



Effect of batch-to-batch variation of spray dried lactose on the performance of feeders

Pauline H.M. Janssen^{a,b,*}, Sri Sharath Kulkarni^a, Carlota Mendez Torrecillas^{c,d}, Florian Tegel^e, Ralf Weinekötter^e, Bernhard Meir^e, Bastiaan H.J. Dickhoff^a

^a DFE Pharma, Klever Strasse 187, 47568 Goch, Germany

^b Department of Pharmaceutical Technology and Biopharmacy, University of Groningen, Antonius Deusinglaan 1, 9713 AV Groningen, the Netherlands

^c EPSRC CMAC FUTURE MANUFACTURING HUB, University of Strathclyde, Technology and Innovation Centre, 99 George Street, G1 1RD Glasgow, United Kingdom

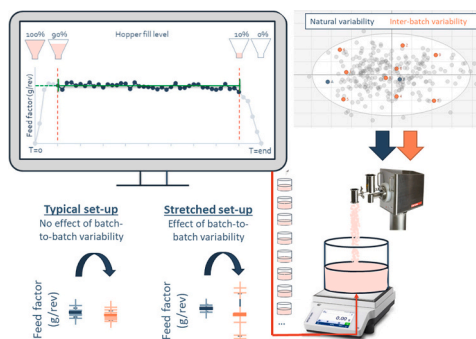
^d Strathclyde Institute of Pharmacy and Biomedical Sciences (SIPBS), University of Strathclyde, 161 Cathedral Street, G4 0RE Glasgow, United Kingdom

^e Gericke AG, Althardstrasse 120, CH-8105 Regensdorf, Switzerland

HIGHLIGHTS

- Impact of variability upon feeding performance was investigated for >200 batches.
- The batch-to-batch variability is neglectable for an optimized feeder set-up.
- Batch-to-batch variability can introduce variability in a stretched feeder set-up.

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:

Excipients
Spray-dried
Batch-to-batch variability
Feeding
Feeders
Continuous manufacturing
Consistency
Lactose
Powder properties

ABSTRACT

With the emergence of quality by design (QbD), it becomes imperative to gain understanding of the impact of batch-to-batch variability of raw materials on the performance of processes. Feeding is the first unit of operation in a continuous manufacturing line and is critical for the final product quality. The performance of feeders defines the content of components that are fed into the system and therefore the composition that ends up in the formulation. In this paper, it is investigated how and to what extent variability of lactose can impact the feeding performance in different feeder set-ups. Spray dried lactose SuperTab 11SD was selected as a material, as it is one of the most widely used filler-binders for direct compression of tablets and can make up to 70% of the tablet content. For the first time, over 200 batches were evaluated regarding the impact of batch-to-batch variability upon feeding performance in volumetric mode. Results show that for an optimized feeder set-up with 22 mm double concave screws rotating at 342 rpm, the batch-to-batch variation was negligible compared to the natural feeding variability. However, for a stretched feeder set-up with 11 mm double concave screws rotating at 514 rpm, variability in material properties introduces additional variation in the obtained feed factor. Excipient variability and feeding set-up are therefore two factors to be considered when optimizing feeding consistency.

* Corresponding author at: DFE Pharma, Klever Strasse 187, 47568 Goch, Germany.

E-mail address: pauline.janssen@dfepharma.com (P.H.M. Janssen).

<https://doi.org/10.1016/j.powtec.2022.117776>

Received 11 May 2022; Received in revised form 8 July 2022; Accepted 22 July 2022

Available online 26 July 2022

0032-5910/© 2022 The Authors. Published by Elsevier B.V. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

1. Introduction

The pharmaceutical industry is changing from batch-wise manufacturing to continuous manufacturing, stimulated by Pharma 4.0. Improved efficiency, reduced manufacturing costs, improved product quality and, an increased flexibility of production scale are some of the advantages of a continuous production process [1–3]. Continuous manufacturing is encouraged by regulatory bodies since it is in line with the quality-by-design (QbD) paradigm for pharmaceutical development [4,5].

A continuous production process for solid dosage forms generally consists of several unit operations, combined through an automated control system [6,7]. Components are continuously fed into the process, and products are continually removed at a constant mass flow rate. At a steady state, the mass flow rate of material entering the process is equal to the mass flow rate leaving the process. Some unit operations such as tableting and roller compaction are inherently continuous. In most pharmaceutical production lines, however, they are combined with batch-wise operations such as powder blending and batch-wise storage and feeding of material between unit operations.

The first unit of operation in a continuous manufacturing line is the feeding of raw material into the processing line [8]. The performance of feeders defines the content of components that are fed into the system and therefore the composition that ends up in the final product [9–11]. The ability to feed powders continuously and consistently is therefore regarded as one of the critical requirements of the overall manufacturing process [9,12,13]. Irregular feeding can lead to quality failures, such as out-of-specification dosage form assay and content uniformity [13]. Jaspers et al. (2021) showed that final blend uniformity depends largely on the consistency of feeding during the entire process [11]. The inability to maintain constant material concentrations in the process stream may result in large fluctuations in drug content, even when the continuous blender provided homogeneous outputs.

Since irregular feeding can have a large impact on final product quality, loss-in-weight or gravimetric feeding is the most commonly used continuous feeding method for pharmaceutical powders [14,15]. Loss-in-weight feeders consist of a volumetric screw feeder, combined with a weighing platform and a gravimetric control system. In the gravimetric feeding mode, the actual weight loss per unit time is compared to the desired weight loss based on a pre-programmed feed rate. Any discrepancy between actual and desired weight loss results in a correction to the speed of the feeding device, ensuring maintenance of a steady feed rate [16]. During start-up and refill, however, a feeder is unable to accurately measure the weight loss in the hopper [17]. It will therefore be run in volumetric mode, with constant volumetric dosing per unit time. During these periods, the mass feed rate can vary as the process is essentially rendered blind to any changes in the bulk density of the incoming material [18]. Density may vary, as it can for example increase due to compression of the existing powder bed, or decrease due to aeration of the powder [19]. Additionally, density differences between batches can be an issue when switching over to a new batch for raw material feeding, especially when this results in increased rejection rates of material. Changes in the density can often be related to variations in the physical characteristics of the feed material [17].

Many authors have reviewed the importance of understanding the physical properties of raw materials and their impact on feeding [9,15–17,20]. Prior knowledge of physicochemical material properties can provide indications of how the powder will behave during processing and can support in the optimal selection of feeder design. For example, compressible material can show a feed factor decay during volumetric feeding, due to reduced pressure on the material at the bottom of the feeder when the hopper level decreases. Bostijn et al. (2019) developed a partial least squares (PLS) model to predict the feed factor and its decay in low feed rate feeders in volumetric mode [17]. Escotet-Espinoza et al. (2018) established a library of material properties with hierarchical clustering, allowing to predict feeding behavior

based on similarities [20]. Wang et al. (2017) developed a principal component analysis (PCA) model based on material properties that can predict which screw will achieve the best feeding performance [21]. These papers all describe a common data-driven approach for the development of feeding behavior models. In a first step, a comprehensive library of material properties is established. Then, PCA is applied to identify similarities and differences as well as correlate the various powder property descriptors. Tahir et al. (2020) took a slightly different approach, as they developed material-specific PLS models to predict feed factor profiles based upon feeder configuration data [15]. Using material-specific databases has the advantage of being highly accurate as they are tuned for just one specific powder.

Even though many different models have been developed so far, the multivariate nature of raw materials results in a lack of consensus on which properties affect the feeding process most substantial in which situation [9]. This is mainly because flow or feeding behavior is the result of the combination of material physical properties that affect the material flow and the equipment used for handling, storing, or processing the material [22]. Flowability can never be expressed as a single value or index. There are however specific bulk characteristics that are commonly mentioned to impact the accuracy of powder feeding. These flow properties include particle size, electrostatic charging, bulk density, cohesive strength, and wall friction [15–17,23].

The goal of the developed models so far has been to predict the feeding behavior of new powders based on the material properties. This allows optimal selection of the most suitable feeder capacity, feeding mechanism, and screw type, thereby leading to more efficient and faster development of new drug products. Cohesive powders have the risk of adhesion to the screws, whereas free-flowing materials on the other hand, risk pulsating flow rates by flushing through the feeder during refill [24].

With the emergence of QbD, it becomes imperative to gain understanding of the impact of batch-to-batch variability on feeder performance. Robust formulations and processes should be able to accommodate typical variation seen in starting materials and process conditions without compromising the product's manufacture, stability, or performance [5,25]. Stauffer et al. have studied the impact of batch-to-batch variability of blends with active pharmaceutical ingredient (API) on the processability using a continuous feeder system [26,27]. Material properties such as bulk density and electrostatic charging were identified to be critical for feeding. Improvements made in flow by reformulation of API using glidant helped to mitigate the material variability and have a consistent feeder dosing. However, the direct impact of batch-to-batch variability on a feeding process was not evaluated.

A key concept in the QbD approach that allows for the identification of typical variation in large data sets is multivariate analysis (MVA). MVA is a set of statistical tools that can be used for the evaluation of relationships within large, complex data sets in a scientific, risk-based way. It can be used to investigate batch-to-batch variation and it allows identification of batches that represent the maximum variation.

In this paper, we investigate how minor batch-to-batch variations of free-flowing spray dried lactose can impact the feeding performance in different feeder set-ups. Material properties of spray dried lactose are varied in a purposeful way, mimicking the typical variation that users can expect when using a specific product [4]. For the first time, over 200 batches were investigated to evaluate the impact of batch-to-batch variation upon feeding performance. Based upon the MVA, nine batches covering the historical knowledge space were selected for experimental evaluation of the impact of batch-to-batch variation in a feeding system. Two different batches at different locations in the knowledge space were selected to evaluate the natural variability in feeding experiments as a reference. Spray dried lactose was selected as a material, as it is one of the most widely used filler-binders for direct compression of tablets and can make up to 70% of the tablet content [28]. The feeding consistency of free-flowing excipients like spray dried

lactose has not yet been evaluated in the literature to this extent. The impact of batch-to-batch variation was evaluated in a typical feeder set-up and in a stretched system set-up with a small pitch length for the screws and a high rotational speed to enlarge potential differences.

2. Materials and methods

2.1. Materials

Out of a set of 235 batches, eleven batches of spray dried lactose monohydrate (SuperTab 11SD, DFE Pharma, Germany) were selected for testing the batch-to-batch variation. Batches were selected by PCA to cover the knowledge space and are numbered 1–9. Two batches at different locations in the PCA plot for testing the natural feeding variability are indicated as batch A and B.

2.2. PCA analysis

Umetrics Simca-P 16 software is used to generate a PCA model based on the available quality analysis data of SuperTab 11SD batches. Two hundred thirty five (235) batches are used to generate the model. The number of principal components was selected so that at least 30% of the total variability was explained. All numerical parameters that are structurally measured for this material are considered, excluding identification tests, limit tests, and micro tests. Parameters that are considered are:

- UV absorbance at 210–220 nm 1% solution
- UV absorbance at 270–300 nm 1% solution
- Colour 10% solution absorbance at 400 nm
- Total moisture content by Karl Fisher titration
- Moisture content by Loss on Drying (2 h, 80 °C)
- Acidity (mL for titration to pH 8.4 with 0.1 N NaOH)
- Bulk density (g/mL)
- Tapped density (g/mL)
- Amorphous content (%w/w)
- Air jet sieving particle size %w/w < 45 µm
- Air jet sieving particle size %w/w < 100 µm
- Air jet sieving particle size %w/w < 250 µm

UV absorbances at 210 nm and 270 nm and colour of solution at 400 nm were measured according to Ph. Eur. The total moisture content ($n = 2$) was determined by Karl Fisher titration according to method A in the Ph. Eur. Particle size fractions were determined by air jet sieving approximately 20 g at 2 kPa for 3 min, according to ISO 4610. The amorphous content ($n = 2$) was determined using an internal method based on differential scanning calorimetry. Samples containing 4–6 mg of lactose and 4–6 mg acid casein were prepared in a 40 µL aluminum pan with a closed lid. Samples are heated from 20 °C to 95 °C with a speed of 5 °C/min. The amorphous content is calculated from the area of the exothermic peak.

2.3. Feeding study

A GZD200.22 feeder (Gericke AG, Switzerland) was used to evaluate the feeding performance of SuperTab 11SD. Inter-batch variability was evaluated in a non-vibrant chamber with the feeder mounted on a vibration free fixture (Gericke AG, Switzerland). The total hopper volume during these trials was 10 L, a 3 L extension to the normal hopper volume of 7 L was used. The natural feeding variability was evaluated in a direct compression production line set-up (CMAC, Glasgow) using the same feeder with a hopper volume of 7 L. For all experiments, the feeder was filled to 95% of the available hopper volume. Priming of the feeder was performed before the start of the experiment to ensure the feeder screws were filled. Fresh material was added to the hopper after priming, to ensure 95% fill level of available volume before starting the

experiment. Fig. 1 shows a graphical representation of the set-up used to perform the tests. Trials were run in volumetric mode until the feeder hopper was empty. Discharged excipients were collected in a bin and weighted every 10 s using a Mettler Toledo weight scale with 0.01–0.02 g resolution, connected to a laptop. The throughput per screw revolution, indicated as the average feed factor (FF), was calculated between 90% and 10% hopper fill level by dividing the instantaneous feed rate (FR) to the screw speed (v_{screw}):

$$FF = \frac{FR}{v_{screw}} \quad (1)$$

The feed factor is an important factor within the feeder operation. Feeders typically use the feed factor profiles as reference to calculate the correct screw speed for delivering the powder mass flow rate at the target setpoint [15]. A feed factor also helps to indicate changing material properties within the hopper.

Two different feeding set-ups were used to evaluate the performance of SuperTab 11SD, referred to as typical and stretched feeding set-up. Feeding set-ups were chosen based on the specifications provided by the feeder manufacturer (Gericke AG, Switzerland) to have similar theoretical throughput. The typical feeding set-up refers to a more ideal set-up with a 22 mm pitch screw that is operated at 50% of its capacity. The stretched feeding set-up challenges the systems performance with a 11 mm pitch screw that is operated at 75% of the capacity and would therefore probably not be used as a real process set-up. The theoretical fill level of the screw (φ) is determined by dividing the feed factor (FF) by the estimated powder density (ρ) and the screw free volume (V_{screw}):

$$\varphi = \frac{FF}{\rho \cdot V_{screw}} \quad (2)$$

Nine batches of spray dried lactose were evaluated to understand the inter-batch variability in the typical set-up, of which six were also tested in the stretched feeding set-up. Inter-batch variability is defined as the relative standard deviation over the average feed factor obtained with different batches. The natural feeding variability is defined as the relative standard deviation over the average feed factor for six runs with a fresh portion of the same batch. The experimental set-up is summarized in Table 1.

3. Results and discussion

3.1. Material selection

Fig. 2 shows a Principal Component Analysis of the 235 SuperTab 11SD batches, based upon available quality data and parameters as described in Section 2.2. All analyzed batches were produced well within specification, and the ellipse indicates the 95% hoteling's interval. The relatively low R^2 -value per component highlights the high influence of random variation, or natural variation, in the dataset. All data points of the model were well within specification and in total 35% of variation can be explained by two components (21% by PC1 and 14% by PC2). Having explained only 35% of the variation with two components indicates that limited trends are present in the data and that there is a high influence of random variation in the dataset. Table 2 provides an overview of the parameters included in the PCA model, together with the considered range of values for each parameter.

Based upon the multivariate analysis, nine batches covering the historical knowledge space were selected to evaluate the batch-to-batch variability on a DC22 screw in a typical feeder set-up. The feeding data of these batches were compared to the natural feeding variability for six repeats of batch A. Batches 1–6 were also used to evaluate the batch-to-batch variability on a DC11 screw in a stretched feeder set-up. Six repeats of two different batches at different locations in the knowledge space (batch A and batch B) were selected to evaluate the natural feeding variability in feeding experiments on DC11.



Fig. 1. Graphical representation of the feeder set-up. Discharged excipients are collected in a bin and weighted every 10 s. The feed factor is calculated as the average throughput per revolution between 90% and 10% hopper fill levels.

Table 1

Overview of the two evaluated feeding set-ups and corresponding parameters. The screw free volume described the theoretical transport volume of a screw with one revolution.

	Typical feeding set-up	Stretched feeding set-up
Abbreviation of feeding set-up	DC22	DC11
Feeder	GZD200.22	GZD200.22
Screw configuration	Double concave	Double concave
Pitch length (mm)	22	11
Screw free volume V_{screw} (mL/rev)	6.2	3.1
Screw speed v_{screw} (rpm)	342	514
Speed of bottom scraper (rpm)	24	36
Theoretical throughput (L/h)	127	95
Batches evaluated for inter-batch variability	No. 1–9	No. 1–6
Batches evaluated for natural feeding variability	A	A + B

3.2. Typical feeder set-up –DC22 with 50% screw speed

Based on the specifications provided by the feeder manufacturer (Gericke AG, Switzerland), a typical feeding set-up was selected to evaluate typical variation in a feeding process. In this set-up, double concave screws of 22 mm with a theoretical feed capacity of 6.2 mL/revolution were operated at a medium speed of 342 rpm. Feed factor profiles of the natural feeding variability study and the inter-batch variability study for the DC22 screw with a screw speed of 342 rpm are shown in Fig. 3 and Fig. 4 respectively. Each data point represents the throughput over 10 s, normalized by the rpm to calculate the feed factor.

Feed factor profiles of the inter-batch variability study and the natural feeding variability study show some small differences. The six repeats of batch A all show a decay in feed factor between hopper fill levels of 1.0 and 0.5, while the nine batches that were evaluated for inter-batch variability did not show such a decay. The decay of feed factor for the natural feeding variability tests of batch A could be a result of the densification of the powder when the hopper was completely filled. A different densification can be the result of many different factors, like material properties, operator filling, priming, hopper fill levels or environmental conditions. Material differences are in this case not expected to be the root cause, as the compressibility of powders by Hausner ratio did not show a significant difference between batch A and the nine other batches. Another possible reason for the difference in

densification could be the use of different feeder set-up and environmental conditions during the experiments. Inter-batch variability was evaluated with the feeder on a vibration-free mounting, while the natural feeding variability was evaluated on a production line which lacked a vibration-free mounting. This difference also explains the irregularities in some of the repeats (A-1 and A-4).

The production line that was used to test the natural feeding variability showed for two tests (A-1 and A-4) larger fluctuation than what has been observed under more controlled lab conditions (minimal vibration environment). Most likely these fluctuations are related to partial aeration of the powder during filling of the nearly empty feed hopper. It should be noted that under normal operation conditions of a gravimetric feeder, this effect is minimized by restricting the amount used for refilling and initiate the refilling at a predefined minimal hopper value.

Average feed factors and standard deviations were calculated for the process range with hopper fills of 10 to 90%. Natural feeding variability in Fig. 3 was evaluated by performing six repeats of batch A. The average feed factor for this study was 3.11 g/rev with a standard deviation of 0.09 g/rev. The inter-batch variability in Fig. 4 was evaluated for nine batches that cover the historical multivariate knowledge space of SuperTab 11SD. The average feed factor was 3.03 g/rev with a standard deviation of 0.09 g/rev. With an assumed powder density of 0.65 g/mL during screw filling, observed feed factors correlate to 75–77% fill levels of the screw.

Fig. 5 provides an overview of the average feed factor and corresponding variability for the tested materials on the typical feeding set-up with a DC22 screw. Diamonds indicate the average feed factor for each feeding trial that was performed. The horizontal bar and standard deviation indicate the average feed factor and standard deviation over the set of trials. No significant difference between the average feed factor for the natural feeding variability study and inter-batch variability study were observed. Variation in the feed factor for both sets of trials was also similar, as indicated by the same standard deviation of 0.09 g/rev. The variation within one batch (natural feeding variability) and the variation between the nine batches covering the historical knowledge space (inter-batch variability) was both approximately 3%. No additional variation in the average feed factor was introduced by batch differences in material properties. SuperTab 11SD can therefore consistently be fed with a DC22 screw set-up at 342 rpm screw speed. The impact of batch-to-batch variation in this set-up was negligible compared to the natural feeding variability.

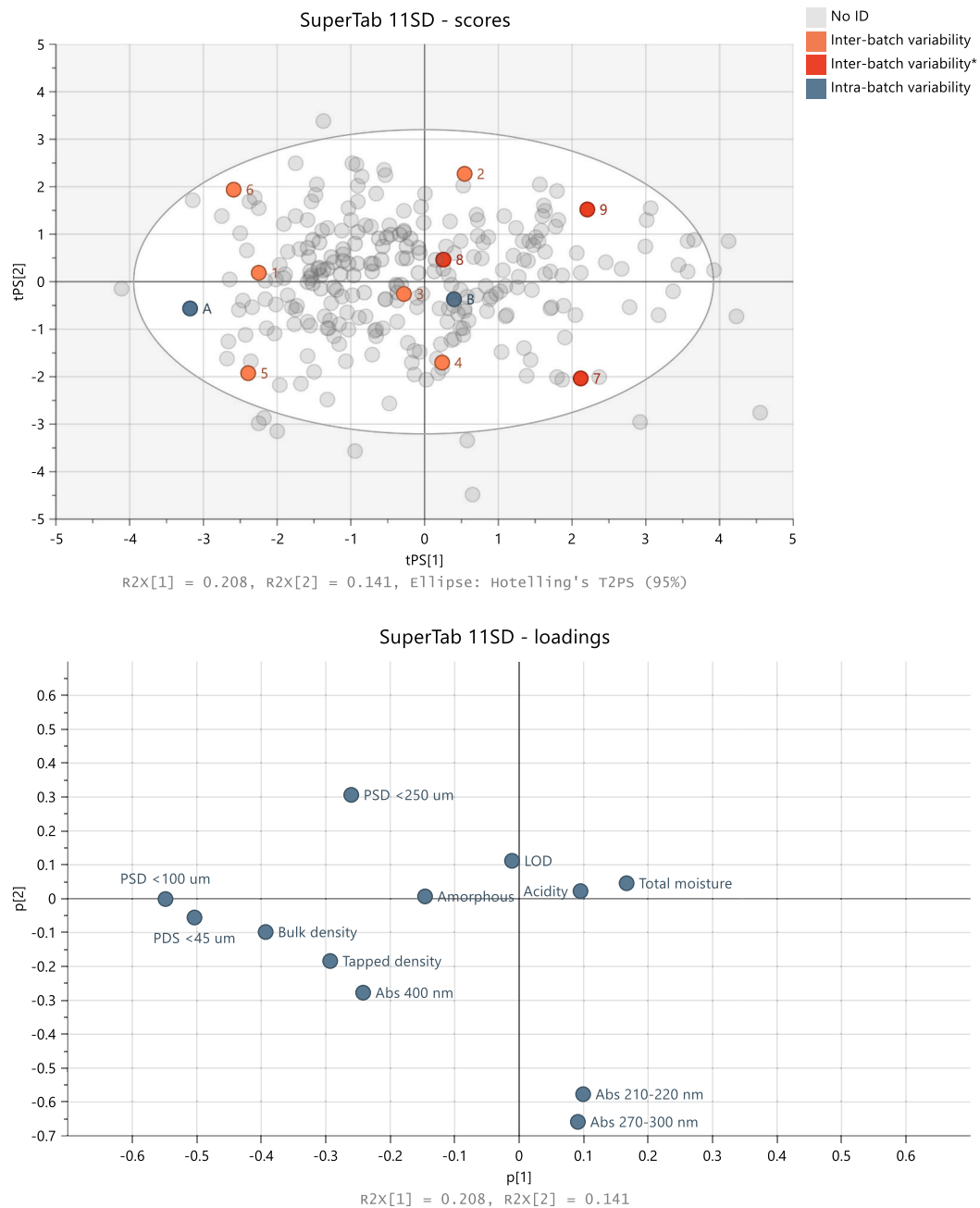


Fig. 2. Principal Component Analysis score plot (top) and loading plot (bottom) for >200 batches of SuperTab 11SD. All data points are well within specification. The inter-batch variability in a stretched feeding set-up is evaluated with batches marked in orange. The inter-batch variability in a typical feeding set-up is evaluated with the batches marked in orange and red. Batches marked in blue are used to evaluate the natural feeding variability. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.3. Stretched feeder set-up –DC11 with 75% screw speed

Based on the specifications provided by the feeder manufacturer (Gericke AG, Switzerland), a small double concave screw of 11 mm was operated at 514 rpm screw speed to stretch the capabilities of the system. This screw has a theoretical feed capacity of 3.1 mL/revolution. This set-up stretches the systems performance to its limits and is expected to enlarge potential batch-to-batch differences in the following ways:

- The smaller pitch of 11 mm might be more challenging to fill than a standard pitch of 22 mm,

- The increased rotating screw speed of 514 rpm compared to 342 rpm results in shorter time to fill the screws,
- Higher rotating screw speed combined with higher speed of the bottom scraper may cause more turbulence, resulting in agitation,
- The lower throughput results in longer residence times in the hopper during which the material can undergo relaxation

Feed factor profiles of the inter-batch variability study, the natural feeding variability study for batch A, and the natural feeding variability study for batch B for the stretched feeder set-up with a DC11 screw are shown in Fig. 5, Fig. 6, and Fig. 7, respectively. Each datapoint represent the throughput over 10 s, normalized by the rpm to calculate the feed factor.

Table 2

An overview of parameters that are used to create the PCA model with 235 batches of SuperTab 11SD batches. Minimal and maximum values for the parameters are provided to indicate the evaluated range.

Parameter	Abbreviation	Range evaluated [min-max]
UV absorbance at 210–220 nm 1% solution	Abs 210–220 nm	0.01–0.06
UV absorbance at 270–300 nm 1% solution	Abs 270–300 nm	0.00–0.02
Colour 10% solution absorbance at 400 nm	Abs 400 nm	0.00–0.01
Total moisture content by Karl Fisher titration	Total moisture	4.8–5.2
Moisture content by Loss on Drying (2 h, 80 °C)	LOD	0.1–0.5
Acidity (mL for titration to pH 8.4 with 0.1 N NaOH)	Acidity	0.13–0.37
Bulk density (g/mL)	Bulk density	0.56–0.64
Tapped density (g/mL)	Tapped density	0.68–0.77
Amorphous content (%w/w)	Amorphous	8.0–13.3
Air jet sieving particle size %w/w < 45 µm	PSD <45 µm	8–13
Air jet sieving particle size %w/w < 100 µm	PSD <100 µm	38–50
Air jet sieving particle size %w/w < 250 µm	PSD <250 µm	99–100

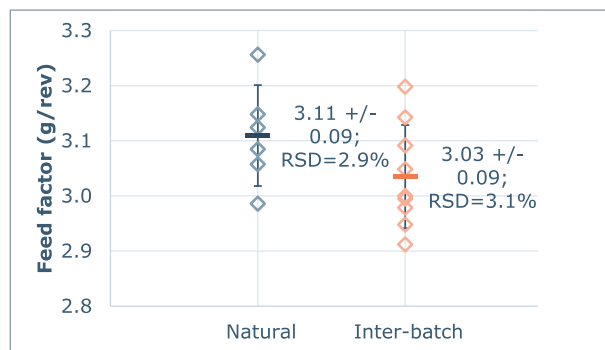


Fig. 5. Average feed factors calculated over a hopper fill of 10–90% for different feeding runs of SuperTab 11SD in a set-up with 22 mm double concave screws and 342 rpm screw speed. The horizontal bars and error bars indicate the average feed factor and standard deviation of the set of trials. Natural feeding variability is evaluated based on six repeats of batch A, with an average of 3.1 g/rev and a standard deviation of 0.09 g/rev (left, blue). Inter-batch variability is evaluated for nine batches that cover the multivariate knowledge space of SuperTab 11SD with an average of 3.0 g/rev and a standard deviation of 0.09 g/rev (right, orange). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

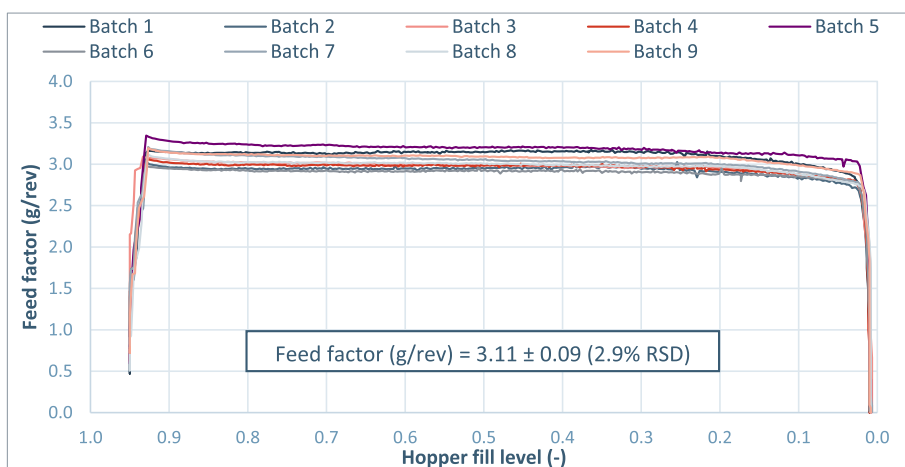


Fig. 3. Feed factors as function of the hopper fill level for six repeats of SuperTab 11SD batch A. Batches are tested on a GZD200.22–2 (production line) that was operating in volumetric mode. The set-up with 22 mm double concave screws operating at 342 rpm screw speed resulted in a decaying feed factor over a range of hopper levels. Average feed factors are varying between the repeats from 2.98 g/rev to 3.23 g/rev.

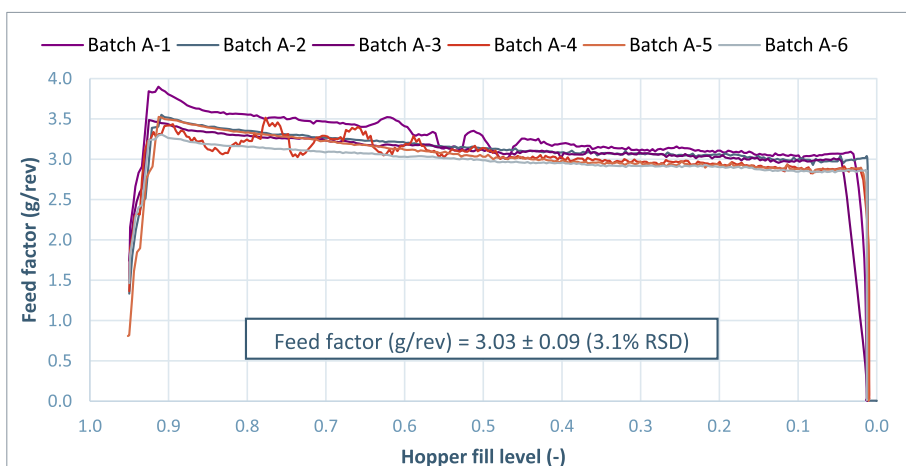


Fig. 4. Feed factors as function of the hopper fill level for nine different batches of SuperTab 11SD that cover the multivariate product space. Batches are tested on a GZD200.22–1 (vibration-free mounting) that was operating in volumetric mode. The set-up with 22 mm double concave screws operating at 342 rpm screw speed resulted in a constant feed factor (parallel lines) for a wide range of hopper levels. Average feed factors are varying between the batches from 2.91 g/rev to 3.20 g/rev.

Just like for the DC22 trials, feed factor profiles of both studies show only small differences. Again, the six repeats of batch A all show a decay in feed factor between hopper levels of 1.0 and 0.5, while the batches that were evaluated for inter-batch variability did not show such a decay. As indicated in the previous section, differences are thought to originate from differences in compression introduced by manual operator filling, priming and the initial hopper fill level as well as the use of different feeders and environmental conditions.

The production line that was used to test the natural feeding variability showed for one test (A-2) larger fluctuation than what has been observed under more controlled lab conditions (with a vibration-free mounting). Most likely these fluctuations are related to partial aeration of the powder during filling of the nearly empty feed hopper. It should be noted that under normal operation conditions of a gravimetric feeder, this effect is minimized by restricting the amount refilling and initiate the refilling at a predefined minimal hopper value. This is also supported by the natural feeding variability of batch B, for which no large fluctuations are observed.

Average feed factors and standard deviations are calculated for the process range with hopper fills of 10 to 90%. Inter-batch variability shown in Fig. 6 was evaluated for six batches that cover a large part of the historical multivariate knowledge space of SuperTab 11SD. The average feed factor was 1.14 g/rev with a standard deviation of 0.10 g/rev. Natural feeding variability shown in Fig. 7 and Fig. 8 is evaluated by performing six repeats of batch A and batch B. The average feed factors for these batches were 1.31 g/rev and 1.16 g/rev with standard deviations of 0.05 g/rev and 0.02 g/rev respectively. With an estimated powder density of 0.65 g/mL during screw filling, observed feed factors correlate to 57–65% fill levels of the screw. These fill levels are approximately 15% lower than in the other set-up, confirming that the system is indeed stretched to the limits of its capabilities.

Fig. 9 provides an overview of the average feed factors and corresponding variability for the tested materials on the stretched feeder set-up with a DC11 screw. Diamonds indicate the average feed factor for each feeding trial that was performed. The horizontal bar and standard deviation indicate the average feed factor and standard deviation over the trial set. No significant difference between the average feed factor for the inter-batch variability and natural feeding variability trials can be observed. Variation in the feed factors however, did show some differences. Natural feeding variability was tested for two batches for which a relative standard deviation of 3.6% and 1.4% was found. The relative standard deviation for inter-batch variability was measured to be significantly larger, namely 8.7%. This shows that batch-to-batch variation of SuperTab 11SD can result in a substantial increase in variability for non-optimized feeding conditions. This is contrary to the earlier results found with a DC22 feeder set-up, where batch-to-batch variability was shown to be negligible compared to the natural

feeding variability.

An important remark is that current trials are executed in a volumetric mode. When moving to a gravimetric feeding process, variability is substantially reduced and an even more accurate and consistent throughput can be obtained. Volumetric feeding behavior is however relevant for feeding performance, as during start-up and refill gravimetric feeders are unable to accurately measure the weight loss in the hopper and will be run in volumetric mode. Additionally, material will be fed in volumetric mode when the raw material batch is changed during a manufacturing campaign. When the feeding behavior of the new batch differs from the previous batch, disturbances take more time to correct, eventually resulting in higher rejection rates. Consistent volumetric feeding is also a predictor for good and easy control in a gravimetric feeding system and is therefore relevant to evaluate the impact of product properties on feeding behavior.

Current research has been performed on free-flowing material. Materials with a poor flow behavior however, are expected to be more susceptible to changes in performance related to batch-to-batch variation. Therefore, studies with materials having poor flow properties are suggested as a continuation of this work.

4. Conclusions

The ability to feed powders consistently and continuously is regarded as one of the critical requirements of a continuous manufacturing process. Feeding consistency depends on many factors, including the set-up of the system and the material properties. In this study, we evaluated how minor variation of free-flowing spray dried lactose can impact the feeding performance in two different feeder set-ups when run in volumetric mode. For the first time, over 200 batches were investigated to evaluate the impact of batch-to-batch variability upon feeding performance. The feed factors showed low variation over the hopper fill level. Average feed factors were calculated between 0.1 and 0.9 hopper fill level to calculate standard deviations that represent the natural feeding variability and inter-batch variability. In a typical feeder set-up with 22 mm double concave screws and 342 rpm screw speed, the natural feeding variability and inter-batch variability were both 3%. This shows that the batch-to-batch variation in this set-up is negligible compared to the natural feeding variability. In a feeder set-up with a 11 mm double concave screws and 514 rpm screw speed, stretching the systems capabilities, the relative standard deviations for natural feeding variability were measured to be 1.4% and 3.6%. The relative standard deviation for inter-batch variability was measured to be substantially larger, namely 8.7%. This shows that minor batch-to-batch variation of SuperTab 11SD only has a substantial effect on feeding performance when the feeding parameters like screw size and screw/scrapper speed are not optimized.

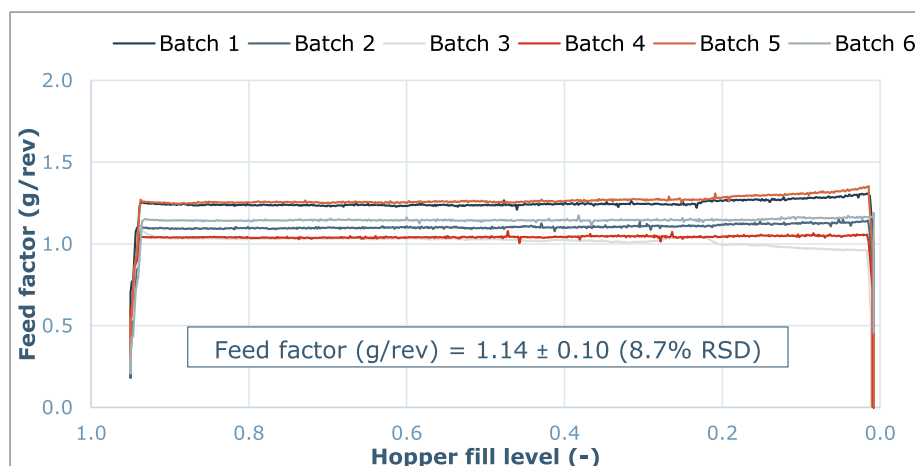


Fig. 6. Feed factors as function of the hopper fill level for six different batches of SuperTab 11SD that cover the multivariate product space. Batches are tested on a GZD200.22-1 (vibration-free mounting) that was operating in volumetric mode. The set-up with 11 mm double concave screws operating at 514 rpm screw speed resulted in a constant feed factor (parallel lines) for a wide range of hopper levels. Average feed factors are varying between the batches from 1.03 g/rev to 1.26 g/rev.

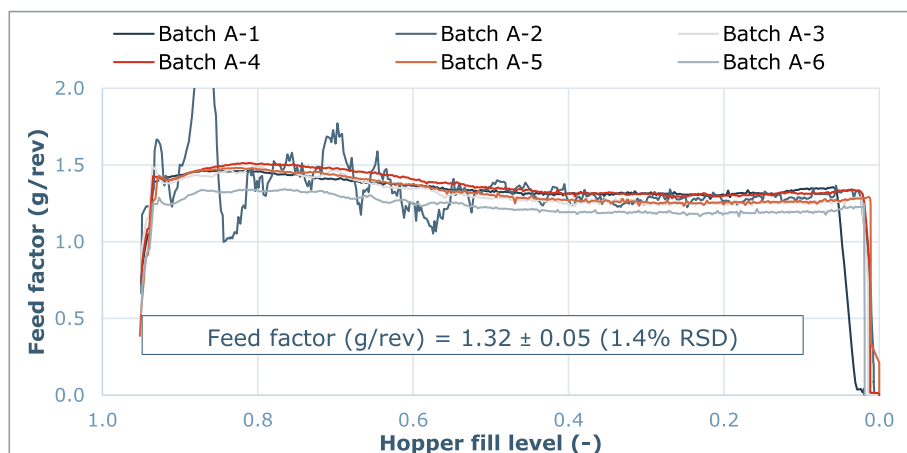


Fig. 7. Feed factors as function of the hopper fill level for six repeats of SuperTab 11SD batch A. Batches are tested on a GZD200.22-2 (production line) that was operating in volumetric mode. The set-up with 11 mm double concave screws operating at 514 rpm screw speed resulted in a decaying feed factor for hopper levels above 0.5. Average feed factors are varying between the repeats from 1.22 g/rev to 1.36 g/rev.

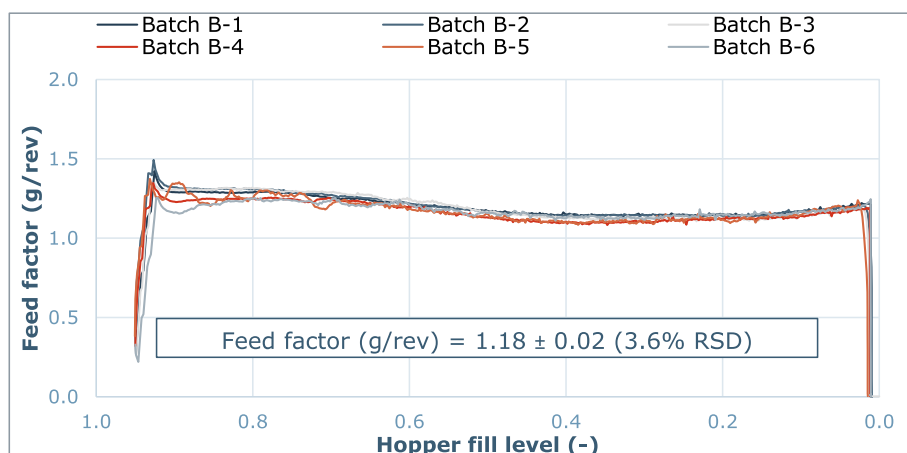


Fig. 8. Feed factors as function of the hopper fill level for six repeats of SuperTab 11SD batch B. Batches are tested on a GZD200.22-2 (production line) that was operating in volumetric mode. The set-up with 11 mm double concave screws operating at 514 rpm screw speed resulted in a decaying feed factor for hopper levels above 0.5. Average feed factors are varying between the repeats from 1.15 g/rev to 1.18 g/rev.

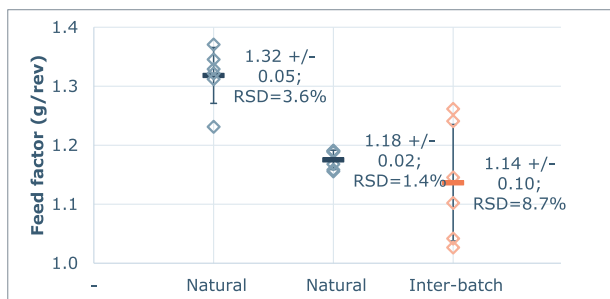


Fig. 9. Average feed factors calculated over a hopper fill of 10–90% for different feeding runs of SuperTab 11SD in a set-up with 11 mm double concave screws and 514 rpm screw speed. The horizontal bars and error bars indicate the average feed factor and standard deviation of the set of trials. Natural feeding variability is evaluated based on six repeats of batch A and B, with average values of 1.31 g/rev and 1.17 g/rev respectively. Standard deviation are 0.05 g/rev (left, blue) and 0.02 g/rev (middle, blue) respectively. Inter-batch variability is evaluated for six batches that cover a large part of the multivariate knowledge space of SuperTab 11SD with an average of 1.14 g/rev and a standard deviation of 0.10 g/rev (right, orange). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Funding acknowledgements

Dr. Mendez Torrecillas from EPSRC CMAC FUTURE MANUFACTURING HUB was supported by the Medicines Manufacturing Innovation Centre (MMIC). MMIC is co-funded by UK Research and Innovation (UKRI) and the Scottish government and is a collaboration between the public and private sector, including GlaxoSmithKline and AstraZeneca. (Innovate UK: 104208 (2018-2021) & 900070 (2017-2018)).

Author contributions

Pauline H.M. Janssen: Conceptualization, Data Curation, Formal Analysis, Investigation, Methodology, Resources, Visualization, Writing – Original Draft Preparation, Writing – Review & Editing. Sri Sharath Kulkarni: Methodology, Resources, Investigation, Project Administration, Writing – Review & Editing. Carlota Mendez Torrecillas: Conceptualization, Investigation, Methodology, Project Administration, Writing – Review & Editing. Florian Tegel: Investigation, Methodology, Project Administration, Resources, Writing – Review & Editing. Bernhard Meier: Resources, Supervision, Writing – Review & Editing. Bastiaan H.J. Dickhoff: Conceptualization, Resources, Supervision, Writing – Review & Editing

Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Carlota Mendez Torrecillas reports financial support was provided by Medicines Manufacturing Innovation Centre (MMiC).

Acknowledgement

The authors would like to thank dr. W.L.J. Hinrichs and prof. dr. H. W. Frijlink for their diligent proofreading of the article.

References

- [1] C.L. Burcham, A.J. Florence, M.D. Johnson, Continuous manufacturing in pharmaceutical process development and manufacturing, *Annu. Rev. Chem. Biomol. Eng.* 9 (2018) 253–281, <https://doi.org/10.1146/annurev-chembioeng-060817-084355>.
- [2] M. Tezyk, B. Milanowski, A. Ernst, J. Lulek, Recent progress in continuous and semi-continuous processing of solid Oral dosage forms: a review, *Drug Dev. Ind. Pharm.* 42 (2015) 1195–1214, <https://doi.org/10.3109/03639045.2015.1122607>.
- [3] S.D. Schaber, D. Gerogiorgis, R. Ramachandran, J.M.B. Evans, P.I. Barton, B. L. Trout, Economic analysis of integrated continuous and batch pharmaceutical manufacturing: a case study, *Ind. Eng. Chem. Res.* 50 (2011) 10083–10092.
- [4] S. Chatterjee, FDA perspective on continuous manufacturing, *IFPAC Annu. Meet. Balt. MD* 26 (2012) 34–42.
- [5] S.L. Lee, T.F. O'Connor, X. Yang, C.N. Cruz, S. Chatterjee, R.D. Madurawe, C.M. V. Moore, L.X. Yu, J. Woodcock, Modernizing pharmaceutical manufacturing: from batch to continuous production, *J. Pharm. Innov.* 10 (2015) 191–199, <https://doi.org/10.1007/s12247-015-9215-8>.
- [6] M. Fonteyne, J. Verbruyse, F. De Leersnyder, B. Van Snick, C. Vervae, J.P. Remon, T. De Beer, Process analytical Technology for Continuous Manufacturing of solid-dosage forms, *TrAC Trends Anal. Chem.* 67 (2015) 159–166, <https://doi.org/10.1016/j.trac.2015.01.011>.
- [7] J.M. Vargas, S. Nielsen, V. Cárdenas, A. Gonzalez, E.Y. Aymat, E. Almodovar, G. Classe, Y. Colón, E. Sanchez, R.J. Románach, Process analytical Technology in Continuous Manufacturing of a commercial pharmaceutical product, *Int. J. Pharm.* 538 (2018) 167–178, <https://doi.org/10.1016/j.ijpharm.2018.01.003>.
- [8] S.P. Simonaho, J. Ketolainen, T. Ervasti, M. Toivainen, O. Korhonen, Continuous manufacturing of tablets with PROMIS-line - introduction and case studies from continuous feeding, blending and tableting, *Eur. J. Pharm. Sci.* 90 (2016) 38–46, <https://doi.org/10.1016/j.ejps.2016.02.006>.
- [9] C.A. Blackshields, A.M. Crean, Continuous powder feeding for pharmaceutical solid dosage form manufacture: a short review, *Pharm. Dev. Technol.* 23 (2018) 554–560, <https://doi.org/10.1080/10837450.2017.1339197>.
- [10] J. Hanson, Control of a system of loss-in-weight feeders for drug product continuous manufacturing, *Powder Technol.* 331 (2018) 236–243, <https://doi.org/10.1016/j.powtec.2018.03.027>.
- [11] M. Jaspers, M.T.W. de Wit, S.S. Kulkarni, B. Meir, P.H.M. Janssen, M.M.W. van Haandel, B.H.J. Dickhoff, Impact of excipients on batch and continuous powder blending, *Powder Technol.* 384 (2021) 195–199, <https://doi.org/10.1016/j.powtec.2021.02.014>.
- [12] L. Pernenkil, C.L. Cooney, A review on the continuous blending of powders, *Chem. Eng. Sci.* 61 (2006) 720–742, <https://doi.org/10.1016/j.ces.2005.06.016>.
- [13] S. Sacher, N. Heindl, J.A. Afonso Urich, J. Kruisz, J.G. Khinast, A solution for low-dose feeding in continuous pharmaceutical processes, *Int. J. Pharm.* 591 (2020), 119969, <https://doi.org/10.1016/j.ijpharm.2020.119969>.
- [14] M.E. Crowley, A.M. Crean, Quality by design in an evolving manufacturing sector, *Eur. J. Parenter. Pharm. Sci.* 20 (2015) 63–69.
- [15] F. Tahir, J. Palmer, J. Khoo, J. Holman, I.K. Yadav, G. Reynolds, E. Meehan, A. Mitchell, G. Bajwa, Development of feed factor prediction models for loss-in-weight powder feeders, *Powder Technol.* 364 (2020) 1025–1038, <https://doi.org/10.1016/j.powtec.2019.09.071>.
- [16] W.E. Engisch, F.J. Muzzio, Loss-in-weight feeding trials case study: pharmaceutical formulation, *J. Pharm. Innov.* 10 (2015) 56–75, <https://doi.org/10.1007/s12247-014-9206-1>.
- [17] N. Bostijn, J. Dhondt, A. Ryckaert, E. Szabó, W. Dhondt, B. Van Snick, V. Vanhoorne, C. Vervae, T. De Beer, 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.* 557 (2019) 342–353, <https://doi.org/10.1016/j.ijpharm.2018.12.066>.
- [18] S. Yang, J.R.G. Evans, Metering and dispensing of powder; the quest for new solid Freeforming techniques, *Powder Technol.* 178 (2007) 56–72, <https://doi.org/10.1016/j.powtec.2007.04.004>.
- [19] W.E. Engisch, F.J. Muzzio, Feedrate deviations caused by hopper refill of loss-in-weight feeders, *Powder Technol.* 283 (2015) 389–400, <https://doi.org/10.1016/j.powtec.2015.06.001>.
- [20] M.S. Escotet-Espinoza, S. Moghtadernejad, J. Scicolone, Y. Wang, G. Pereira, E. Schäfer, T. Vigh, D. Klingeleers, M. Ierapetritou, F.J. Muzzio, Using a material property library to find surrogate materials for pharmaceutical process development, *Powder Technol.* 339 (2018) 659–676, <https://doi.org/10.1016/j.powtec.2018.08.042>.
- [21] Y. Wang, T. Li, F.J. Muzzio, B.J. Glasser, Predicting feeder performance based on material flow properties, *Powder Technol.* 308 (2017) 135–148, <https://doi.org/10.1016/j.powtec.2016.12.010>.
- [22] J.K. Prescott, R.A. Barnum, On powder Flowability, *Pharm. Technol.* 24 (2000) 60–84+236.
- [23] S.S. Oka, M. Sebastian Escotet-Espinoza, R. Singh, J.V. Scicolone, D.B. Hausner, M. Ierapetritou, F.J. Muzzio, Design of an Integrated Continuous Manufacturing System, *Contin. Manuf. Pharm.* (2017) 405–446, <https://doi.org/10.1002/9781119001348.ch12>.
- [24] W.K. Hsiao, T.R. Hörmann, P. Toson, A. Paudel, P. Ghiotti, F. Stauffer, F. Bauer, S. Lakio, O. Behrend, R. Maurer, et al., Feeding of particle-based materials in continuous solid dosage manufacturing: a material science perspective, *Drug Discov. Today* 25 (2020) 800–806, <https://doi.org/10.1016/j.drudis.2020.01.013>.
- [25] B. Carlin, The Role of Excipients in Quality by Design (QbD), in: W.S. Schildwein, M. Gibson (Eds.), *Pharmaceutical Quality by Design: A Practical Approach*, John Wiley & Sons Ltd, 2017, pp. 97–116. ISBN 9781118895238.
- [26] F. Stauffer, V. Vanhoorne, G. Pilcer, P.F. Chavez, M.A. Schubert, C. Vervae, T. De Beer, Managing active pharmaceutical ingredient raw material variability during twin-screw blend feeding, *Eur. J. Pharm. Biopharm.* 135 (2019) 49–60, <https://doi.org/10.1016/j.ejpb.2018.12.012>.
- [27] F. Stauffer, V. Vanhoorne, G. Pilcer, P.F. Chavez, S. Rome, M.A. Schubert, L. Aerts, T. De Beer, Raw material variability of an active pharmaceutical ingredient and its relevance for Processability in secondary continuous pharmaceutical manufacturing, *Eur. J. Pharm. Biopharm.* 127 (2018) 92–103, <https://doi.org/10.1016/j.ejpb.2018.02.017>.
- [28] G. Rassu, A.C. Eissens, G.K. Bolhuis, Tableting properties of an improved spray-dried lactose, *J. Drug Deliv. Sci. Technol.* 16 (2006) 455–459, [https://doi.org/10.1016/S1773-2247\(06\)50087-5](https://doi.org/10.1016/S1773-2247(06)50087-5).