Model-based approach to the design of pharmaceutical roller-compaction processes

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Abstract

This work presents a new model based approach to process design and scale-up within the same equipment of a roller compaction process. The prediction of the operating space is not performed fully in-silico, but uses low-throughput experiments as input. This low-throughput data is utilized in an iterative calibration routine to describe the behavior of the powder in the roller compactor and improves the predictive quality of the mechanistic models at low and high-throughput. The model has been validated with an experimental design of experiments of two ibuprofen formulations. The predicted sweet spots in the operating space are in good agreement with the experimental results.

Abbreviations

| Symbol | Description                                      |
|--------|--------------------------------------------------|
| D      | roller diameter [m] [cm]                         |
| W      | roller width [m] [cm]                            |
| S      | roller gap [m] [mm]                              |
| Rs     | roller force [N] [N]                             |
| SCF    | specific compaction force [N/m] [N/cm]          |
| Nk     | roller speed [1/s] [rpm]                         |
| Ns     | screw speed [1/s] [rpm]                          |
| \( \rho_{\text{eff}} \) | effective angle of internal friction [rad] [°] |
| \( \phi_{\text{w}} \) | wall friction angle [rad] [°]                    |
| cT     | screw constant [kg] [g]                          |
| K      | compressibility factor [-]                       |
| \( \gamma_{\text{p}} \) | pre-consolidation solid fraction [-]             |
| \( \gamma_{\text{g}} \) | in-gap ribbon solid fraction [-]                 |
| \( \gamma_{\text{r}} \) | ribbon solid fraction [-]                        |
| T      | ribbon thickness [m] [mm]                        |
| mS     | feeding screw mass flow rate [kg/s] [kg/h]       |
| mR     | mass flow rate between rolls [kg/s] [kg/h]       |
| mobs   | observed mass throughput [kg/s] [kg/h]           |
| P0     | feed pressure [Pa] [kPa]                         |
| \( P_{\text{max}} \) | maximum pressure at roller gap [Pa] [kPa]        |
| F      | force factor [kg/s] [kg/h]                       |
| \( \beta \) | angular position at roller, \( \beta = 0 \) at gap [rad] [°] |
| \( \alpha \) | nip angle [rad] [°]                              |
| \( \sigma \) | shear stress [Pa] [kPa]                          |
| RSD    | residual standard deviation [-]                  |

1. Introduction

Dry granulation technology via roller compaction (RC) is increasingly applied in the pharmaceutical industry to produce solid oral dosage forms, mainly tablets, as well as capsules and sachets (Chang et al., 2008; Lopes et al., 2016). The granulation step primarily addresses the poor flowability of powders and other issues, such as dustiness, low bulk density and propensity for segregation. Unlike wet granulation, RC does not require solvents and a drying step to remove them, which is especially advantageous for moisture- and heat-sensitive active pharmaceutical ingredients (APIs). Moreover, since RC involves fewer processing steps, it is suitable for continuous processing lines (Kleinebudde, 2004; Miller, 2005; Guigon et al., 2007; Leane et al., 2015; Rowe et al., 2013; Martinetz et al., 2018). However, an RC process poses several challenges. Firstly, roller compaction formulations generally require higher amounts of excipients and therefore...
lower drug loading compared to wet granulation. The exact formulation also depends on the compactability of the API. Secondly, the powder blend compressibility may be compromised when forming granules that are subsequently compressed into tablets (Sun and Kleinebudde, 2016).

During the compaction process development, a special emphasis is made on maintaining the same product quality, e.g., during scale-up and technology transfer (Nesarikar et al., 2012; Souhi et al., 2015; Perez-Gago et al., 2017). To that end, current approaches often rely on labor-intensive experimental trials to explore the full design space for various throughputs or even various types of equipment, resulting in considerable material and operational costs (Kleinebudde, 2004; Teng et al., 2009). Additionally, since in the early stages of drug product development the available quantities of API are limited, process design has to be performed either via model compounds mimicking the API or via reduced flow rates on the equipment. As a result, complex interactions between the material attributes and process parameters may hinder extracting relevant information from the experiments performed (Michrafy et al., 2017).

The aim of this work is to reduce the material consumption in a systematic design of experiment (DoE). A mechanistic approach based on the models described by (Johanson, 1965) and (Reynolds et al., 2010) has been developed in order to replace the experiments with higher throughput and material consumption (high roller and screw speeds) with model predictions. The key is an iterative calibration sequence that employs the experimental data at low throughput to improve the predictions at both low and high throughputs. This approach has been validated by comparing the resulting operating space with a fully experimentally obtained one.

2. Roller compaction modeling

2.1. Working principle and relevant models

Fig. 1 shows a schematic diagram of an RC process. First, the material is fed into the hopper (1) and transported by the conveyor screws (2 and 3) onto two counter-rotating rollers (5). By applying a specific compaction force, the material is compressed into a so-called ribbon. It is subsequently milled into granules (6) using various mills and milling parameters, which are known to affect the properties of final granules (Perez-Gandarillas et al., 2016). Ribbon density or solid fraction, defined as the mass of material per volume of ribbon, is commonly considered a critical quality attribute (CQA) of an RC process (Vervaet and Remon, 2005; Fonteyne et al., 2015; Park et al., 2018). The ribbon solid fraction is actively measured and controlled in a continuous manufacturing process (Gupta et al., 2005; Singh et al., 2012). In order to predict the ribbon density, only a small fraction of the RC process has to be modeled (rectangular region (5) in Fig. 1).

The process parameters of interest during the compaction step are the roller speed \( N_R \), screw speed \( N_S \), specific compaction force between the rollers (SCF), and gap width \( S \) (Inghelbrecht and Remon, 1998; Vervaet and Remon, 2005; Dumarey et al., 2011; Csordas et al., 2018). The roller gap and force are often correlated with the screw speed of the feed, depending on the control scheme and the equipment manufacturer (Guigon and Simon, 2003; Rowe et al., 2017). There are two major operation modes:

- Gap-controlled mode (also termed ‘automatic mode’). The operator can set the roller speed, the roller force and the roller gap width. The screw speed is the machine’s response via an internal feedback loop to obtain the desired roller gap and force. This is the most common operation mode for industrial processes.
- Screw-controlled mode (also termed ‘manual mode’). The operator can set the roller speed, the roller force and the screw speed. The parameters selected and the characteristics of the material compressed result in a certain roller gap.

Depending on the control mode of the roller compactor, an appropriate process model should be selected: Johanson’s model is better suited for the gap-controlled mode, whereas Reynolds’ model is better for the screw-controlled mode.

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However, applying these models directly usually leads to an overestimation of the ribbon density (Dec et al., 2003; Bi et al., 2014). One way to improve the results is a better prediction of the stresses acting on the powder between the rolls. (Katashinskii, 1966) developed an analytical model that considers the stress gradient in trapezoidal “slabs” in the roller region. With better computational resources it became possible to solve the pressure distribution with the finite element method (FEM) (PM Modnet Modelling Group, 1999; Wang and Karabin, 1994), or even a combined approach of discrete element method (DEM) and FEM simulations (Mazor et al., 2018). While these methods give and insight to the roller compaction process, performing FEM simulations for every process condition and powder blend is not feasible.

One source of discrepancy between the predictions of Johanson’s and Reynolds’ model and the ribbon density measurements is the different compaction behavior of the powder in the roller compactor compared to uniaxial compression tests (Reynolds et al., 2010). (Reimer and Kleinebudde, 2019) demonstrated that the roller compactor and a compaction simulator lead to different ribbon densities and built a model to account for that difference.

In addition to the differences in the compaction behavior, the mechanistic models predict strictly speaking not the solid fraction of the final ribbon \( \gamma_f \), but the solid fraction density in the roller gap \( \gamma_i \). In this case, the elastic recovery of the ribbon is neglected.

In this work, roller compaction experiments at low screw speeds have been utilized to calibrate a compaction profile that relates the maximum pressure in the roller gap to the final ribbon density. (Sajjia et al., 2017) used a similar approach to predict the ribbon densities in screw-controlled mode. Section 2.4 introduces a calibration routine for ribbon density and throughput in both gap-controlled and screw-controlled mode.
2.2. Prediction of ribbon density and throughput in the gap-controlled mode

Johanson’s model is one of the first mechanistic models of an RC process. It accounts for the powder properties (compaction profile, angle of friction) and the geometry of the rolls (width, diameter, and gap) but neglects the roller and screw speeds (Johanson, 1965). It is well-suited for predicting the ribbon density in the gap-controlled mode since the actively-controlled process parameters (the gap and the roller force) are input for the model, whereas the changing process parameter (screw speed) is neglected. Once the ribbon density is known, it is possible to predict the throughput based on the geometrical considerations and the roller speed. However, the throughput calculation was not part of Johanson’s initial work.

Johanson categorized the regions containing the compacted material into a slip region (1), where the rollers move faster than the powder, and a nip region, where there is no slip between the roller and the powder (2) as shown in Fig. 2.

The stress gradients in the nip region are higher than those in the slip region, indicating that most of the compaction takes place in the nip region. Based on the geometrical considerations, it is possible to define a normalized stress gradient in the nip region \( \left( \frac{\partial \sigma}{\partial \bar{g}} \right)_{\text{nip}} \) and the slip region \( \left( \frac{\partial \sigma}{\partial \bar{g}} \right)_{\text{slip}} \). The stress is applied in horizontal direction, i.e. normal to the direction of the initial feed pressure \( P_0 \).

Johanson derived expressions for both stress gradients as:

\[
\left( \frac{\partial \sigma}{\partial \bar{g}} \right)_{\text{slip}} = \frac{4\sigma}{\bar{g}} \left( \frac{\pi - \alpha - \nu}{2} \right) \tan \delta_{\text{e}} ;
\]

\[
\left( \frac{\partial \sigma}{\partial \bar{g}} \right)_{\text{nip}} = \frac{K\sigma}{\bar{g}} \left( \frac{2\cos \theta - 1 - S/D \tan \theta}{(1 + \frac{\pi}{\nu} - \cos \theta) \cos \theta} \right) ;
\]

where

\[
A = \frac{\theta + \nu + \pi/2}{2} ;
\]

\[
2\nu = \pi - \sin^{-1} \frac{\sin \phi_w}{\sin \delta_e} - \phi_w ;
\]

Nip angle \( \alpha \) is defined as an angular roller position (\( \theta = \alpha \)) in which the material transforms from the slip condition to the non-slip condition, i.e., the boundary between the slip and nip regions. At this point, the stress gradients of the slip and nip regions are equal. Therefore, nip angle \( \alpha \) can be calculated by applying this condition based on Eqs. (1) and (2):

\[
f(\pi - \alpha - \nu)\tan \delta_e = \frac{K(2\cos \alpha - 1 - S/D \tan \alpha)}{\cos \alpha} \cot(A - \mu) - \cot(A + \mu) ;
\]

Eq. (5) shows that the nip angle solely depends on material-related parameters, such as effective angle of internal friction \( \delta_e \), wall friction angle (\( \phi_w \)) and compressibility constant \( K \).

To link peak pressure \( P_{\text{max}} \) exerted on the material at the minimum roller gap \( S \) with the roller force, Johanson applies an analytical expression of roller force \( R_f \) as follows:

\[
R_f = \frac{WDP_{\text{max}}F}{2}
\]

where \( W \) is the roller width, \( D \) is the roller diameter and \( F \) is an integral over the nip region, as shown below: Because the pressures in the slip region are small compared to the nip region, it can be neglected in the calculation of the roller force (Johanson, 1965)

\[
F = \int_0^\alpha \left[ \frac{\frac{s}{\bar{g}}}{\frac{1}{\bar{g}} - \cos \theta} \cos \theta \right]^K \cos \delta \theta
\]

Johanson described his model as an initial value problem: if feeding pressure \( P_0 \) in the beginning of the slip region is known, integrating over the stress gradients in Eqs. (1) and (2) makes it possible to obtain \( P_{\text{max}} \), the maximum pressure applied to the powder in the roller gap. Once \( P_{\text{max}} \) is known, roller force \( R_f \) can be extracted using Eqs. (6) and (7). In contrast to older systems, nowadays modern roller compactors can measure and actively control their roller force either directly or using some parameter that can easily be converted into the roller force, e.g., the hydraulic roller pressure. In this case, equipment suppliers provide a conversion factor to translate the roller pressure into the roller force.

If roller force \( R_f \) is known, Eqs. (6) and (7) can be used to extract the peak pressure \( P_{\text{max}} \). There is no need to assume feeding pressure \( P_0 \) and numerically integrate over the stress gradients (which can still be used to obtain nip angle \( \alpha \), as shown in Eq. (5)).

Assuming that material compression follows a compression power law, ribbon solid fraction at the gap \( \chi_i \) can be calculated as:

\[
\chi_i = \chi_i \left( P_{\text{max}} \right)^{1/K}
\]

where \( K \) is the compressibility constant of the material and \( \chi_i \) is the pre-consolidation solid fraction. Incorporating Eqs. (6) and (7) into Eq. (8) expresses the relationship between process output (ribbon solid fraction) and process parameters (roller force, minimum roller gap, roller diameter, roller width) as follows:

\[
\chi_i = \chi_i \left( \frac{2R_f}{K} \right)^{1/K} \left( \frac{WDP_{\text{max}}F}{2} \right)^{-1/K}
\]

(Reynolds et al., 2010) considered the mass balance around the roller gap. If the roller speed, the roller geometry, the true density of powder and the solid fraction of the ribbon are known, the mass throughput can be calculated as:

\[
m_{\text{out}} = nDN_{\text{t}}WS\rho_{\text{true}} \chi_i
\]

2.3. Prediction of ribbon density and throughput in the screw-controlled mode

Johanson’s model can be used for equipment in the gap-controlled mode. However, since the roller speed and screw speed are not
considered process parameters in terms of predicting the ribbon solid fraction, the model cannot be used for equipment in the screw-controlled operation mode. Reynolds et al. addressed this issue by solving the mass balance around the roller gap as a function of roller width, roller speed \( N_R \) and feeding screw speeds \( N_S \) (Reynolds et al., 2010).

Reynolds assumed a linear relationship between the mass flow on the feeding screw and the screw speed:

\[
m_t = c_s N_s
\]

(11)

where \( c_s \) is the screw constant which depends on the powder properties and screw geometry and can be established via a linear regression between the throughput and the screw speed. For the purposes of the model, \( c_s \) is treated as constant material parameter.

Mass flow \( m_{\text{tot}} \) in the roller gap is given by Eq. (10). An effective gap size can be obtained by setting \( m_t = m_{\text{tot}} \) and solving for a non-dimensional gap \( S/D \):

\[
\left( \frac{S}{D} \right)_R = \frac{c_s}{\alpha_s} N_s \frac{N_R}{N_S}
\]

(12)

Substituting \( \left( \frac{S}{D} \right)_R \) for \( \frac{S}{D} \) in Eq. (9) makes it possible to calculate the final ribbon density in the screw-controlled mode at the cost of having to use a calibration factor \( c_t \).

Eq. (12) assumes that the ribbon solid fraction \( y_s \) – the output of the model – is known. Thus, \( y_s \) has to be computed numerically in an iterative manner rather than via a single analytical expression. Let us assume \( y_{s,0} \) to be the ribbon solid fraction that is used to calculate the effective gap size \( \left( \frac{S}{D} \right)_R \) and \( y_{s,0} \) to be the result of Eq. (9). The iteration varies \( y_{s,0} \) in the expected range and calculates \( y_{s,\text{out}} \). Only if the value of \( y_{s,0} \) has been assumed correctly, it matches the result of the calculation \( y_{s,\text{out}} \). The result of the iteration is then the value of \( y_{s,0} \) that produced the minimal deviation between \( y_{s,0} \) and \( y_{s,\text{out}} \).

The accuracy of this iteration can be chosen freely by setting the step size of potential \( y_{s,0} \) candidates: A step size of 0.001 will produce results accurate to 0.1% points of ribbon solid fraction. This iteration is denoted by the small loop symbol in the screw controlled branch in the flow chart in Fig. 3. In contrast, there is no iteration needed to solve for the ribbon density in gap controlled mode: a single evaluation of Eq. (9) suffices.

The throughput is simply calculated based on the two input parameters, screw speed \( N_S \) and screw constant \( c_s \), given by Eq. (11).

### 2.4. Iterative calibration in low-throughput experiments

The previous sections addressed the prediction of ribbon density and throughput using a single set of process parameters in the gap- or screw-controlled mode. However, there are two sources of discrepancies between the predicted and measured results which are unaccounted for by the models:

First, the compaction behavior of powders in a roller compactor is typically different from that in the uniaxial compression test, requiring a different set of \( K, \gamma \) parameters to describe the compression profile (Reynolds et al., 2010). This means that even if the calculation of peak pressure \( P_{\text{max}} \) is correct, the resulting predicted ribbon density in the roller gap \( y_s \) will not match the experimental one. Second, the elastic recovery of the ribbon must be considered. The measured ribbon thickness \( T \) is greater than roller gap size \( S \). Thus, the predicted ribbon density in the gap \( y_s \) does not match the experimentally-obtained ribbon density \( y_s \). Both of the above factors influence the prediction of ribbon density and resulting throughput. Several theoretical and empirical efforts have been undertaken to account for the elastic recovery and to improve the compression profile in a roller compactor (Cunningham, 2005; Peter et al., 2010).

The objective of this work is to develop a model for the operating space under the assumption that low-throughput measurements are available. The rationale behind such a strategy is that low-throughput is generally associated with low API consumption. As such, the low-throughput data can be used to calibrate the models in order to improve the ribbon density and throughput predictions at both low and high throughputs.

The first step is calibration of the compression profile, i.e., finding a \( K, \gamma \) pair that matches the powder behavior in the roller compactor. Since the compressibility factor \( K \) is used not only in the compression profile computation in Eq. (8) but also in the peak pressure \( P_{\text{max}} \) calculation in Eqs. (6) and (7), the most suitable compression profile must be established iteratively.

#### Step 1: Defining initial \( K \) and \( \gamma_0 \)

In the beginning of the iteration process, to determine the final values of \( K \) and \( \gamma_0 \), the initial values of \( K \) and \( \gamma_0 \) have to be defined. They can be obtained from uniaxial compression experiments or chosen arbitrarily within their expected range. The closer the initial choice of \( K \) and \( \gamma_0 \) is to the final values, the fewer iterations are required.

#### Step 2. Calculation of peak pressures

For each data point in the low-throughput measurements, the peak pressure \( P_{\text{max}} \) is obtained by solving Eq. (7) either directly (gap-controlled mode) or iteratively by substituting Eq. (12) (screw-controlled mode).

#### Step 3. Regression to improve \( K \) and \( \gamma_0 \)

An improved compression profile with \( K', \gamma \) can be established via a linear regression over the logarithmic form of the compression profile:

\[
\log(y_s) = \frac{1}{K} \log(p_{\text{max}}) + \log(y_s')
\]

(13)

using predicted peak pressures \( P_{\text{max}} \) and measured ribbon densities \( y_s \).

#### Step 4. Check ribbon densities and repeat

The improved compression profile \( K', \gamma \) is then used to predict ribbon densities \( y_s \). If the predicted values match the measured data with the desired accuracy, stop the iteration. If not, assign \( K = K' \) and \( \gamma_0 = y_s' \) and repeat with Step 2.

Since in the screw-controlled operation mode the throughput is a direct result of the screw speed and the screw constant, no further calibration is required for the throughput prediction.

In the gap-controlled mode, the throughput prediction can be made based on the ribbon geometry and the roller speed (Eq. (10)). However, the model is calibrated with the density of relaxed ribbon \( y_s \) rather than the ribbon density in gap \( y_s \) that is generally higher (Nkansa et al., 2008; Gamble et al., 2010). As such, elastic recovery \( \beta \) can be introduced to back-calculate the ribbon density in the gap using the relaxed ribbon density predicted by the model:

\[
m_{\text{tot}} = \pi DN_s WSP_{\text{roll}} y_0 = \pi DN_s WSP_{\text{roll}} y_s \beta
\]

(14)

\( \beta \) can be determined by plotting the process throughput (kg/h) over the calculation of mass flow rate exiting the rollers (Eq. (14)). \( \beta \) is the slope of the regression line (with \( y = 0 \) intercept).

Alternatively, \( \beta \) can be determined via the ratio of measured ribbon thickness (T) and the roller gap (S) using the low-speed experiments, as shown in Eq. (15). With regard to the prediction of high throughput, it is assumed that increasing the roller speed does not have a significant impact on the ribbon relaxation.

\[
\beta = \frac{y_s}{y_s} = \frac{T}{S}
\]

(15)

#### 2.5. Determining the screw constant

In the screw-controlled mode, \( m_t \) can be calculated via Eq. (11). The screw constant can be calculated using two approaches. First, the screw constant \( c_{s1} \) can be calculated based on the experimentally observed throughput \( m_{\text{obs}} \) as follows:
Secondly, the screw constant $c_{S2}$ can be calculated using the mass balance, as proposed by (Reynolds et al., 2010):

$$c_{S2} = \frac{m_{\text{roll}}}{N_S}$$ (17)

In this work, $c_{S1}$ and $c_{S2}$ are compared to evaluate how accurately they can predict the throughput.

2.6. In silico design space exploration

The previous sections contained equations for predicting the ribbon solid fraction and the throughput as a function of material properties and RC process parameters. These correlations are leveraged to define a design space for the formulation using a specific roller compactor.

Fig. 3 shows a roadmap for developing and experimentally confirming this design space. RC experiments are performed at low throughput to generate data for calculating the compression properties of a powder blend via iteration using the applicable RC mechanistic model (see previous section). The data obtained allows running the design of experiments (DoEs) in silico and determining the in silico design space for various process parameters (roller gap, screw speed, roller speed) as a function of process output (ribbon solid fraction and throughput).

Since this design space is obtained in silico, it has to be experimentally confirmed in the center and along the extremes. In this work, a full factorial DoE was performed both in silico and experimentally to evaluate the model’s predictive capabilities for the ribbon solid fraction and throughput. This model-based approach involves less experimental work. The experimental methodology is explained below.
For a gap-controlled RC process, two to four roller compactor experiments are required. A minimum roller speed ($N_R$) is used in every run to minimize the consumption of material. Ideally, all four combinations of minimum and maximum roller gap (S) and compaction force (SCF) are performed experimentally. The number of experiments can be further reduced to two, if necessary. In this case, the experiments should cover the process conditions with minimum and maximum expected ribbon density: highest roller gap with lowest compaction force, and lowest roller gap with highest compaction force. A minimum of two experiments is needed to uniquely define the compression profile with the two parameters $K$ and $\chi_i$.

The two measured process outputs are the ribbon solid fraction and the throughput. The iterative calibration method yields an improved compression profile $K$, $\chi_i$ and elastic recovery parameter $\beta$. These calibrated values are subsequently used for the high-throughput prediction purposes.

The ideal set of low throughput experiments in screw-controlled mode consists of four operating points, similar to the gap-controlled mode. The roller speed $N_R$ is set to the minimum to minimize material consumption. Specific compaction force (SCF) and screw-to-roller-speed ratios ($N_S/N_R$) are set to two the highest and lowest values expected in the operating space. If desired, the number of experiments can be further reduced to two. Again, the two operating conditions should result into the highest and lowest ribbon density: high compaction force with high screw-to-roller-speed ratios, and low compaction force with low $N_S/N_R$ ratios.

In screw controlled mode, there are two ways to calculate the screw constant. The screw constant obtained from Eq. (16) is denoted $c_{si}$, the screw constant obtained from Eq. (17) is denoted $c_{sb}$. The influence on the results is discussed in the Results section.

Full factorial DoEs have been performed experimentally. The critical process parameters are:

- In the gap-controlled mode: roller gap, compaction force and roller speed.
- In the screw-controlled mode: screw-to-roller-speed ratio, compaction force and roller speed.

The predicted operating space relies on the low-throughput (low $N_R$) results and has been validated with the fully experimentally obtained operating space. The virtual DoEs use either the modified Johanson model for the gap-controlled operation mode or Reynolds’ model for the screw-controlled operation mode to reflect the critical process parameters as input parameters to the model. The key modification to models found in literature is the differentiation between in-gap ribbon density $\chi_i$ and final ribbon density $\chi_f$. This relationship can be established using the iterative calibration in the previous section. Table 1 provides an overview of which input parameters are required in each RC operation mode. The process is shown graphically in Fig. 3.

3. Experimental and analytical work

3.1. Materials

Ibuprofen (Janssen Pharmaceutical, Beerse, Belgium) was used as a model API, mannitol (Pearlitol® 200 SD Roquette GmbH, Frankfurt, Germany) and microcrystalline cellulose (Avicel® PH-101, FMC Biopolymer, Brussels, Belgium) as a filler/binder, and magnesium stearate (Parteck LUB MST, Merck KGaA, Darmstadt, Germany) as a lubricant.

Two formulations were created. Each consisted of 49.75 %w/w API (Ibuprofen), 49.75 %w/w excipient (microcrystalline cellulose in the IbuMCC formulation, mannitol in the IbuMannitol formulation), and 0.5% w/w lubricant (magnesium stearate in both formulations).

The formulations were blended in a Bohle LM40 (L.B. Bohle Maschinen + Verfahren GmbH, Enningloeh, Germany) bin blender. After 18 min of blending, magnesium stearate was added and the blending continued for additional 2 min. The blender was operated at 20 rpm.

4. Methodology

4.1. Density measurement

Pycnometric density of raw excipients was determined using an AccuPyc® 1330 helium pycnometer (Micromeritics, Norcross, USA). Three measurements were performed each time. The pycnometric density of the formulation was calculated as weighted harmonic mean of raw materials $\bar{X}$ as:

$$\bar{X} = \left( \frac{\sum_{i=1}^{N} n_i}{\sum_{i=1}^{N} \frac{1}{X_i}} \right)^{-1}$$

where $N$ is the number of components, $i$ is the index of the component, $x_i$ is the density of the $i$-th component, and $n_i$ is the fraction of the $i$-th component. The individual fractions $n_i$ sum up to 1.

4.2. Shear cell measurement

The angle of internal friction powders and granules was measured in a ring shear tester (RST-01, Dr. Schulze Schuettguttechnik, Wolfenbuettel, Germany). The samples were carefully filled into the measuring cell to avoid measurement artefacts. Prior to each measurement, a smooth surface was created with a spoon. A normal stress of 5000 Pa was applied for pre-shearing. Stresses of 1000, 2000, 3000, 4000 Pa were used for shear deformation in the ascending order. Subsequently, the measuring point at 1000 Pa was repeated to establish potential changes in the samples. Based on the results, the effective angle of internal friction was calculated by the software of the ring shear tester.

4.3. Compressibility measurement

A rotary die tablet press equipped with 8 mm flat-faced punches was applied for the compressibility analysis (PRESSIMA, IMA Pharma, Bologna, Italy). 200 ± 2 mg of each formulation was weighed by hand, and at least 11 tablets were compressed at 2.5 kN, 5 kN, 7.5 kN, 10 kN, 12.5 kN and 15 kN. Tablet height, width, diameter, mass and breaking strength were analyzed using a SmartTest 50 (SOTAX AG, Lorrach, Germany), n = 6 for IbuMannitol and n = 10 for IbuMCC.

4.4. Roller compaction trials

For RC trials, a Gerteis MINI-PACTOR® (Gerteis Maschinen + Process Engineering AG, Jona, Switzerland) equipped with knurled rolls and rim roller sealing was used. The roller diameter was 25 cm and the roller width was 2.5 cm. The adjustable settings were the roller speed ($N_R$), the roller gap (S) and the specific compaction force (SCF). When the process settings were changed, samples were drawn only after the process equilibrium was reached. Gap-controlled operation mode was used while recording the equilibrium screw speed of the equipment. 490 g to 800 g of IbuMCC.
ribbons and 140 g to 410 g of IbuMannitol ribbons were collected. A 2^3 factorial design with three repetitions at the center point was used. Table 3 shows the process settings used for the different formulations.

5. Results and discussion

5.1. Formulation characterization

IbuMCC and IbuMannitol are two different formulations chosen to contain a plastically-deforming filler and a brittle filler, respectively (Table 2). Table 3 shows that IbuMCC has a lower compressibility factor \((K)\), indicating that lower pressure was required to achieve the same degree of densification. True densities and pre-consolidation densities of the two formulations were similar, while the effective angle of internal friction of IbuMCC was higher due to higher cohesion forces of MCC. The angle of wall friction was not experimentally determined, and a value of 15° was assumed for both formulations since the value generally ranges between 10° and 20° (Nesarikar et al., 2012; Souihel et al., 2015; Perez-Gago et al., 2017). Our previous studies (not shown) indicated that the effect of this parameter on the prediction of solid fraction is minimal.

5.2. Determining \(K\) and \(\gamma_0\)

The compression profile obtained from the tableting experiments is only an estimate of the compression profile in the roller compactor. Fig. 4 compares the compression profiles for both formulations. The uniaxial compression profile is directly obtained from the tableting data, whereas the RC profile is the result of the calibration routine. IbuMCC is significantly less compressible in the RC compared to the tableting machine. The compression profiles of IbuMannitol match in the range from...
60 to 130 MPa.

Fig. 5 shows the influence of the different compression profiles and compares predicted and observed ribbon solid fraction of IbuMCC obtained in the low throughput ($N_R = 1$ rpm) RC experiments. The initial values of $K$ (7.84) and $\gamma_0$ (0.5) estimated based on the uniaxial compression test resulted in over-prediction of the ribbon solid fraction using Johanson’s model (■). The iteration process described in the section above was performed to obtain the final values of $K$ and $\gamma_0$.

Since the screw speed was monitored during the experiment, the same process was repeated for Reynolds’ model (simulating the screw-controlled operation mode). The throughput measured in the RC experiments at a roller speed of 1 rpm was used to obtain the value of $\beta$ and $cS1$.

Table 5 presents the $K$ and $\gamma_0$ values obtained after the calibration routine for both models (Johanson and Reynolds) representing the two modes of operation: gap and screw controlled, respectively. In screw controlled mode, the two equations for calculating the screw constant are compared: $cS1$ from Eq. (16) and $cS2$ from Eq. (17). The compression profile of the IbuMCC formulation shows a large deviation from the uniaxial compression test (see Fig. 4), indicating different compression behavior of a blend when compacted by a uniaxial compression machine and a roller compactor. In the calculations for predicting the ribbon solid fraction and throughput, the values of $K$ and $\gamma_0$ from the iteration were used. The iteration relates the pressure in the roller gap to the solid fraction of the final ribbon, after relaxation. To offset this effect, the parameter $\gamma_0$, which is classically related to the pre-consolidation density, also changed during the iteration.

The section below presents the results of predicting the ribbon solid fraction and the throughput. The mean %Error was calculated to provide a parameter of the model’s accuracy as:

$$\text{%Error} = \left| \frac{Y_R_{\text{observed}} - Y_R_{\text{predicted}}}{Y_R_{\text{predicted}}} \right| \times 100\% \quad (19)$$

5.3. Predicting the ribbon solid fraction

Fig. 6 shows the predicted ribbon solid fraction plotted against the experimentally observed ribbon solid fraction for IbuMCC and IbuMannitol performed in gap-controlled mode, indicating that both
models predicted the ribbon solid fraction well. This was confirmed by a low-average error percentage of the ribbon solid fraction prediction stated in Table 6 (0.8–1.0% for both formulations, regardless of the model and the screw constant calculation).

5.4. Prediction of throughput

Fig. 7 shows the predicted throughput plotted over the experimentally observed throughput. An accurate throughput prediction was achieved in the gap-controlled mode. In the screw-controlled mode with screw constant $c_{S2}$ the throughput was lower than the observed one for every single data point.

The predictions in the screw-controlled mode with $c_{S1}$ were accurate at low-throughput data points (up to 10 kg/h). However, at higher predicted throughputs the corresponding observed value was lower. Table 7 shows that the average error percentage for $c_{S1}$ is much higher than the one for the throughput prediction in the gap-controlled mode.

Predictions for the screw-controlled mode using screw constant $c_{S1}$ are on average approximately 25% higher than those using $c_{S2}$ since the latter does not account for the ribbon relaxation and roller surface effects. Generally, the throughput prediction using screw constant $c_{S1}$ results in over-prediction, $c_{S2}$ to under-prediction at high throughputs (Fig. 7). The average error is smaller for screw constant $c_{S1}$.

A classical assumption is that the screw constant is independent from screw speed (Reynolds et al., 2010). To verify, the screw constant $c_{S1}$ has been calculated at different operating conditions with the experimentally observed throughput and screw speed (Eq. (17)). Fig. 8 shows that the screw constant $c_{S1}$ (Eq. (17)) changes as a function of screw speed. At high screw speeds, the amount of formulation that is transported by each rotation of the screw decreases due to at least one of the following phenomena: First, at high screw speeds the feeding of the screw from the hopper is less effective. Secondly, at high screw speeds there might be higher powder slippage on the screw surface, resulting in a lower transport efficiency.

A possible expansion to the model could incorporate the change of the screw constant with screw speed. The advantage would be an improved predictability at high throughputs. However, the cost is one additional experiment at high throughput in order to calibrate the behavior of the screw constant at high screw speeds.

### Table 6

| Run # | IbuMCC | IbuMannitol |
|-------|--------|-------------|
|       | Obs. $\gamma_R$ | Gap | Screw $c_{S1}$ | Screw $c_{S2}$ | Obs. $\gamma_R$ | Gap | Screw $c_{S1}$ | Screw $c_{S2}$ |
| 1*    | 0.692 | 0.687 | 0.684 | 0.684 | 0.860 | 0.848 | 0.843 | 0.845 |
| 2     | 0.679 | 0.688 | 0.679 | 0.680 | 0.855 | 0.849 | 0.843 | 0.844 |
| 3*    | 0.646 | 0.651 | 0.651 | 0.651 | 0.808 | 0.816 | 0.818 | 0.819 |
| 4     | 0.648 | 0.651 | 0.643 | 0.642 | 0.825 | 0.816 | 0.813 | 0.813 |
| 5*    | 0.796 | 0.803 | 0.800 | 0.800 | 0.913 | 0.918 | 0.916 | 0.917 |
| 6     | 0.793 | 0.803 | 0.795 | 0.795 | 0.903 | 0.918 | 0.908 | 0.909 |
| 7*    | 0.767 | 0.759 | 0.762 | 0.762 | 0.882 | 0.882 | 0.885 | 0.884 |
| 8     | 0.774 | 0.760 | 0.757 | 0.755 | 0.886 | 0.881 | 0.878 | 0.877 |
| 9     | 0.736 | 0.732 | 0.728 | 0.728 | 0.861 | 0.866 | 0.863 | 0.863 |
| 10    | 0.726 | 0.732 | 0.728 | 0.728 | 0.871 | 0.866 | 0.863 | 0.863 |
| 11    | 0.736 | 0.732 | 0.728 | 0.728 | 0.849 | 0.866 | 0.863 | 0.863 |
| Mean %Error | 0.9 | 0.8 | 0.9 | 0.9 | 1.0 | 1.0 |

Fig. 7. Prediction of throughput for the IbuMCC and IbuMannitol formulations in the gap-controlled model with relaxation factor $\beta$ (■) and the screw-controlled model with either $c_{S1}$ (△) or $c_{S2}$ (○).
Table 7

| Run # | IbuMCC     |           | IbuMannitol |           |
|-------|------------|-----------|-------------|-----------|
|       | Observed Throughput | Gap | Screw cS1 | Screw cS2 | Observed Throughput | Gap | Screw cS1 | Screw cS2 |
| 1*    | 2.77       | 2.61      | 2.67        | 2.14      | 3.31           | 3.99      | 3.37        | 2.77       |
| 2     | 8.54       | 7.85      | 8.70        | 6.97      | 10.06          | 9.28      | 10.45       | 8.58       |
| 3*    | 4.87       | 4.95      | 4.82        | 3.86      | 5.72           | 5.94      | 5.68        | 4.66       |
| 4     | 14.38      | 14.86     | 17.17       | 13.75     | 17.42          | 17.81     | 19.54       | 16.04      |
| 5*    | 3.07       | 3.06      | 3.28        | 2.62      | 3.73           | 3.34      | 3.54        | 2.91       |
| 6     | 9.81       | 9.16      | 10.61       | 8.49      | 10.50          | 10.02     | 12.04       | 9.88       |
| 7*    | 5.79       | 5.78      | 5.83        | 4.67      | 6.27           | 6.42      | 6.38        | 5.24       |
| 8     | 17.28      | 17.34     | 19.07       | 15.27     | 19.12          | 19.25     | 22.25       | 18.26      |
| 9     | 8.32       | 8.34      | 8.95        | 7.17      | 9.69           | 9.46      | 10.35       | 8.52       |
| 10    | 8.40       | 8.34      | 8.95        | 7.17      | 9.42           | 9.46      | 10.35       | 8.52       |
| 11    | 8.57       | 8.34      | 8.95        | 7.17      | 9.72           | 9.46      | 10.35       | 8.52       |
| av. % Error | 2.8     | 6.2   | 15.7        |           | 4.0           | 7.1       | 12.9        |           |

5.5. Design space prediction

In this section, multiple linear regression (MLR) was used to obtain the design space for both formulations. The design space obtained experimentally was then compared to the predicted one in the gap-controlled mode.

Fig. 9 shows the scaled and centered coefficient plots of the solid fraction response for both formulations. The factor interactions were insignificant and were excluded from Fig. 9 and from the final model. The coefficient plots for both formulations show that the roller speed factor is small and insignificant in terms of predicting the solid fraction in both formulations. As such, it was excluded from the final model. The confidence intervals of the coefficients for simulated data are narrower compared to experimental data. When evaluating the experimental data, there are two effects that might increase the confidence interval: (1) the experimental error which is evaluated from the triplicate center point and (2) the deviation from the experimental data points from the regression surface. The results from the model are perfectly reproducible, and thus the confidence intervals only describe the deviation between results and regression surface (2). The coefficients obtained using the data from the simulated DoE are very close to those obtained using the experimental values.

Fig. 10 shows the scaled and centered coefficients of the throughput prediction. The factor interactions were found to be insignificant and are not shown here. Since the roller force was found to be statistically insignificant for both formulations, it was removed and the model was refitted. This result is somewhat unexpected since the SCF is the main parameter that affects the ribbon density which is used for the throughput prediction in Eq. (10).

The regression analysis parameters goodness of fit (R^2) and goodness of prediction (Q^2) are listed in Table 8. The regression models for the solid fraction response were especially well-fitted with the simulated data, with R^2 and Q^2 being > 0.995 for both formulations. The regression models for the throughput response showed a very similar quality of fit, with Q^2 and R^2 being practically the same in all DoEs. Thus, the regression model is a good approximation for arbitrary operating points within the design space and using the regression model is thus expected to be small. The RSD in the analysis of variance (ANOVA) at a 95% confidence level is shown in Table 8.

The proposed regression models can be used to predict design space for the desired ribbon solid fraction and throughput. Fig. 11 provides a visual comparison between the simulated and experimental design space, showing the region of operability (or sweet spot) that IbuMCC requires for obtaining a target ribbon solid fraction of 0.725 (min = 0.700, max = 0.750) and a throughput of 10 kg/h (min = 9 kg/h, max = 11 kg/h). The target solid fraction of 0.725 has been chosen as compromise between ribbon strength (high solid fractions preferred) and tabletability of the granules (low levels of pre-compaction preferred). The target throughput of 10 kg/h is the throughput of the complete continuous production line and variations between the different unit operations have to be minimized.

Fig. 11 indicates that the design spaces obtained based on the simulated and experimental DoEs are very similar. This offers a considerable reduction of experimental efforts and material consumption related to spot-checking the sweet spot in the center and along the extremes. The sweet spot analysis for the IbuMannitol formulation provides a similarly good prediction, because the correlation coefficients match between simulation and experiment (Fig. 9 for ribbon density, Fig. 10 for throughput).

Robustness of dry granulation process is a key element in process validation that should be ensured within the drug product development stage. The presented approach has the value of providing in-silico validation that should be ensured within the drug product development stage.
design spaces allowing a robustness simulation based on mechanistic modeling using limited number of real experiments. Additionally, the key input to this model can be communicated directly from the RC to predict the solid fraction of the ribbon being produced in real-time. This will eventually enable the application of RC model as a soft sensor in the strive towards robust and reliable RC processes, ensuring high quality product and increased economic profit.

6. Conclusion

In practice, RC mechanistic models are highly sensitive to the compressibility factor ($K$) and the pre-consolidation density ($\gamma_0$). Characterizing these properties in tableting machines delivers inaccurate results. The exact compression profile of the formulation depends on the equipment used. This is reflected by different $K$ and $\gamma_0$ values.

Table 8
Quality parameters of regression for simulated and experimental data for both formulations: goodness of fit $R^2$, goodness of prediction $Q^2$ and standard deviation of residuals (RSD).

|                | Solid fraction | Throughput |
|----------------|----------------|------------|
|                | IbuMCC         | IbuMannitol| IbuMCC       | IbuMannitol   |
|                | Exp.           | Sim.       | Exp.         | Sim.          |
| $R^2$          | 0.985          | 0.997      | 0.930        | 1.000         |
| $Q^2$          | 0.972          | 0.995      | 0.872        | 0.999         |
| RSD            | 7.4x10^{-3}    | 3.2x10^{-3}| 9.2x10^{-3}  | 7.6x10^{-4}   |
|                | Exp.           | Sim.       | Exp.         | Sim.          |
| $R^2$          | 0.958          | 0.957      | 0.968        | 0.968         |
| $Q^2$          | 0.924          | 0.923      | 0.945        | 0.950         |
| RSD            | 5.7x10^{-2}    | 5.8x10^{-2}| 4.8x10^{-2}  | 5.0x10^{-2}   |

Fig. 9. Scaled and centered coefficients for ribbon solid fraction for the IbuMCC and IbuMannitol formulations using experimental and simulated data. $N = 11$.

Fig. 10. Scaled and centered coefficients for throughput for the IbuMCC and IbuMannitol formulations using experimental and simulated data. $N = 11$. 

Table 8 Quality parameters of regression for simulated and experimental data for both formulations: goodness of fit $R^2$, goodness of prediction $Q^2$ and standard deviation of residuals (RSD).
values for the same formulation in different equipment types, resulting in additional trials and formulation consumption. Thus, in this work, we introduced a roadmap to the RC process development and scale-up on the same equipment. The key is an iteration process for calibrating the $K$ and $\gamma_0$ values, which can reduce the material amount required, the number of RC experiments and the material characterization efforts at a low software expense.

Additionally, we proposed a simple method that uses the RC throughput to calculate the volume relaxation that the ribbon experiences after exiting the rollers. This parameter ($\beta$) can be used to predict the throughput with an acceptable accuracy.

We demonstrated that, based on a limited number of experiments, a design space for a broad range of throughputs can be predicted with a high accuracy. It may be used in the future as a soft sensor for RC processes operating in continuous manufacturing lines for in-line adjustment of throughput while maintaining the desired ribbon solid fraction. In order to calibrate the model for a new material in gap-controlled mode, it is necessary to perform the calibration routine to extract the compression profile $K$, $\gamma_0$ and the relaxation factor $\beta$. Then it is possible to reliably predict the ribbon density with Eq. (9) and the throughput with Eq. (14). With a better prediction of the ribbon density and throughput, the process can be controlled better.

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Fig. 11. Graphical exploration around the optimal point ($\gamma_R=0.725$; $m_{obs}=10$ kg/h) comparing the MLR model based on the experimental data with the MLR model based on the simulated data for IbuMCC. The four experimental data points used to calibrate the mechanistic model are marked ●.
Update

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Erratum regarding missing Conflict of Interest statements in previously published articles

Declaration of Competing Interest statements were not included in published version of the following articles that appeared in previous issues of *International Journal of Pharmaceutics: X*. Hence, the authors of the below articles were contacted after publication to request a Declaration of Interest statement:

“Preparation and Characterization of Alendronate Depot Microspheres Based on Novel Poly(-ε-caprolactone)/Vitamin E TPGS Copolymers” [International Journal of Pharmaceutics: X 1 (2019) 100014] doi: https://doi.org/10.1016/j.ijpx.2019.100014

“Model-based approach to the design of pharmaceutical roller-compaction processes” [International Journal of Pharmaceutics: X 1 (2019) 100005] doi: https://doi.org/10.1016/j.ijpx.2019.100005

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