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A multivariate approach to predict the volumetric and gravimetric feeding behavior of a low feed rate feeder based on raw material properties

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Abstract

In this study, the volumetric and gravimetric feeding behavior of 15 pharmaceutical powders on a low feed rate feeder was correlated with their material properties through a multivariate approach. The powders under investigation differ substantially in terms of material properties, making the selected powders representative for powders typically used in pharmaceutical manufacturing. The material properties were described by 25 material property descriptors, obtained from a rational selection of critical characterization techniques that provided maximal information with minimal characterization effort. From volumetric feeding experiments (i.e., powder feed rate not controlled), the maximum feeding capacity (maximum feed factor (FF_{max})) and optimal hopper fill level at which the feeder should be refilled during gravimetric feeding (feed factor decay (FF_{decay})) were obtained. During gravimetric feeding experiments (i.e., powder feed rate controlled), the variability on the feed rate (relative standard deviation (RSD)) and the difference between the setpoint and mean feed rate (relative error (RE)) were determined. Partial least squares (PLS) regression was applied to correlate the volumetric and gravimetric feeding responses (Y) with the material property descriptors (X). The predictive ability of the developed PLS models was assessed by predicting the feeding responses of two new powders (i.e., validation set). Overall, the volumetric feeding responses (FF_{max} and FF_{decay}) were predicted better than the gravimetric feeding responses (RSD and RE), since in gravimetric mode the impact of material properties on the feeding behavior is reduced due to the control system of the feeder. Especially RE was weakly correlated with material properties as RE of most powders varied around zero with only a small numerical variation. Interestingly, this confirms that the control system is working properly and that

the feeder is capable of feeding different powders accurately at low feed rates. The developed models allowed to predict the feeding behavior of new powders based on their material properties. Consequently the number of feeding experiments during process development can be greatly reduced, thereby leading to a more efficient and faster development of new drug products.

Keywords

Continuous manufacturing, Twin screw feeding, Material properties, Material characterization, Multivariate data analysis.

Abbreviations

200M, lactose monohydrate; API, active pharmaceutical ingredient; API M, API micronized; API SD, spray dried API; AV, air velocity; CL, crospovidone; DCP, dibasic calcium phosphate; FF_{decay}, feed factor decay; FF_{max}, maximum feed factor; HD90, silicified microcrystalline cellulose; LIW, loss-in-weight; MgSt, magnesium stearate; P D, paracetamol dense; P M, paracetamol micronized; P P, paracetamol powder; PCA, principal component analysis; PH105, microcrystalline cellulose; PLS, partial least squares; PLSC, partial least squares component; Q^2, predictive ability; R^2, goodness of fit; RE, relative error; rpm, revolutions per minute; RSD, relative standard deviation; S1500, pre-gelatinized starch; SD, standard deviation; UV, unit variance.

1. INTRODUCTION

In a continuous manufacturing line, feeding of the raw materials is generally the first unit operation and is crucial towards the success of the complete manufacturing process (Simonaho et al., 2016). Inaccurate and inconsistent feeding of raw materials can lead to an impaired product quality (e.g., incorrect active pharmaceutical ingredient (API) concentration), since the composition of the final product is determined by the feed rate of the individual raw materials (Ervasti et al., 2015). Loss-in-weight (LIW) feeders consist of a feeding device, weighing platform and control system (Engisch and Muzzio, 2015a). The feeding device is placed on the weighing platform, which measures the weight of the feeding device together with the powder in the feeding device. A LIW feeder can work in two modes, i.e., gravimetric or volumetric. In gravimetric mode, the control system acquires the mass of the feeding device and its content from the weighing platform as a function of time during feeding. The actual feed rate is calculated from the difference in mass, measured by the weighing platform, divided by the difference in time between consecutive measurements. The control system minimizes the difference between the actual feed rate and the feed rate setpoint by adjusting the dispensing rate (e.g., screw speed) of the feeding device (Coperion K-Tron, 2012). Thus in gravimetric mode the powder feed rate is controlled to account for sources of variability, such as variations in material density when the powder level in the hopper changes during feeding (Van Snick et al., 2017a). The volumetric mode is characterized by the displacement of a constant material volume per unit of time instead of a constant mass per unit of time as in gravimetric mode. The screw speed of the feeding device is kept constant during volumetric feeding, implying that the powder feed rate is not controlled (Blackshields and

Crean, 2017). For pharmaceutical applications, where the feeding accuracy of the individual raw materials is critical and the density of the processed powders can vary, the gravimetric feeding mode is preferred. A LIW feeder operating in gravimetric mode will switch to volumetric mode during hopper refill, because the weight loss cannot be accurately measured when material is entering and leaving the feeder at the same time (Engisch and Muzzio, 2015b).

APIs and excipients used in pharmaceutical formulations differ a lot in terms of material properties (e.g., density, particle size, flowability) and these differences can be reflected in the process behavior (El Hagrasy et al., 2013; Engisch and Muzzio, 2015a; Fonteyne et al., 2015; Herting and Kleinebudde, 2007). Therefore, an approach that captures the variability in material properties of different powders and subsequently correlates this with process behavior at different unit operations can facilitate product and process development. The first step is to establish a database containing all the appropriate material properties from a wide selection of representative powders. Such an extensive raw material property database was recently developed by Van Snick et al. (Van Snick et al., 2018a), in which more than 50 pharmaceutical powders were characterized in detail using a wide variety of techniques resulting in more than 100 material property descriptors. The included raw materials ranged from excipients used during direct compression, roller compaction and wet granulation to different types of APIs. Subsequently, principal component analysis (PCA) was used to reveal the correlations between the included raw materials and their material properties.

In a next step, the material properties can be linked via multivariate models with the process behavior at different unit operations of a continuous manufacturing line (e.g., feeders, blenders) (Clayton, 2015). Research has already been successfully conducted using this approach for granulation and tableting processes (Fonteyne et al., 2014; Garcia-Munoz, 2014; Haware et al., 2009a, 2009b; Thoorens et al., 2015; Van Snick et al., 2018b; Willecke et al., 2017). Once a predictive platform is developed for a unit operation, the characterization of a small amount of powder is sufficient to predict the behavior of that material at the specific unit operation. This significantly reduces the otherwise numerous experiments to a handful of confirmatory experiments to verify the predicted process behavior. Such an approach is especially useful during the early stages of drug product development, when only a limited amount of API is available. By being able to predict the process and product performance, the material consumption and development time can be greatly reduced, leading to a more efficient and faster development of new drug products (Wang et al., 2017). In addition, a surrogate powder with similar material properties as the API can be selected and used during experiments instead of the original API, thereby further limiting the API consumption (Boukouvala and Ierapetritou, 2013).

Wang et al. developed a model for predicting the gravimetric feeding behavior of a K-Tron KT20 twin screw LIW feeder based on the material flow properties of seven raw materials using PLS regression (Wang et al., 2017). Three feeder screws, differing in feeding capacity and self-cleaning ability, were tested and the gravimetric feeding performance was described by the consistency of the feed rate (RSD) and the difference between the mean and target feed rate (RE). They concluded that feeding performance was affected by the material flow properties and that the predicted feeding responses were in good agreement with the experimental results. In addition, a strong correlation between the initial feed factor and the material flow properties was observed. This initial feed factor was determined during the volumetric calibration and refers to the maximum feeding capacity for a given screw and material (Engisch and Muzzio, 2012). Van Snick et al. investigated the importance of volumetric feeding experiments on a GEA compact feeder and introduced the feed factor profile, in which the feed factor was plotted as a function of hopper fill level (Van Snick et al., 2017a). From these feed factor profiles, the maximum feeding capacity was derived and a suitable refill strategy was selected for each tested material. The maximum feeding capacity correlated with bulk density and partly with flow properties, whereas highly compressible powders with a low density exhibited a feed factor decrease at higher hopper fill levels.

The feeders used by Wang et al. and Van Snick et al. are high feed rate feeders (feed rate > 1 kg/h), while the correlation of material properties with the feeding behavior of low feed rate feeders (feed rate < 1 kg/h) is not yet described in literature. Developing such predictive models is especially relevant for low feed rate feeders as these feeders are generally used for low-dosed raw materials (e.g., APIs). In addition, the growing interest within the pharmaceutical industry for high-potency active pharmaceutical ingredients further encourages the need of a predictive platform for these types of feeders (Besenhard et al., 2016).

This study is an application of the raw material property database developed by Van Snick et al (Van Snick et al., 2018a). While they developed a PCA model and identified the correlated and relevant material property descriptors, the current study aims at linking these relevant material property descriptors with the volumetric and gravimetric feeding behavior of a low feed rate feeder. The 15 pharmaceutical powders included in this study were selected from the powders used by Van Snick et al., making the selection representative for powders commonly used in pharmaceutical manufacturing. The material properties of the powders were determined and described by 25 material property descriptors obtained from seven characterization techniques. These characterization techniques were identified by Van Snick et al. as the rational selection of critical characterization techniques that provide maximal information with minimal characterization effort. The volumetric feeding experiments were used to construct feed factor profiles, from which the maximum feed factor and feed factor decay were obtained. During gravimetric feeding experiments, the variability on the feed rate (RSD) and the difference between the setpoint and mean feed rate (RE) were determined. Next, the material property descriptors were correlated with both the volumetric and gravimetric feeding responses via PLS regression. The predictive performance of the models was assessed by predicting the feeding responses of two validation powders.

2. MATERIALS AND METHODS

2.1. Materials

The raw materials included in this study were selected from the raw material database described by Van Snick et al (Van Snick et al., 2018a). Furthermore, additional APIs were included as these APIs will be used in an application where the studied feeder will be implemented in a continuous manufacturing line for pharmaceutical semi-solid and liquid formulations (Bostijn et al., 2018). The following 15 raw materials were used in this study: lactose monohydrate (200M) (Lactose 200M, DFE, Goch, Germany), microcrystalline cellulose (PH105) (Avicel PH-105, FMC, Philadelphia, PA, USA), dibasic calcium phosphate (DCP) (Emcompress AN, JRS, Rosenberg, Germany), silicified microcrystalline cellulose (HD90) (Prosolv HD90, JRS, Rosenberg, Germany), crospovidone (CL) (Kollidon CL, BASF, Ludwigshafen, Germany), pre-gelatinized starch (S1500) (starch 1500, Colorcon, Dartford, UK), magnesium stearate (MgSt) (Ligamed MF-2-V, Peter Greven, Bad Münstereifel, Germany), spray dried API (API SD) (Janssen, Beerse, Belgium), paracetamol dense (P D) (Mallinckrodt, Dublin, Ireland), paracetamol powder (P P) (Mallinckrodt, Dublin, Ireland), paracetamol micronized (P M) (Mallinckrodt, Dublin, Ireland), API 1 (Janssen, Beerse, Belgium), API 2 (Janssen, Beerse, Belgium), API 3 (Janssen, Beerse, Belgium) and API micronized (API M) (Janssen, Beerse, Belgium). In total, seven excipients and eight APIs were investigated. The powders were divided in a calibration and validation set (section 2.2.4.). S1500 (excipient) and API 3 were selected as powders for the validation set since both exhibited a different feeding behavior and the values of their material property descriptors fell within the numerical ranges of the calibration set. The details of some APIs are not provided due to confidentiality reasons.

2.2. Methods

2.2.1. Equipment

2.2.1.1. K-Tron MT12 LIW feeder

The feeder used in this study was a K-Tron MT12 twin screw co-rotating LIW feeder (Coperion K-Tron, Niederlenz, Switzerland) (figure 1). The motor and weighing platform were enclosed within the feeder base and the feeding screws were connected to the motor via a gearbox (gear ratio of 1:1). A drive command of 100% corresponded to a maximum screw speed of 60 rpm. Concave coarse screws were used with a diameter of 12 mm and a pitch distance of 5.75 mm. The hopper, having a volume of 1 L, was equipped with an agitator. At the bottom part of the agitator, three blades consistently filled the flights of the screws. The vertical rods of the agitator promoted the material flow in the hopper and prevented material from bridging on the side walls. The feeder was not equipped with a refill system and the hopper was not manually refilled during the experiments.

Operating the feeder was done via the K-Tron control module. All feeder data (screw speed, net weight, …) was logged every 1 s during the experiments. Before the start of an experiment, the empty feeder was tared. Next, the hopper was filled and the screws were primed with powder. After priming, the hopper was filled up to 1 L and the corresponding weight was recorded and considered as maximal (i.e., 100% hopper fill level).

2.2.1.2. Catch scale

A catch scale (Coperion K-Tron, Niederlenz, Switzerland) was placed under the outlet of the feeder to record the powder feed rate every 1 s and the fed powder was collected in a beaker (figure 1). The catch scale was used to obtain the raw feed rate, because the feed rate calculated by the feeder is already pre-treated according to an algorithm from the feeder manufacturer. If the feed rate of the feeder would be used, it would be difficult to compare feeder performance between feeders of different manufacturers.

2.2.2. Feeder characterization methodology

2.2.2.1. Volumetric feeding

After performing the start-up feeder protocol (i.e., taring, priming of the screws and determining the maximum weight in the hopper), each powder was volumetrically fed at three different screw speeds: 10, 50 and 90% of the maximum screw speed (60 rpm), corresponding to screw speeds of 6, 30 and 54 rpm, respectively. These screw speeds cover the screw speed range that is generally used during manufacturing. Because the volumetric mode was selected, the control system did not control the feed rate by correcting the screw speed and thus the screw speed remained constant during each experiment. All volumetric experiments were stopped when the hopper ran empty.

The aim of the volumetric experiments was to obtain a feed factor profile of each powder at each tested screw speed. In a feed factor profile, the feed factor is plotted as a function of the hopper fill level (%) (figure 2). The feed factor (g/revolution) (eq. 1) is the powder mass dispensed per screw revolution and was calculated from the actual feed rate (kg/h), obtained from the catch scale, and the screw speed (revolutions/s) using the following equation:

$$feed\ factor\ \left(\frac{g}{revolution}\right) = \frac{feed\ rate\ \left(\frac{kg}{h}\right)}{screw\ speed\ \left(\frac{revolutions}{s}\right) \times 3.6} \quad (1)$$

with 3.6 the conversion factor to convert kg/h into g/s. The feed rate (kg/h) (eq. 2) was calculated using the difference in weight ($\Delta W_{catch\ scale}$) (g) measured by the catch scale divided by the difference in time (1 s) between consecutive catch scale measurements (Δt) (s):

$$feed\ rate\ \left(\frac{kg}{h}\right) = \frac{\Delta W_{catch\ scale}\ (g)}{\Delta t\ (s)} \times 3.6 \qquad (2)$$

with 3.6 the conversion factor to convert g/s into kg/h. In order to compare feed factor profiles of powders with a different density (i.e., different net weight of a full hopper), the net weight of the hopper (kg) was normalized for the maximum powder mass in the hopper (kg) for a specific powder and expressed as the hopper fill level % (eq. 3):

$$fill\ level\ \% = \frac{net\ weight\ (kg)}{maximum\ net\ weight\ (kg)} \times 100 \qquad (3)$$

Once a feed factor profile was obtained for a specific material at a given screw speed, the maximum feed factor (FF_{max}) and feed factor decay (FF_{decay}) were extracted (figure 2). Prior to the determination of these volumetric feeding responses, the disturbance of a beaker replacement was removed from the feed factor profile. The remaining data was averaged (i.e., moving average of 20 s) to enhance the interpretability of the feed factor profiles. FF_{max} expresses the maximum feeding capacity of a feeder for a specific material and can be used to calculate the maximum achievable feed rate in gravimetric mode. FF_{max} was determined from the feed factor profile as the highest observed feed factor at each tested screw speed (figure 2).

In general, the feed factor is highest (i.e., FF_{max}) at 100% hopper fill level and gradually decreases during feeding (i.e., decreasing hopper fill level) (figure 2). This decrease in feed factor was described by FF_{decay}, defined as the % hopper fill level where the feed factor drops to 90% of FF_{max}. FF_{decay} can help to define the hopper refill strategy during gravimetric feeding, thereby reducing the variability induced by a hopper refill. Since the feeder is operating in volumetric mode during a hopper refill, the feeder is not able to compensate for the increasing density of the powder inside the hopper (i.e., increase in feed factor) when incoming material compresses this powder. In addition, the feeder screw speed can suddenly change when the feeder returns to gravimetric mode after a refill because of the changed density (Nowak, 2016). Therefore, selecting the optimal hopper fill level at which the hopper should be refilled is essential to minimize the deviation from the feed rate setpoint during and after a refill. The threshold of 90% of FF_{max} was selected as a lower % will result in a larger difference in feed factor before and after a refill and a higher % will require the feeder to be refilled too frequently (Engisch and Muzzio, 2015b). The impact of screw speed on FF_{max} and FF_{decay} was also investigated, since these volumetric feeding responses were determined at three different screw speeds. Hence, FF_{max} and FF_{decay} at a screw speed of 6, 30 and 54 rpm were obtained for each powder (from now on referred to as FF_{max} 6, 30 and 54 rpm and FF_{decay} 6, 30 and 54 rpm).

2.2.2.2. Gravimetric feeding

After performing the start-up feeder protocol (i.e., taring, priming of the screws and determining the maximum weight in the hopper), the feeder was calibrated in volumetric mode to determine the feed rate at the maximum screw speed (60 rpm). Next, the hopper was refilled to reach a fill level of 100% after the calibration. For the gravimetric experiments (i.e., controlled feed rate), the powders were tested at a low and high feed rate setpoint (0.1 and 0.55 kg/h) and each experiment was stopped after 20 minutes. These feed rate setpoints were selected based on another study where the gravimetric feeding behavior of a K-Tron KT20 and GEA compact feeder was determined (Van Snick et al., 2017b). By selecting the same feed rate setpoints, the gravimetric feeding performance between the different feeders can be directly compared.

The standard deviation (SD) (kg/h) (eq. 4), relative standard deviation (RSD) (%) (eq. 5) and relative error (RE) (%) (eq. 6) (i.e., relative difference between the mean and target feed rate) were calculated from the feed rate (kg/h) measured by the catch scale (figure 3):

$$SD = \sqrt{\frac{\sum_{1}^{k}(feed\ rate - \overline{feed\ rate})^2}{k}} \qquad (4)$$

$$RSD = \frac{SD}{\overline{feed\ rate}} \times 100 \qquad (5)$$

$$RE = \frac{\left|\overline{feed\ rate} - target\ feed\ rate\right|}{target\ feed\ rate} \times 100 \qquad (6)$$

with $\overline{\mathrm{feed\ rate}}$ (kg/h) the mean feed rate and k the number of time points. RSD and RE were used to express the variability on the feed rate and deviation of the mean feed rate from the setpoint, respectively. Data outside the ± 3 SD interval were excluded together with 7 s of data before and after an outlier. After filtering, SD, RSD and RE were recalculated. This pre-treatment was necessary to remove disturbances that were not related to the feeding but rather to the sensitivity of the catch scale (e.g., opening and closing of a door). In total, four gravimetric feeding responses were obtained for each powder: RSD and RE at the feed rate setpoints of 0.1 and 0.55 kg/h (from now on referred to as RSD 0.1 and 0.55 kg/h and RE 0.1 and 0.55 kg/h).

2.2.3. Powder characterization techniques

An overview of the used characterization techniques, corresponding material property descriptors and abbreviations is provided in table 1.

2.2.3.1. Laser diffraction

Laser diffraction (Mastersizer S, Malvern Instruments, Worcestershire, UK) was used to measure the particle size of the powders. All measurements were conducted with a MS64 dry powder feeder unit using a 300 RF lens at a feed rate of 3.0 G. Each measurement was carried out in triplicate. The particle size was reported as a volume equivalent sphere diameter. The 50% cumulative undersize of the volumetric distribution was described as dv50 (µm). Particle size analysis was done via the Mastersizer S software.

2.2.3.2. Density and porosity

Bulk (ρ_b) and tapped (ρ_t) density (g/ml) were measured in triplicate with a graduated cylinder mounted on an automatic tapping device (PT TD200, PharmaTest, Hainburg, Germany). A known mass (M) (g) of powder was poured into a graduated cylinder and the initial volume (V_0) (ml) was determined. After 1250 taps the volume (V_{1250}) (ml) was also measured. The bulk density was calculated as M/V_0 and the tapped density as M/V_{1250}. Furthermore, the Hausner ratio (HR) was calculated as V_0/V_{1250} and the Carr index (CI) as $(V_0 – V_{1250})/V_0$.

The true density (ρ_{true}) (g/ml) was determined using an AccuPyc 1330 helium pycnometer (Micromeritics, Norcross, GA, USA). The equilibration rate was 0.0050 psig/min and the number of purges 10. The powder bed porosity (ε) (%) was calculated as described by equation 7:

$$\varepsilon = 1 - \frac{\rho_b}{\rho_{true}} \quad (7)$$

2.2.3.3. Ring shear tester

The flowability of the powders was measured in triplicate with a ring shear tester (Type RST-XS, Dietmar Schulze Schüttgutmesstechnik, Wolfenbüttel, Germany). In a first step, the 30 cm³ XS-Mr shear cell was filled with powder and a normal load of 1000 Pa was applied during the pre-shear step. For the actual measurements, the powder was sheared under three different consolidation stresses (400, 600 and 800 Pa). The flowability of the powders was evaluated via the flow function coefficient (ffc) (eq. 8), which was calculated from the unconfined yield strength (σ_1) (Pa) and major principal stress (FC) (Pa). The bulk density-weighed flow was expressed as ffp (eq. 9) and gives information about the flow under gravity. ρ_w is the density of water (1 g/ml).

$$ffc = \frac{\mathrm{FC}}{\sigma_1} \qquad (8)$$

$$ffp = ffc \times \frac{\rho_b}{\rho_w} \qquad (9)$$

The wall friction angle (WFA) (°) was measured in triplicate using a XS-WL shear cell with a 316 stainless steel bottom plate (surface roughness: 0.28 µm). After filling the cell with ± 4 mm of powder, the wall friction was determined under decreasing wall normal stresses (4000, 3280, 2560, 1840, 1120 and 400 Pa). WFA was calculated from the resulting wall yield locus.

2.2.3.4. FlowPro

The flow rate (FR) (mg/s) through an orifice was measured (n = 5) using the FlowPro™ (iPAT, Turku, Finland). The system consists of a sample holder with orifice and analytical scale. The sample holder moves vertically and the upward motion breaks the powder arch enabling the powder to flow freely through the orifice. The volume of the sample holder is

5.96 ml and the diameter of the orifice 3 mm. The flow rate was calculated from the data obtained by the analytical scale (Seppälä et al., 2010).

2.2.3.5. FT4 powder rheometer

Cylindrical vessels (diameter: 50 mm) were used during material characterization with the FT4 powder rheometer.

2.2.3.5.1. Stability and variable flow rate

At the start of the stability and variable flow rate experiments, the vessel was filled with 160 ml of sample. To ensure reproducible starting conditions, the sample was subjected to a conditioning cycle before the start of each experiment. Flow energy (mJ) data was collected from the energy generated by moving a blade through the powder from the top of the vessel to the bottom (test cycle) with a blade tip speed of 100 mm/s. The test cycle was repeated seven times to achieve stable flow energy (flow energy test 1 – 7). The sensitivity of the powder to shear rate was evaluated by gradually reducing the blade tip speed (100, 70, 40 and 10 mm/s) during cycle 8 – 11. The variables obtained from this experiment are the basic flow energy (BFE) (mJ) (eq. 10), RSD on basic flow energy (RSD BFE) (%) (eq. 11), normalized BFE (nBFE) (mJ/g) (eq. 12), flow rate index (FRI) (eq. 13) and specific energy (SE) (mJ/g) (eq. 14):

$$BFE = flow\ energy\ test\ 7 \quad (10)$$

$$RSD\ BFE = \frac{standard\ deviation\ (flow\ energy\ test\ 1-7)}{mean\ (flow\ energy\ test\ 1-7)} \times 100 \quad (11)$$

$$nBFE = \frac{BFE}{sample\ mass} \quad (12)$$

$$FRI = \frac{flow\ energy\ test\ 11}{flow\ energy\ test\ 8} \qquad (13)$$

$$SE = \frac{(up\ energy\ cycle\ 6 + up\ energy\ cycle\ 7)/2}{sample\ mass} \qquad (14)$$

2.2.3.5.2. Compressibility

For the measurement of compressibility, the normal stress of a vented piston was gradually increased (0.5, 1, 2, 4, 6, 8, 10, 12 and 15 kPa) and the percentage of change in volume was recorded. The compressibility at 15 kPa was reported (C 15kPa) (%).

2.2.3.5.3. Aeration

A vessel with aeration base was filled with sample (160 ml) and pre-conditioned to standardize the state of the powder bed before each measurement. Initially, the flow energy (AE 0) (mJ) was measured without aeration. Next, the air velocity (AV) was gradually increased (AV: 0.5, 1, 2, 4, 6, 8, 10, 15, 20, 30 and 40 mm/s) while measuring the corresponding flow energy (AE AV) (mJ). The reduction in flow energy caused by transitioning from a densely stirred to a fluidized powder bed was quantified by normalizing the aerated flow energies with the initial flow energy (AR AV) (eq. 15). Finally, the maximum normalized aeration sensitivity (NAS) (s/mm) was calculated as the difference in normalized flow energy divided by the difference in air velocity.

$$AR\ AV = \frac{AE\ AV}{AE\ 0} \qquad (15)$$

2.2.3.6. Charge density

Triboelectric charging of the powders was measured using a GranuCharge (GranuTools, Awans, Belgium). Powders were fed into the device using a vibratory feeder. Electrostatic charge was created during flow through a 316L stainless steel V-shaped tubing system consisting of 2 separate tubes that form a 90° angle. The tubes have a combined length of 700 mm and an internal diameter of 47 mm. At the end of the tubing system, samples were collected inside a Faraday cup connected to an electrometer. Per test, 30 ml of powder was used and measurements were performed in triplicate. Charge density (CD) (nC/g) was calculated by dividing the net charge by the mass of the powder bed.

2.2.4. Multivariate data analysis

For each of the four determined feeding responses (FF_{max}, FF_{decay}, RSD and RE) a separate PLS model was developed (table 2). The models were developed by regressing the material property descriptors (X) versus the feeding responses (Y) of the powders included in the calibration set (13 powders). In the models of the volumetric responses, the applied screw speeds were also included in the X matrix since the volumetric feeding responses (FF_{max} and FF_{decay}) were determined at three screw speeds. Similarly, the feed rate setpoint was added to the X matrix in the RSD and RE model as these gravimetric feeding responses were measured at a low and high feed rate setpoint. Screw speed was not included because the screw speed did not remain constant during the gravimetric feeding experiments.

Prior to PLS regression, the data was pre-treated. First, the absolute value of charge density was used in the PLS models, since charge density centered around zero and varied in both the positive and negative direction. Without using the absolute value of charge density, a powder with a very negative charge density value (i.e., highly charged) would otherwise be categorized as a powder with a very low electrostatic charge (Van

Snick et al., 2018a). Furthermore, the data was scaled to unit variance (UV) and mean-centered prior to PLS regression. UV-scaling was performed by dividing each value by the standard deviation of that variable and was necessary to normalize for the different numerical ranges of the variables. For mean-centering, the mean of each variable was subtracted from the data of that variable. Mean-centering results in a repositioning of the coordinate system and makes the average point the origin, which improves the interpretability of the model. Finally, a logarithmic transformation was applied on non-normally distributed variables (dv50, ffc, ffp, BFE, RSD and RE) to approximate a normal distribution (Eriksson et al., 2015).

The goodness of fit and predictive ability of the developed PLS models were assessed by calculation of R^2 and Q^2, respectively. Q^2 values were obtained after performing a leave-one-out cross-validation, in which sub-models were developed from a reduced calibration dataset and the excluded data was predicted by the sub-models (Eriksson et al., 2015). The number of PLS components providing the highest Q^2 value was selected. The predictive performance of the developed models was also assessed by predicting the feeding responses of two external validation powders (S1500 and API 3). The relative prediction error was calculated as the relative difference between the actual and predicted feeding responses of the validation set.

Excluding some material property descriptors resulted in models with an improved predictive performance. A first explanation for an improved predictive ability is that some material property descriptors were highly correlated because they describe the same material property (e.g., HR and CI). The problem of multiple descriptors representing one material property, is that such a material property can artificially dominate the model due to a numerical overweight. Therefore, some of these highly correlated descriptors were excluded, ensuring that the material properties had an equal weight in the model (Van Snick et al., 2018a). Finally, material property descriptors that correlated poorly with the feeding responses were excluded as these descriptors only introduce interfering variability in the model. By selecting the material property descriptors with the highest correlation for a specific feeding response, the predictive performance of the models was optimized individually. An overview of the excluded material property descriptors for each model is given in table 2. The PLS models were created using the SIMCA software (Version 15, Umetrics, Umeå, Sweden).

3. RESULTS AND DISCUSSION

3.1. Correlation between material properties and feeding behavior

A four component PLS model was developed for FF_{max} which explained 81.1 and 97.1% of the variation in the X and Y dataset, respectively (table 2). The loadings plot was used to understand how the material property descriptors are related to each other and which material property descriptors have an impact on the feeding responses (Eriksson et al., 2015). In the PLS component (PLSC) 1 vs 2 loadings plot of the FF_{max} model (figure 4b), FF_{max}, bulk and tapped density were located in the top right corner. This suggests a positive correlation between FF_{max} and density, signifying that the numerical value of FF_{max}, bulk and tapped density will change in the same way. Consequently, porosity (ε) was located at the opposite side of the origin (i.e., bottom left corner), meaning that FF_{max} was negatively correlated with porosity. The positive correlation between density and FF_{max} (i.e., negative correlation between porosity and FF_{max}) can be explained by the constant volume that is dispensed per screw revolution. For the same volume, a powder with a high density will have a higher powder mass dispensed per screw revolution (i.e., feed factor) than a powder with a low density (Van Snick et al., 2017a). The scores plot reveals how the powders are related to each other based on their material properties and feeding behavior. The scores and loadings plots are complementary and superimposable, meaning that materials with a specific location on the scores plot possess high values for variables (i.e., material and feeding properties) with a similar location on the corresponding loadings plot and low values for variables at the opposite side of the origin. For the FF_{max} model, it was observed that APAP D was located in the top right corner of the PLSC 1 vs 2 scores plot (figure 4a). This is because APAP D possessed the highest FF_{max}, bulk and tapped density of the investigated powders. AE 10 and FF_{max} were also positively correlated and was related to density as a dense powder requires more flow energy to aerate its powder bed (figure 4b).

FF_{max} was not only dependent on the density as FF_{max} 30 rpm of CL (0.244 g/revolution) was clearly higher compared to PH105 (0.172 g/revolution), despite the similar bulk density (± 0.32 g/ml) of both powders. The flow descriptors (ffp and BFE) and FF_{max} had similar PLSC 1 loadings, suggesting that powder flow and FF_{max} were positively correlated (figure 4b). The better flow of CL explains why the FF_{max} of CL was higher compared to PH105 (ffp of 1.88 (CL) compared to 0.55 (PH105)). Free-flowing powders flow more easily in the flight of the screws and therefore have a higher screw filling degree than powders with a poor flowability. Overall, the density and powder flow were the material properties with the largest impact on FF_{max}. Based on the loadings plot and the correlation matrix (- 7%) (not shown) it can be concluded that the screw speed (within the studied ranges of 10 and 90% of the maximum screw speed) was weakly anti-correlated with FF_{max}.

In the feed factor profiles of the tested powders, FF_{max} was located at 100% hopper fill level and the feed factor decreased when emptying the hopper (figure 2). At 100% hopper fill level, the powder mass in the hopper is at its maximum and the powder at the screw inlet is compressed under the influence of the high powder mass in the hopper (i.e., maximum density at the screw inlet). When the powder mass in the hopper decreases during feeding, the powder is less compressed resulting in a reduction of the density at the screw inlet and consequently the feed factor decreases. FF_{decay} was used to describe this decrease in feed factor and was defined as the % hopper fill level where the feed factor drops to 90% of FF_{max}. A model with three components was developed for FF_{decay}, explaining 55.8 and 80.9% of the variation in the X and Y dataset, respectively (table 2). FF_{decay} was positively correlated with the descriptors that describe the compressibility of a powder bed (C 15kPa, HR and CI) (figure 5b). Powders with a high compressibility had a high FF_{decay}, thus the decrease of feed factor already occurred at higher hopper fill levels. For powders with a low compressibility, the compressive forces (i.e., powder mass in the hopper) have a minimal impact on the density at the screw inlet resulting in an almost unchanged feed factor during emptying of the hopper. The lowest FF_{decay} was observed for powders with the lowest compressibility of the dataset (HD90 and DCP) (figure 5a). However, the FF_{decay} of 200M was lower than API SD (table 3), despite having a similar compressibility (C 15kPa: ± 22%). The reason for the lower FF_{decay} of 200M was due to its better flow properties and higher density. Consequently, 200M can longer maintain a constant feed factor because the powder flows more easily in the screw flights.

The negative correlation of flow and density with FF_{decay} was confirmed by their opposite location in the loadings plot (figure 5b). The loadings plot reveals that the screw speed was weakly anti-correlated with FF_{decay} (figure 5b). According to the correlation matrix (not shown), the magnitude of this correlation was low (- 11%) and was therefore considered as irrelevant.

The model of the gravimetric feeding response RSD consisted of three PLSCs, which explained 63.1 and 77.8% of the variation in the X and Y dataset, respectively (table 2). From the PLSC 1 vs 2 loadings plot, it was observed that feed rate and RSD were clearly negatively correlated, since they were located at opposite sides of the origin (figure 6b). Consequently, a lower feed rate variability (RSD) will be observed when feeding at higher throughputs. However, the value of SD was similar at low and high feed rates, but because SD was divided by a higher mean feed rate for runs at a high feed rate, the calculated RSD was lower compared to low feed rate runs (Ervasti et al., 2015). The correlation of RSD with the material property descriptors was weaker as the highest correlation observed in the correlation matrix (not shown) was only 40% (HR). From the loadings plot, it can be concluded that the highest variability on the feed rate was observed for powders with a low density, poor flow, high compressibility and small particle size, and that this was primarily related to the ability to consistently fill the screws (figure 6b).

Two components were fitted in the RE model explaining 52.4 and 51.6% of the variation in the X and Y dataset, respectively (table 2). From the PLSC 1 vs 2 loadings plot follows that RE was positively correlated with porosity and negatively with both bulk and tapped density (figure 7b). At the lowest feed rate setpoint of 0.1 kg/h, all powders could reach the setpoint and the observed RE was close to zero. In contrast, powders with a low density were not capable of reaching the highest feed rate setpoint (0.55 kg/h). For these powders, the mean feed rate was much lower than 0.55 kg/h, resulting in a large RE. The maximum feeding capacity of these powders was not high enough due to their low density. This also explains why feed rate and RE were positively correlated because only for runs at a high feed rate (0.55 kg/h) a high RE was observed. The location of material properties such as flowability and compressibility with respect to RE can also be explained by the inability of low density powders to reach the highest feed rate setpoint as these powders typically possess a poor flow and high compressibility. RE of most powders at both the low and high feed rate setpoints, apart from the ones with a low density, was close to zero (table 3).

3.2. Predicting of the feeding responses

The actual and predicted feeding responses (FF_{max}, FF_{decay}, RSD and RE) of S1500 and API 3 are displayed in table 4. The highest relative prediction error for the FF_{max} was - 5.01% (FF_{max} 6 rpm of S1500). For FF_{decay}, the highest relative prediction error was observed for FF_{decay} 54 rpm of S1500 (- 25.07%). All other FF_{decay} values were predicted with a relative prediction error lower than 10%. For both validation powders, FF_{max} was predicted better than FF_{decay} and can be explained by the stronger correlation of FF_{max} with the material properties. The strongest correlation between FF_{max} and a material property descriptor was - 91% (ε), whereas for FF_{decay} the strongest correlation was only - 63% (ffp).

The highest relative prediction error for RSD was - 39.00% and was observed for the RSD 0.1 kg/h of S1500, while the prediction error on the RSD 0.55 kg/h of S1500 and API 3 was - 8.53 and - 0.62%, respectively. The predictability of the RE model was low as the Q^2 value of this model was only 0.033 and the highest relative prediction error was 1895.97% (RE 0.1 kg/h of S1500). However, the magnitude of the relative prediction error should not be overestimated as the actual RE of this run was 0.01% and the predicted 0.20%. More important for the RE model is that both the actual and predicted RE values were close to zero for both validation powders, meaning that the model captured that the density and maximum feeding capacity of these powders was high enough to reach the investigated feed rate setpoints.

A reason for the low Q^2 value of the RE model can be explained by the small numerical variation in this gravimetric feeding response. Furthermore, the low Q^2 value is an indication of a weak relationship between the material properties and RE (Eriksson et al., 2008), which is not desirable for an approach that aims to predict feeding behavior based on material properties. However, the question is whether it is relevant to predict this gravimetric feeding response, since a control system that is working properly will be able to feed different powders at a feed rate close to the setpoint (i.e., low RE value). Interestingly, since RE was close to zero and was similar for most powders, it can be concluded that the feeder was capable of feeding the powders accurately at the low feed rates tested in this study. The only powders for which a large RE value was observed, were powders with a low density that could not reach the highest feed rate setpoint of 0.55 kg/h, even when the control system selected the maximum screw speed. For these powders, predicting RE is advantageous since it expresses the maximum feeding capacity of that powder. However, the maximum feeding capacity was already captured by FF_{max} and could be predicted with a very low prediction error. Therefore, when FF_{max} of a powder is known, predicting RE does not provide additional information regarding the maximum feeding capacity of that powder.

Overall, the volumetric feeding responses (FF_{max} and FF_{decay}) were predicted better than the gravimetric feeding responses (RSD and RE). This is because the material properties were more correlated with the volumetric feeding responses (FF_{max}: - 91% (ε); FF_{decay}: - 63% (ffp)) than with the gravimetric feeding responses (RSD: 40% (HR); RE: - 60% (ρ_b)). In gravimetric mode, the control system tries to minimize the variability on the feed rate and keeps the feed rate as close as possible to the setpoint, independently from the powder that is being fed. This is in contrast with feeding in volumetric mode, where the differences in feeding behavior are entirely related to the material properties since the feed rate is not controlled. Finally, most feeding responses were predicted better for API 3 compared to S1500. A two component PCA model (R^2X: 0.617 and Q^2: 0.313) was constructed, including all material property descriptors and all powders (both calibration and validation powders). This allowed to investigate how the validation powders were related to the calibration powders based on their material properties. The scores plot of this PCA model reveals that more calibration powders were situated in the same region as API 3 than in the region of S1500 (figure 8), meaning that the calibration set contained more powders with similar material properties as API 3. This emphasizes that the size of the calibration set is critical for this multivariate approach to be successful. Therefore, models should be updated when material properties and feeding responses of new powders are obtained (Wang et al., 2017). This will further improve the predictability of the models as the probability will increase that the material properties and feeding responses of a new powder are closely related to a powder in the calibration set.

4. CONCLUSIONS

In this study, multivariate models (PLS) were developed that allow to predict the volumetric and gravimetric feeding behavior of a low feed rate feeder based on material properties. The maximum feed factor (FF_{max}) and decay in feed factor (FF_{decay}) were determined during volumetric feeding experiments. From gravimetric feeding experiments, the variability on the feed rate (RSD) and the difference between the mean feed rate and setpoint (RE) were obtained. Overall, the volumetric feeding responses (FF_{max} and FF_{decay}) were predicted with the highest accuracy as they correlated better with the material properties than the gravimetric responses. This is because in gravimetric mode, the feed rate is controlled by the control system, which reduces the impact of material properties on the feeding behavior. For RE, almost no variation was observed between the different powders. Only for low density powders, where the highest gravimetric feed rate setpoint could not be reached, RE was a measure of the maximum feeding capacity. However, the maximum feeding capacity was already obtained from FF_{max}. Therefore, developing a model that correlates material properties with RE might be unnecessary. Finally, API 3 was predicted better than S1500 since the calibration set contained more powders with similar material properties as API 3. Hence, updating the models with new powders is important to further improve the predictive performance. The used multivariate models assume linear relationships between the variables. However these relationships do not always tend to be linear. Therefore, one of the future perspectives is to investigate modelling approaches that can handle non-linearity in the data with the aim of further improving the predictive performance of the developed models. The approach applied in this study will allow to reduce the number of feeding experiments during process development, leading to a more efficient and faster development of new drug products.

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Characterization technique	Material property descriptor	Abbreviation
Laser diffraction	50% cumulative undersize of the volumetric distribution	dv50
Tapping device and pycnometer	Bulk density Tapped density Hausner ratio Carr index True density Porosity	ρ_b ρ_t HR CI ρ_{true} ε
Ring shear tester	Flow function coefficient Unconfined yield strength Major principal stress Bulk density-weighed flow Wall friction angle	ffc σ_1 FC ffp WFA
FlowPro	Flow rate	FR
FT4 powder rheometer	Basic flow energy RSD on basic flow energy Normalized basic flow energy Flow rate index Specific energy Compressibility at 15 kPa Flowability energy at air velocity of 10 and 40 mm/s Normalized flowability energy at air velocity of 10 and 40 mm/s Normalized aeration sensitivity	BFE RSD BFE nBFE FRI SE C 15kPa AE 10 and AE 40 AR 10 and AR 40 NAS
GranuCharge	Charge density	CD

Table 1. Overview of the characterization techniques, corresponding material property descriptors and abbreviations.

	FF_{max}	FF_{decay}	RSD	RE
Excluded material property descriptors	HR, σ_1, FC, RSD BFE, FRI, SE, AR 10 and CD	ρ_{true} and FC	CI, FRI and NAS	HR
R^2X	0.811	0.558	0.631	0.524
R^2Y	0.971	0.809	0.778	0.516
Q^2	0.946	0.585	0.344	0.033
# of PLS components	4	3	3	2

Table 2. Overview of the developed PLS models.

Material	FF_{max} 6 rpm (g/revolution)	FF_{max} 30 rpm (g/revolution)	FF_{max} 54 rpm (g/revolution)	FF_{decay} 6 rpm (%)	FF_{decay} 30 rpm (%)	FF_{decay} 54 rpm (%)	RSD 0.1 kg/h (%)	RSD 0.55 kg/h (%)	RE 0.1 kg/h (%)	RE 0.55 kg/h (%)
P M	0.141	0.082	0.075	86.8	93.7	68.3	59.5	27.3	0.5	46.2
P P	0.302	0.287	0.267	66.0	70.2	69.0	87.3	17.2	1.9	0.3
P D	0.712	0.703	0.684	53.5	58.7	52.1	76.0	12.3	0.3	0.0
API SD	0.148	0.092	0.109	97.4	69.8	92.1	220.0	52.0	1.0	43.2
200M	0.484	0.473	0.452	36.0	41.3	43.9	60.1	6.1	0.3	0.4
PH105	0.175	0.172	0.164	41.4	38.5	29.8	29.0	7.9	0.1	0.6
DCP	0.384	0.400	0.402	15.5	14.3	18.0	73.6	12.4	1.6	0.0
HD90	0.263	0.253	0.251	18.3	15.4	6.8	57.7	14.3	1.9	1.1
CL	0.188	0.244	0.175	61.2	73.3	85.8	72.0	12.3	0.9	0.8
MgSt	0.140	0.124	0.116	65.2	91.1	88.5	106.7	38.4	4.1	30.2
API 1	0.042	0.045	0.048	84.2	77.6	79.4	191.8	115.5	3.1	64.4
API 2	0.205	0.108	0.089	71.9	47.4	35.1	140.6	28.1	1.2	14.0
API M	0.054	0.027	0.026	85.7	43.1	21.5	52.2	69.0	0.2	76.7
API 3	0.226	0.209	0.191	65.2	62.6	58.9	124.3	25.7	1.9	0.7
S1500	0.470	0.426	0.424	33.7	32.8	35.7	79.5	13.2	0.0	0.5

Table 3. Feeding responses of the tested powders.

	S1500			API 3		
	Actual	Predicted	Relative prediction error (%)	Actual	Predicted	Relative prediction error (%)
FF_{max} 6 rpm (g/revolution)	0.470	0.447	- 5.01	0.226	0.224	- 0.88
FF_{max} 30 rpm (g/revolution)	0.426	0.429	0.61	0.209	0.207	- 0.94
FF_{max} 54 rpm (g/revolution)	0.424	0.411	-3.05	0.191	0.189	- 1.01
FF_{decay} 6 rpm (%)	33.7	34.3	1.87	65.2	65.2	0.00
FF_{decay} 30 rpm (%)	32.7	30.5	- 6.81	62.6	61.4	- 1.88
FF_{decay} 54 rpm (%)	35.7	26.7	- 25.07	58.9	57.7	- 2.11
RSD 0.1 kg/h (%)	79.5	48.5	- 39.00	124.3	102.7	- 17.41
RSD 0.55 kg/h (%)	13.2	12.1	- 8.53	25.7	25.5	- 0.62
RE 0.1 kg/h (%)	0.01	0.20	1895.97	1.94	0.78	- 60.07
RE 0.55 kg/h (%)	0.45	0.36	- 19.34	0.70	1.41	101.25

Table 4. Overview of the actual and predicted feeding responses of the validation powders.

Figure 1. Overview of the experimental setup: K-Tron MT12 twin screw LIW feeder (left) and catch scale (right).

Figure 2. Feed factor profile of lactose monohydrate (200M) at a screw speed of 6, 30 and 54 rpm used to determine the volumetric feeding responses: maximum feed factor (FF_{max}) and feed factor decay (FF_{decay}).

Figure 3. Gravimetric feeding data of lactose monohydrate (200M) at 0.55 kg/h used to determine the gravimetric feeding response: standard deviation (SD).

Figure 4. PLSC 1 vs 2 scores (a) and loadings (b) plot of the FF_{max} model. The abbreviations of the powders in the scores plot and of the descriptors in the loadings plot are described in the materials and methods section. Only the runs performed at a screw speed of 30 rpm are displayed in the scores plot since the runs at the three screw speeds largely overlap in the scores plot (not shown).

Figure 5. PLSC 1 vs 2 scores (a) and loadings (b) plot of the FF_{decay} model. The abbreviations of the powders in the scores plot and of the descriptors in the loadings plot are described in the materials and methods section. Only the runs performed at a screw speed of 30 rpm are displayed in the scores plot since the runs at the three screw speeds largely overlap in the scores plot (not shown).

Figure 6. PLSC 1 vs 2 scores (a) and loadings (b) plot of the RSD model. The abbreviations of the powders in the scores plot and of the descriptors in the loadings plot are described in the materials and methods section. The runs performed at the low (L) and high (H) feed rate setpoint (0.1 and 0.55 kg/h) are displayed in the scores plot.

Figure 7. PLSC 1 vs 2 scores (a) and loadings (b) plot of the RE model. The abbreviations of the powders in the scores plot and of the descriptors in the loadings plot are described in the materials and methods section. The runs performed at the low (L) and high (H) feed rate setpoint (0.1 and 0.55 kg/h) are displayed in the scores plot.

Figure 8. Scores plot of the PCA model constructed of the material properties of all investigated powders. The abbreviations of the powders in the scores plot are described in the materials section.