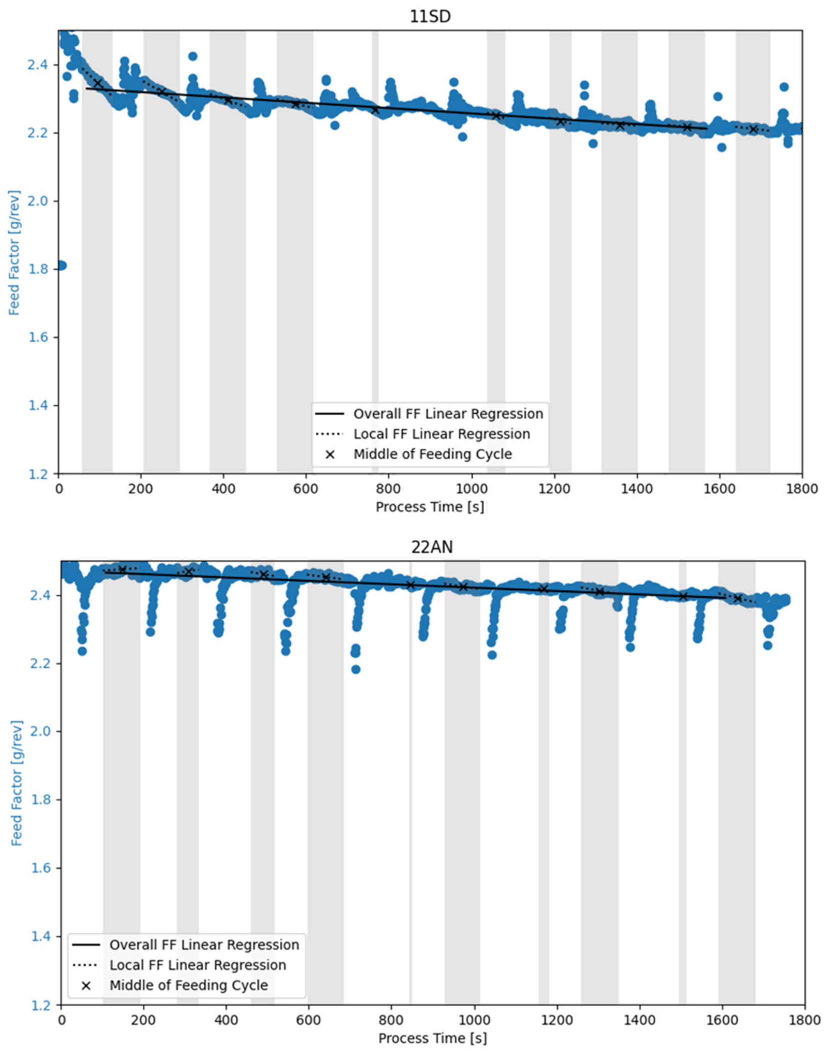

Figure 4. Feeding of 11SD (**top**) and 22AN (**bottom**). The blue dots represent FF per second. Gray regions indicate recognized feeding cycles. The dotted black lines indicate the degree of powder densification in the feeder hopper. The solid black line reflects screw layering during continuous feeding.

It is worth noting that the data presented in this study pertain to continuous tableting process data [19,20]. Consequently, the feeding duration varies for the investigated materials. However, to ensure a fair comparison, the data were evaluated within a standardized processing time consistent across all investigated materials. The results from longer run results are included in the Supplementary Materials of this publication.

The results of feeding 22AN (Figure 4, bottom graph) indicated no densification, but showed evidence of screw layering. This is indicated by the negative slope of the overall FF linear regression. Each new feeding cycle for 22AN started at a lower FF compared to the previous cycle, suggesting slight screw layering. Unlike 11SD, the slope of the overall FF linear regression (indicator of screw layering) for 22AN does not flatten out over time.

The feeding of 22AN did not indicate densification during the feeding cycles, indicating that 22AN is less sensitive to refills. To validate this observation, it is recommended that further studies be conducted investigating the impact of refill portions and the frequency of refills.

The feeding results for the granulated lactose grades, 24AN (anhydrous lactose), 30GR (lactose monohydrate), and 40LL (co-processed), are shown in Figure 5. Interestingly, all granulated lactose products, whether anhydrous, monohydrate, or co-processed with lactitol, showed low variation in feeding. Continuous feeding of 24AN and 30GR showed no indication of densification or screw layering, as the slopes of both the overall and local FF linear regressions remained flat. For 40LL, slight screw layering was observed at the beginning of feeding, which then clearly flattened out after 800 s.

In general, the granulation process appears to make these powders less sensitive to refills and eliminates the screw layering effect. Granulation is effective in reducing the number of fines by agglomerating smaller particles into larger, more uniform granules. This consolidation of fines can improve handling and reduce issues like dusting, which might contribute to screw layering. Another hypothesis is that the granulated particles exhibit cleaning capabilities. As the screw passes through the material, the granules introduce additional shear and force, which may dislodge and remove smaller particles that tend to adhere to the screws. However, further investigation is required to validate these findings by examining the impact of refill portions and refill frequency in longer feeding runs.

The feeding results for PH102 and preblend are shown in Figure 6. Surprisingly, feeding PH102 alone indicated no densification or screw layering; however, its blend with 24AN (i.e., the preblend of PH102:24AN at a 50:50% w/w ratio) showed densification. This can be attributed to differences in particle size and density. Smaller particles can fill the voids between larger particles, leading to densification in the hopper-screw zone. Additionally, the density differences between the two components in the blend may cause segregation in the feeder hopper. These results underscore the importance of understanding blend properties, as they can significantly differ from the properties of individual components. This consideration is crucial, as highlighted by Fathollahi et al. [14]. Additionally, the findings indicate that feeding preblends may be suboptimal and suggest that using co-processed excipients could mitigate this issue.

Generally, for all investigated materials, densification could be effectively managed by the control systems of the LIW feeder. Over time, the feeder reaches a state of control where densification becomes predictable and precisely controllable. However, a higher degree of densification can pose a risk to consistent powder flow in manufacturing processes. When a material undergoes densification, it tends to compact, potentially affecting its flow properties. Materials that do not show densification are generally easier to handle in manufacturing processes. Their consistent flow characteristics make them more predictable and reliable during the feeding and processing stages. Thus, while consistent feeding was achievable for all tested excipients, selecting materials with minimal densification can facilitate smoother and more reliable manufacturing processing.

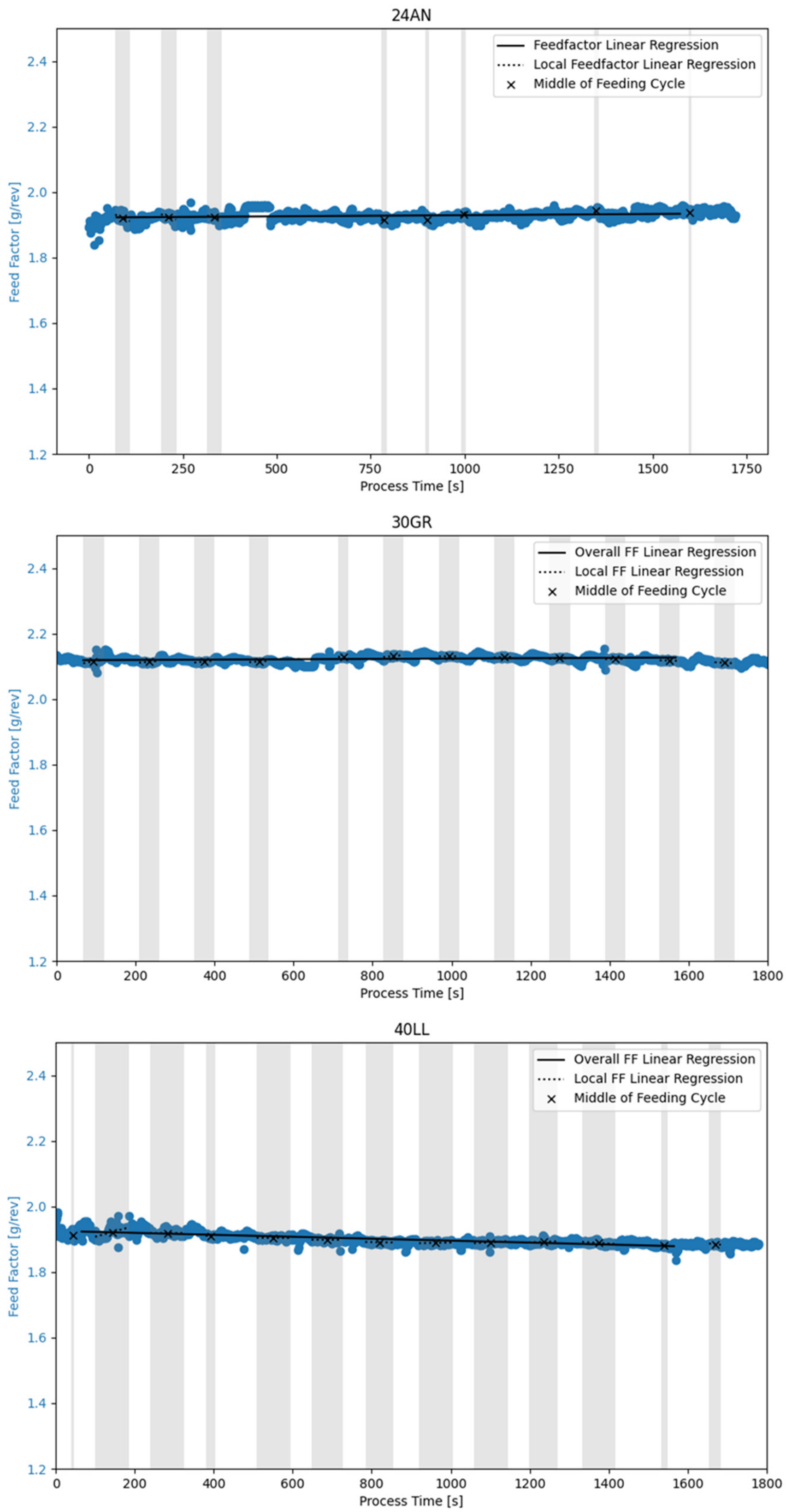

Figure 5. Feeding of 24AN (**top**), 30GR (**middle**), and 40LL (**bottom**). The blue dots represent FF per second. Gray regions indicate recognized feeding cycles. The dotted black lines indicate the degree of powder densification in the feeder hopper. The solid black line reflects screw layering during continuous feeding.

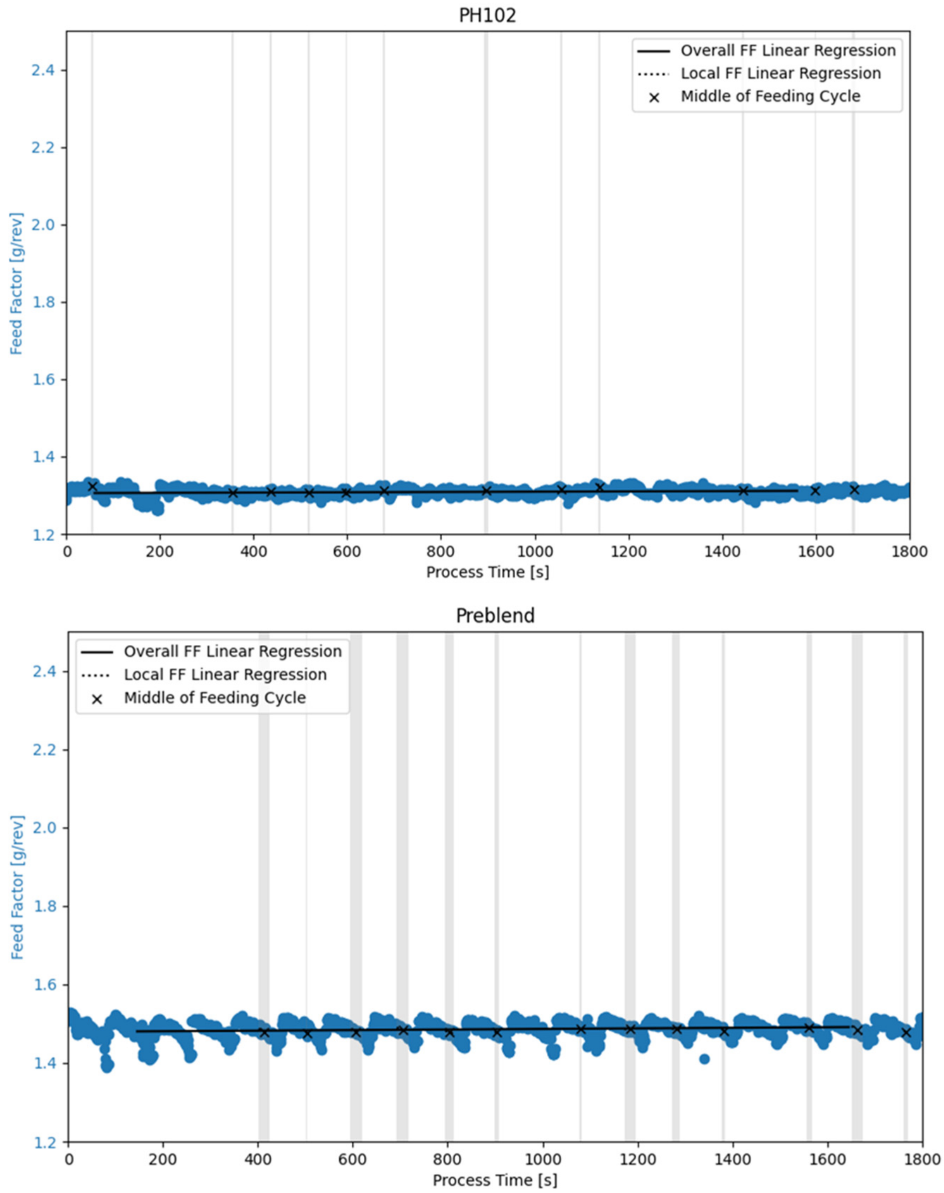

Figure 6. Feeding of PH102 and preblend (PH102:24AN with 50:50% w/w). The blue dots represent FF per second. Gray regions indicate recognized feeding cycles. The dotted black lines indicate the degree of powder densification in the feeder hopper. The solid black line reflects screw layering during continuous feeding.

On the other hand, if screw layering becomes too severe, the feeder motor may reach its maximum capacity, preventing the feeder from achieving the desired MF. Therefore, screw layering can significantly impact the manufacturing process and should be thoroughly assessed. Additionally, there is also the risk of losing the accumulated material from the screw, leading to sudden increases in MF.

In summary, the results demonstrate that both densification and screw layering can be successfully quantified. The FF graphs clearly illustrate the effects of densification and screw layering. The slope of the local FF linear regression for each feeding cycle indicates powder densification in the feeder's hopper-screw zone between two consecutive refills. The slope of the overall FF linear regression, standardized to a process time of 1500 s for fair comparison among the investigated materials, indicates screw layering.

3.4. Quantification of Screw Layering and Densification

The slopes of local FF linear regression were calculated as a measure of densification. Results are shown in Figure 7 as a box plot, summarizing the local FF linear regression slopes for feeding cycles within the standardized process time of 1500 s. This figure illustrates the extent of densification comparison between the investigated materials, highlighting the higher densification of the preblend and 11SD. These statistical results align with the visual observations from the FF graphs. The box plot displays the minimum, maximum, average, first quartile, median (second quartile), and third quartile values of calculated slopes. The median represents the center, while the remaining values indicate dispersion, with the cross representing the average value. For 22AN, 24AN, and 40LL, the box plots cross zero, indicating that the slopes are on average close to zero, with some feeding cycles having a slightly positive slope. Results of 30GR show one outlier feeding cycle with a positive slope, and the rest are very consistently close to zero with a slight negative slope. PH102 results show that the slopes are entirely positive, but close to zero (average of +0.0002). One possible explanation for these positive slopes could be attributed not directly to the feeder itself but to the dynamics of the upstream system components, such as the bowl valve and the buffer volume of the top-up system [31]. During the stationary phase, material densification can occur, leading to the introduction of more densely packed material with each refill. Another contributing factor could be the shorter duration of the feeding cycles (gray regions in Figure 6), often disrupted by feeding mode switching. This disruption can lead to positive slopes due to insufficient data for accurate slope calculation. Since no data averaging was performed in this study, the feeder's data were analyzed on a per second basis. This approach can capture short-term fluctuations and disruptions more clearly, which may contribute to the observed positive slopes due to insufficient data for accurate slope calculation. Note that these are acknowledged as hypotheses and currently lack specific references for support. Further investigation is necessary to validate these claims.

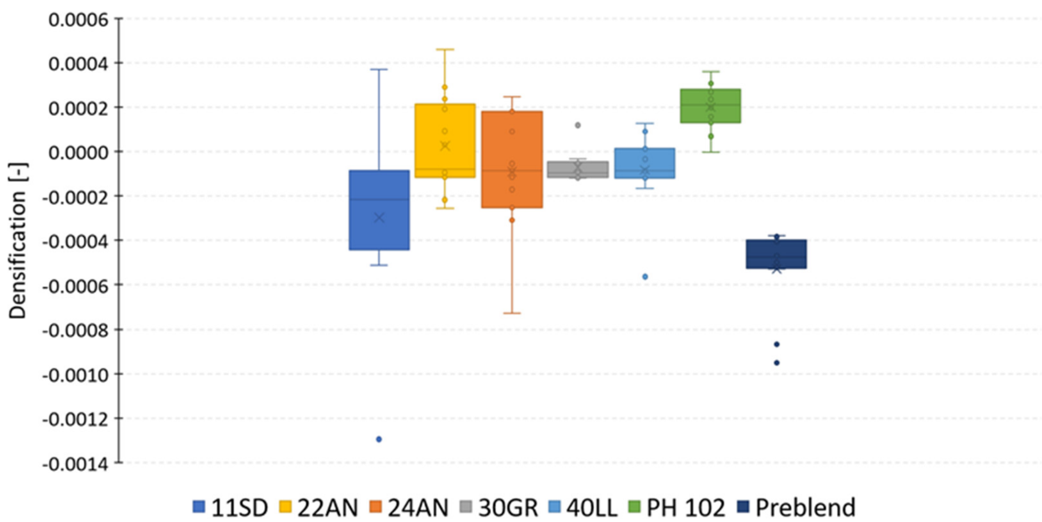

Figure 7. Summary of statistically quantified densification for the investigated materials.

In general, the slopes of local FF linear regression for 22AN, 24AN, 40LL, 30GR, and PH102 confirmed the negligible densification (as observed in their FF graphs). On the other hand, the preblend showed clear densification in all feeding cycles, as indicated by the calculated slopes of local FF linear regression (less than -0.0004). The comparison of preblend with other materials was conducted using ANOVA, revealing highly significant differences, with p-values ranging from 8.81×10^{-10} to 2.69×10^{-5}. These values indicate that the densification behavior of preblend was statistically distinct from that of the other materials, with all p-values well below the conventional significance threshold of 0.05. This suggests that the densification in the preblend was significantly different from that in the other materials, supporting the behavior observed in the feeding performance across all materials. The 11SD excipient showed densification (average of −0.0003), with values crossing zero, indicating the reduction of densification over time, as observed in Figure 4.

Furthermore, the results of statistically quantifying screw layering are shown in Figure 8. The figure compares the slopes of the overall FF linear regression for all investigated materials. The screw layering of 11SD and 22AN is the highest, followed by 40LL, with slight initial screw layering. The extent of screw layering for all other investigated materials is negligible (very close to zero). These results align with the visual conclusions from the feeding graphs. In the case of feeding only excipients, the minor extent of screw layering observed does not pose a problem. However, when feeding a preblend of API and excipients, the results recommend using granulated products such as 30GR and 24AN to mitigate potential feeding issues.

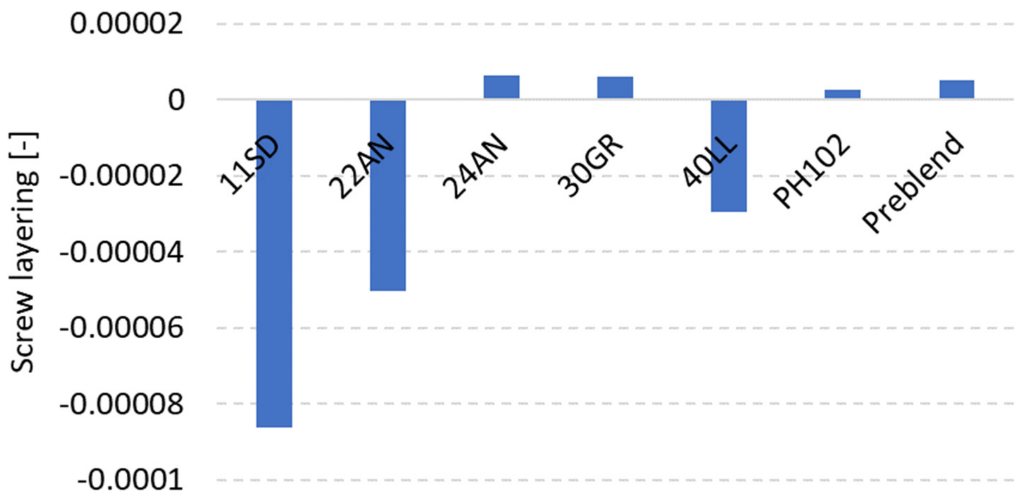

Figure 8. Summary of statistically quantified screw layering for the investigated materials.

In summary, this study highlights the critical importance of understanding material behavior in the feeding process for continuous manufacturing. It identifies potential challenges, such as screw layering in the feeding unit operation, and introduces methods for quantifying densification and screw layering. Furthermore, by tailoring the feeding parameters to the characteristics of the material being processed, the feeding process can be better optimized within the powder-to-tablet production system. Although detailed tooling design recommendations are beyond the scope of this study, the results suggest that these findings could inform the design and selection of appropriate tooling, such as screw configurations and hopper designs. Future research is recommended to explore these factors further to optimize feeding performance tailored to different materials.

4. Summary and Conclusions

The feeding performance of various excipients and a preblend was evaluated within an operational powder-to-tablet continuous production line. To the best of our knowledge, this study introduces for the first time a method for quantifying densification and screw layering. The statistical results aligned with visual observations from the FF graphs.

The results indicated that densification for 11SD (spray-dried lactose) occurred primarily during the initial feeding cycles and decreased gradually over time, whereas densification for the preblend of MCC–lactose (PH102:24AN at 50:50% w/w) remained consistent throughout the feeding process. The control system of LIW feeders effectively managed densification; however, addressing screw layering in severe circumstances poses greater challenges. These findings support the use of granulated lactose products to prevent or delay screw layering.

Preblending of API and excipients is commonly employed by manufacturers to mitigate challenges in API feeding, thereby reducing the number of feeders and simplifying production processes. This research suggests that when dealing with APIs prone to severe screw layering, selecting granulated lactose products (24AN and 30GR) for preblending could offer advantages. In comparison to other excipients studied in this research, granulated anhydrous lactose (24AN) and granulated lactose monohydrate (30GR) show superior performance in continuous feeding, with no indication of densification or screw layering. This makes them optimal choices for optimizing continuous manufacturing processes by ensuring consistent feeding.

Drug product manufacturers commonly use blends to minimize the number of feeders and simplify the continuous manufacturing process. The results showed that densification occurred in the investigated preblend, even though neither component showed this effect individually. Additionally, since the granulated grades did not show densification (or screw layering), the findings indicate a potential advantage of using co-processed excipients over preblends in CM. However, further studies are needed to compare the physical blend and co-processed forms of the same components to confirm this potential advantage.

Furthermore, this approach and data can be used for several advancements in the pharmaceutical industry. Firstly, they address market questions about continuous manufacturing by assessing the feasibility of nonstop operation, which is particularly relevant for estimating the feedability of APIs. While the results showed minor screw layering for excipients, this issue could be more extensive for APIs, highlighting the need for thorough evaluation.

Additionally, the findings enable material-specific adjustments in feeding processes, allowing for the study of material properties' effects and aiding in the selection of appropriate tooling, such as screw sizes and screens. This tailored approach ensures optimal feeding performance for different materials.

The potential for developing advanced control systems is another significant advancement. Insights gained from long-term continuous feeding data can be used to develop iterative learning and other control systems, improving the overall efficiency and reliability of the manufacturing process.

Reducing startup time is also a key benefit, leading to cost savings and faster production. By minimizing the time required to achieve steady-state feeding, manufacturers can enhance productivity and reduce operational costs.

Lastly, extending feeder models beyond single refills offers valuable insights into longer runs with multiple refills. This comprehensive understanding of feeder behavior over extended periods supports more robust and reliable continuous manufacturing processes, ultimately contributing to higher quality and consistency in the final drug products.

These developments can significantly enhance the efficiency and reliability of continuous manufacturing processes in the pharmaceutical industry.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/powders3040026/s1. Figure S1: Feeding of 11SD; Figure S2: Feeding of 30GR; Figure S3: Feeding of PH102; Figure S4: Feeding of preblend; Figure S5: Feeding of 11SD, second run.

Author Contributions: Conceptualization, S.F., P.H.M.J., B.B., V.V. and B.H.J.D.; methodology, S.F., P.H.M.J., B.B., V.V. and B.H.J.D.; validation, S.F., P.H.M.J., B.B., D.V., V.V. and B.H.J.D.; formal analysis, S.F.; investigation, S.F., P.H.M.J., B.B., V.V. and B.H.J.D.; data curation, S.F.; writing—original draft preparation, S.F.; writing—review and editing, P.H.M.J., B.B., D.V., V.V. and B.H.J.D.; visualization, S.F. and P.H.M.J.; resources, V.V. and B.H.J.D.; supervision, V.V. and B.H.J.D.; project administration, V.V. and B.H.J.D. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data will be made available on request.

Acknowledgments: The authors would like to thank James Holman for scientific support, as well as Lisa Buijvoets, Timo Roelofs, and Nino Franssens for their support with the execution of the trials.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. FDA. Quality Considerations for Continuous Manufacturing Guidance for Industry. 2019; pp. 1–27. Available online: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm (accessed on 1 August 2024).
2. FDA. Advancement of Emerging Technology Applications for Pharmaceutical Innovation and Modernization Guidance for Industry. 2017; pp. 1–8. Available online: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm (accessed on 1 August 2024).
3. FDA. Guidance for Industry, PAT—A Framework for Innovative Pharmaceutical Development, Manufacturing and Quality Assurance. 2004. Available online: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm070305.pdf (accessed on 1 August 2024).
4. Fisher, A.C.; Liu, W.; Schick, A.; Ramanadham, M.; Chatterjee, S.; Brykman, R.; Lee, S.L.; Kozlowski, S.; Boam, A.B.; Tsinontides, S.C.; et al. An audit of pharmaceutical continuous manufacturing regulatory submissions and outcomes in the US. *Int. J. Pharm.* **2022**, *622*, 121778. [CrossRef] [PubMed]
5. Lee, S.L.; O'Connor, T.F.; Yang, X.; Cruz, C.N.; Chatterjee, S.; Madurawe, R.D.; Moore, C.M.V.; Yu, L.X. Modernizing Pharmaceutical Manufacturing: From Batch to Continuous Production. *J. Pharm. Innov.* **2015**, *10*, 191–199. [CrossRef]
6. Rossi, C.V. A Comparative Investment Analysis of Batch Versus Continuous Pharmaceutical Manufacturing Technologies. *J. Pharm. Innov.* **2022**, *17*, 1373–1391. [CrossRef]
7. Badman, C.; Cooney, C.L.; Florence, A.; Konstantinov, K.; Krumme, M.; Mascia, S.; Nasr, M.; Trout, B.L. Why We Need Continuous Pharmaceutical Manufacturing and How to Make It Happen. *J. Pharm. Sci.* **2019**, *108*, 3521–3523. [CrossRef] [PubMed]
8. Markl, D.; Warman, M.; Dumarey, M.; Bergman, E.L.; Folestad, S.; Shi, Z.; Manley, L.F.; Goodwin, D.J.; Zeitler, J.A. Review of real-time release testing of pharmaceutical tablets: State-of-the art, challenges and future perspective. *Int. J. Pharm.* **2020**, *582*, 119353. [CrossRef] [PubMed]
9. PA. Technology. Guideline on Real Time Release Testing (Formerly Guideline on Parametric Release) Guideline on Real Time Release Testing (Formerly Guideline on Parametric Release) Table of Contents. 2012, Volume 44, pp. 1–10. Available online: https://www.gmp-compliance.org/ (accessed on 1 August 2024).
10. Kim, E.J.; Kim, J.H.; Kim, M.; Jeong, S.H.; Choi, D.H. Process Analytical Technology Tools for Monitoring Pharmaceutical Unit Operations: A Control Strategy for Continuous Process Verification. *Pharmaceutics* **2021**, *13*, 919. [CrossRef]
11. Panzitta, M.; Calamassi, N.; Sabatini, C.; Grassi, M.; Spagnoli, C.; Vizzini, V.; Ricchiuto, E.; Venturini, A.; Brogi, A.; Brassier Font, J.; et al. Spectrophotometry and pharmaceutical PAT/RTRT: Practical challenges and regulatory landscape from development to product lifecycle. *Int. J. Pharm.* **2021**, *601*, 120551. [CrossRef] [PubMed]
12. Schaber, S.D.; Gerogiorgis, D.I.; Ramachandran, R.; Evans, J.M.B.; Barton, I.; Trout, B.L. Economic analysis of integrated continuous and batch pharmaceutical manufacturing: A case study. *Ind. Eng. Chem. Res.* **2011**, *50*, 10083–10092. [CrossRef]
13. Nasr, M.M.; Krumme, M.; Matsuda, Y.; Trout, B.L.; Badman, C.; Mascia, S.; Cooney, C.L.; Jensen, K.D.; Florence, A.; Johnston, C.; et al. Regulatory Perspectives on Continuous Pharmaceutical Manufacturing: Moving from Theory to Practice: September 26–27, 2016, International Symposium on the Continuous Manufacturing of Pharmaceuticals. *J. Pharm. Sci.* **2017**, *106*, 3199–3206. [CrossRef]
14. Fathollahi, S.; Faulhammer, E.; Glasser, B.J.; Khinast, J.G. Impact of powder composition on processing-relevant properties of pharmaceutical materials: An experimental study. *Adv. Powder Technol.* **2020**, *31*, 2991–3003. [CrossRef]
15. Fathollahi, S.; Kruisz, J.; Sacher, S.; Rehrl, J.; Escotet-Espinoza, M.S.; DiNunzio, J.; Glasser, B.J.; Khinast, J.G. Development of a Controlled Continuous Low-Dose Feeding Process. *AAPS PharmSciTech* **2021**, *22*, 247. [CrossRef] [PubMed]
16. Moghtadernejad, S.; Escotet-Espinoza, M.S.; Oka, S.; Singh, R.; Liu, Z.; Román-Ospino, A.D.; Li, T.; Razavi, S.; Panikar, S.; Scicolone, J.; et al. A Training on: Continuous Manufacturing (Direct Compaction) of Solid Dose Pharmaceutical Products. *J. Pharm. Innov.* **2018**, *13*, 155–187. [CrossRef]
17. Fathollahi, S.; Sacher, S.; Escotet-espinoza, M.S.; Dinunzio, J.; Khinast, J.G. Performance Evaluation of a High-Precision Low-Dose Powder Feeder. *AAPS PharmSciTech* **2020**, *21*, 301. [CrossRef]
18. Blackshields, C.A.; Crean, A.M. Continuous powder feeding for pharmaceutical solid dosage form manufacture: A short review. *Pharm. Dev. Technol.* **2018**, *23*, 554–560. [CrossRef]
19. Janssen, P.H.M.; Fathollahi, S.; Bekaert, B.; Vanderroost, D.; Roelofs, T.; Vanhoorne, V.; Vervaet, C.; Dickhoff, B.H.J. Impact of material properties and process parameters on tablet quality in a continuous direct compression line. *Powder Technol.* **2023**, *424*, 118520. [CrossRef]

20. Bekaert, B.; Janssen, P.H.M.; Fathollahi, S.; Vanderroost, D.; Roelofs, T.; Dickhoff, B.H.J.; Vervaet, C.; Vanhoorne, V. Batch vs. continuous direct compression—A comparison of material processability and final tablet quality. *Int. J. Pharm.* **2024**, *2023*, 100226. [CrossRef]
21. Janssen, P.H.M.; Kulkarni, S.S.; Torrecillas, C.M.; Tegel, F.; Weinekötter, R.; Meir, B.; Bastiaan, H.J. Dickhoff. Effect of batch-to-batch variation of spray dried lactose on the performance of feeders. *Powder Technol.* **2022**, *409*, 117776. [CrossRef]
22. Engisch, W.E.; Muzzio, F.J. Method for characterization of loss-in-weight feeder equipment. *Powder Technol.* **2012**, *228*, 395–403. [CrossRef]
23. Bekaert, B.; Penne, L.; Grymonpré, W.; Van Snick, B.; Dhondt, J.; Boeckx, J.; Vogeleer, J.; De Beer, T.; Vervaet, C.; Vanhoorne, V. Determination of a quantitative relationship between material properties, process settings and screw feeding behavior via multivariate data-analysis. *Int. J. Pharm.* **2021**, *602*, 120603. [CrossRef]
24. Van Snick, B.; Kumar, A.; Verstraeten, M.; Pandelaere, K.; Dhondt, J.; Di Pretoro, G.; De Beer, T.; Vervaet, C.; Vanhoorne, V. Impact of material properties and process variables on the residence time distribution in twin screw feeding equipment. *Int. J. Pharm.* **2019**, *556*, 200–216. [CrossRef] [PubMed]
25. Wang, Y.; Li, T.; Muzzio, F.J.; Glasser, B.J. Predicting feeder performance based on material flow properties. *Powder Technol.* **2017**, *308*, 135–148. [CrossRef]
26. Menth, J.; Maus, M.; Wagner, K.G. Continuous twin screw granulation and fluid bed drying: A mechanistic scaling approach focusing optimal tablet properties. *Int. J. Pharm.* **2020**, *586*, 119509. [CrossRef] [PubMed]
27. Hsiao, W.K.; Hörmann, T.R.; Toson, P.; Paudel, A.; Ghiotti, P.; Stauffer, F.; Bauer, F.; Lakio, S.; Behrend, O.; Maurer, R.; et al. Feeding of particle-based materials in continuous solid dosage manufacturing: A material science perspective. *Drug Discov. Today* **2020**, *25*, 800–806. [CrossRef]
28. Hörmann-Kincses, T.R.; Beretta, M.; Kruisz, J.; Stauffer, F.; Birk, G.; Piccione, P.M.; Holman, J.; Khinast, J.G. Predicting powder feedability: A workflow for assessing the risk of flow stagnation and defining the operating space for different powder-feeder combinations. *Int. J. Pharm.* **2022**, *629*, 122364. [CrossRef]
29. Beretta, M.; Kruisz, J.; Hörmann, T.R.; Viktoria, K.; Meishan, M.; Majid, G. Assessment of Tribo—Charging and Continuous Feeding Performance of Direct Compression Grades of Isomalt and Mannitol Powders. *AAPS PharmSciTech* **2023**, *24*, 91. [CrossRef] [PubMed]
30. Beretta, M.; Hörmann, T.R.; Hainz; Hsiao, W.K.; Paudel, A. Investigation into powder tribo-charging of pharmaceuticals. Part I: Process-induced charge via twin-screw feeding. *Int. J. Pharm.* **2020**, *591*, 120014. [CrossRef] [PubMed]
31. Bekaert, B.; Van Snick, B.; Pandelaere, K.; Dhondt, J.; Di Pretoro, G.; De Beer, T.; Vervaet, C.; Vanhoorne, V. In-depth analysis of the long-term processability of materials during continuous feeding. *Int. J. Pharm.* **2022**, *614*, 121454. [CrossRef]
32. Bostijn, N.; Dhondt, J.; Ryckaert, A.; Szabó, E.; Dhondt, W.; Van Snick, B.; Vanhoorne, V.; Vervaet, C.; De Beer, T. A multivariate approach to predict the volumetric and gravimetric feeding behavior of a low feed rate feeder based on raw material properties. *Int. J. Pharm.* **2019**, *557*, 342–353. [CrossRef]
33. Engisch, W.E.; Muzzio, F.J. Feedrate deviations caused by hopper refill of loss-in-weight feeders. *Powder Technol.* **2015**, *283*, 389–400. [CrossRef]
34. Engisch, W.E.; Muzzio, F.J. Loss-in-Weight Feeding Trials Case Study: Pharmaceutical Formulation. *J. Pharm. Innov.* **2014**, *10*, 56–75. [CrossRef]
35. Jones-Salkey, O.; Chu, Z.; Ingram, A.; Windows-Yule, C.R.K. Reviewing the Impact of Powder Cohesion on Continuous Direct Compression (CDC) Performance. *Pharmaceutics* **2023**, *15*, 1587. [CrossRef]
36. Johanson, J. Modular Mass-Flow Bin. U.S. Patent 4,958,741, 25 September 1990. Available online: https://patents.google.com/patent/US4958741A/en (accessed on 19 August 2024).
37. Fernandez, J.W.; Cleary, W.; McBride, W. Effect of screw design on hopper drawdown of spherical particles in a horizontal screw feeder. *Chem. Eng. Sci* **2011**, *66*, 5585–5601. [CrossRef]
38. Li, X.; Hou, Q.; Dong, K.; Zou, R.; Yu, A. Promote cohesive solid flow in a screw feeder with new screw designs. *Powder Technol.* **2020**, *361*, 248–257. [CrossRef]
39. Motaln, M.; Lerher, T. Innovative Approaches to Wear Reduction in Horizontal Powder Screw Conveyors: A Design of Experiments-Guided Numerical Study. *Appl. Sci.* **2024**, *14*, 3064. [CrossRef]
40. Fathollahi, S.; Demiri, V.; Hörmann-Kincses, T.; Maljuric, S.; Massoner, J.; Mehos, G.; Khinast, J.G. Improving Continuous Loss-in-weight Feeding Accuracy by a Novel Hopper Design. *J. Pharm. Innov.* **2024**, *19*, 57. [CrossRef]
41. Eilbeck, J.; Rowley, G.; Carter, A.; Fletcher, E.J. Effect of contamination of pharmaceutical equipment on powder triboelectrification. *Int. J. Pharm.* **2000**, *195*, 7–11. [CrossRef]
42. Holman, J.; Tantuccio, A.; Palmer, J.; Van Doninck, T.; Meyer, R. A very boring 120 h: 15 million tablets under a continuous state of control. *Powder Technol.* **2021**, *382*, 208–231. [CrossRef]
43. Yadav, I.K.; Holman, J.; Meehan, E.; Tahir, F.; Khoo, J.; Taylor, J.; Benedetti, A.; Aderinto, O.; Bajwa, G. Influence of material properties and equipment configuration on loss-in- weight feeder performance for drug product continuous manufacture. *Powder Technol.* **2019**, *348*, 126–137. [CrossRef]

44. Tahir, F.; Palmer, J.; Khoo, J.; Holman, J.; Yadav, I.K.; Reynolds, G.; Meehan, E.; Mitchell, A.; Bajwa, G. Development of feed factor prediction models for loss-in-weight powder feeders. *Powder Technol.* **2019**, *364*, 1025–1038. [CrossRef]
45. Bisong, E. NumPy. In *Building Machine Learning and Deep Learning Models on Google Cloud Platform*; Apress: Berkeley, CA, USA, 2019. [CrossRef]