Powder Technology 434 (2024) 119369

Contents lists available at ScienceDirect

Powder Technology

journal homepage: www.journals.elsevier.com/powder-technology

Advancing tablet lubrication: A systematic comparison of feed frame lubrication and internal lubrication

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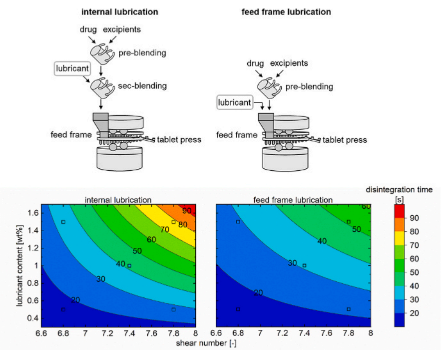
HIGHLIGHTS

- Inherent blending capacity of feed frame sufficient for lubricant blending.
- Novel lubrication type based on feed frame blending capacity.
- Feed frame lubrication features tablets with increased quality.
- Decreased surface coverage leads to harder and faster disintegrating tablets.
- Process chain reduced by second blending step.

GRAPHICAL ABSTRACT



ARTICLE INFO

Keywords:
Tableting
Compaction
Lubrication
Rotary press
Powder compression

ABSTRACT

For the continuous manufacturing of tablets, internal lubrication is often utilized. Here, lubricant is added to a pre-blend in an additional blending step. However, over-lubrication may occur, with a negative impact on the tablet quality. This study consequently focuses on the systematic comparison of internal lubrication to an alternative, named feed frame lubrication. This method represents a new lubrication type, where the lubricant is fed into the feed frame without prior blending.

A design of experiments with shear number and lubricant content as factors was used. Target properties were tensile strength, disintegration time and contact angle. Based on the data, multiple linear regression models were created and optimized using backward stepwise regression.

Feed frame lubrication exhibited similar or even improved tablet properties compared to internal lubrication. The tablets turned out to be harder with decreased disintegration times. Finally, feed frame lubrication reduces the need for an additional blending step.

1. Introduction

In the pharmaceutical industry, a current strategy for optimizing drug product quality is the implementation of continuous manufacturing methods. This is associated with higher effectiveness due to processing in a dynamic steady state. Additional benefits in comparison to batch manufacturing are simplified adjustment of the production scale just by the run-time, reduction of the plant footprint and

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https://doi.org/10.1016/j.powtec.2024.119369
Received 30 September 2023; Received in revised form 24 December 2023; Accepted 2 January 2024

increased flexibility overall [1–3].

In this context, continuous tablet production is of particular importance, as tablets represent the most common oral dosage form [4]. Production is mainly carried out with rotary tablet presses. The process can be divided into five sub-processes: powder feeding, blending, filling, compression (pre- and main-compression) and ejection. In the first step, the powders are typically fed via loss-in-weight feeders into a blender followed by a hopper. This machine part is usually conical and eccentric to provide sufficient flow, and it is mounted to the feed frame, the internal filling system [5]. Here, the powder is transported in the dies, while the die table and punches rotate simultaneously. Afterwards, compression force is applied to the material via the punches. Finally, the tablets are ejected and collected.

With respect to the processing conditions in tableting, the die filling process has faced enhanced research interest over the last decade. This includes the corresponding critical process parameters and the influence of feed frame settings on material parameters [6]. In this context, a higher feed frame speed leads to higher shear stress in the powder [7]. In accordance with this, an altered particle size distribution after passage of the feed frame was found [8]. A numerical analysis of the die-filling process enables the estimation of the applied forces on the particle, as well as the residence time distribution (RTD) of the material [9]. In this way the influence of various aspects on the RTD in the feed frame and tablet press was determined, including the geometric and parametric setup, feed frame component and powder property variations. Furthermore, a significant decrease of the mean residence time at higher feed frame speeds, and narrower RTDs at slower feed frame speeds, were shown. Thus, a higher residence time width implies a higher blending capacity [10–13]. The resulting blending capacity is sufficient to homogenously distribute the active pharmaceutical ingredient (API) in the powder [14]. Furthermore, the feed frame blending capacity also depends on the powder flow [15].

Blending of the material is especially relevant with respect to tablet formulation and the use of lubricants. These excipients are utilized to enable higher tableting speeds by reducing the interfacial friction and the wall friction [16]. Most frequently used are metallic salts of fatty acids like magnesium stearate [17,18]. These substances are characterized by a comparatively low shear interface. For tableting, boundary lubrication is particularly preferred because it is characterized by a strong bond to the surface [19]. In this process, the lubricant covers the bulk particles, which shear slightly during tangential motion, and reduces internal powder friction [20]. However, two relevant types of lubrication can be distinguished based on processing, namely internal and external lubrication [21].

With internal lubrication, the lubricant is part of the powder formulation. APIs and excipients are pre-blended in a first step. Then the lubricant is added, and a second blending is performed [22]. Here, the process intensity in combination with the lubricant weight fraction affects the final tablet quality. An inadequate blending time with high shear stress input and an excessive amount of lubricant decreases the tablet hardness [7,23] and increases the disintegration and dissolution time [24,25]. This effect is known as over-lubrication. In this situation, there is high surface coverage of lubricant on the powder particles, which acts as a physical barrier and reduces bonding forces [26]. Since the lubricants are mostly hydrophobic, the disintegration and dissolution time are also negatively affected. However, the magnitude of this effect depends on the applied shear forces and amount of lubricant [27–32].

In the case of external lubrication, the lubricant is not part of the powder formulation. Instead, this method involves the modification of the punches and dies, or the external application of lubricant via spray nozzles. This results in a reduction in the amount of lubricant in the tablet, thereby reducing its negative effect on tablet properties. However, uniformity problems may occur, and an additional lubrication device is required. [33–36]

The aim of this study is to develop an alternative lubrication method. Here, the lubricant is directly fed into the feed frame of the rotary tablet press without any pre-blending of lubricant and other excipients. This utilizes the inherent blending capacity of the feeding process. Thus, the need for a second blending step and the associated equipment is not needed. Consequently, the shear input is decreased and blending is achieved more gently with less risk of over-lubrication. This method is referred to as feed frame lubrication, and was systematically compared to internal lubrication with a focus on the tablet properties. The design space included variations of feed frame speed and lubricant content. Target properties are tensile strength, disintegration time and contact angle. The two different lubrication types are evaluated separately due to their blending characteristics. For this purpose, a backwards stepwise regression was performed.

2. Materials and methods

2.1. Material

The powder formulation consists of 59.7 wt% lactose monohydrate (Lactose Monohydrate 310, Foremost Farms USA, Baraboo, USA), 29.8 wt% microcrystalline cellulose (Emcocel 90 M, JRS Pharma, Rosenberg, Germany) (MCC), 10 wt% theophylline monohydrate (Theophylline monohydrate, Thermo Fisher Scientific, Waltham, USA) and 0.5 wt% magnesium stearate (Ligamed MF-2-V, Peter Greven, Bad Münstereifel, Germany) as lubricant. Higher amounts of magnesium stearate (1 and 1.5 wt%) were realized by reducing the lactose content.

2.2. Tablet preparation

Lactose, MCC and theophylline were pre-blended in a 3D shaker mixer (Turbula, Willy A. Bachofen AG, Muttenz, Switzerland) with a 20 l blending volume for 10 min at 32 rpm. For internal lubrication, a second blending step was performed for 1.5 min after adding the lubricant. Tableting was executed on a rotary tablet press (102i, Fette Compacting, Schwarzenbek, Germany) with 10 kN of main compression force and 50,000 tablets per hour throughput. Here, the compression force was kept constant by adjusting the compression parameters. The tablet press was fitted with 24 pairs of EU 19 punches with an 8 mm diameter for biconvex tablets. Tablet weight was set to 260 mg. The powder was dosed into the hopper of the feed frame using a gravimetric twin-screw feeder (KT-20, Cooperion, Niederlenz, Switzerland), while the filling level in the feed frame was monitored using a centimeter scale, with the objective of maintaining a consistent residence time within the feed frame. For filling the dies with powder, the rotary tablet press was equipped with a three-chamber feed frame (FOM, Fette Compacting, Schwarzenbek, Germany) with round spokes paddle wheels and operated at 40, 80 or 120 rpm.

2.3. Design of Experiments

The experiments were performed based on a Design of Experiments (DoE) and assessed via variance analyses (MODDE 10, Sartorius, Göttingen, Germany). In accordance with this, screening experiments with a full factorial design were performed using multiple linear regression (MLR) at a significance level of $\alpha = 0.05$. The centre point was performed three times. Feed frame speed and lubricant content were investigated as factors (Table 1). The set points based on the design space of this DoE were executed for both investigated lubrication methods. Responses were tensile strength, disintegration time and the

Table 1

Experimental design space for internal lubrication and feed frame lubrication.

	−1	0	+1
Shear number [−]	6.8	7.4	7.8
Lubricant content [wt%]	0.5	1	1.5

contact angle with water.

2.4. Shear number

The total shear applied to the powder formulation by the moving feed frame paddle wheels and the stationary walls was calculated according to Narang et al. [23]. Whereby the total shear was estimated in terms of a shear number (S_N), which is a function of shear rate (SR), shear frequency (SF) and residence time (RT) (Eq. (1)).

$$S_N = f\{SR\ x\ SF\ x\ RT\} \tag{1}$$

Furthermore, an empirical equation was derived to obtain the dimensionless shear number (Eq. (2)).

$$S_N = \left(\frac{\pi d_s n}{c}\right)(kn)\left(\frac{m}{wsn'}\right)^2 \tag{2}$$

Within the shear number, the diameter of the spokes of the feed frame wheels (d_s), the feed frame speed (n), the clearance between spokes and base (c), the number of spokes (k), the mass of powder in feeder during equilibrium operation (m), the tablet weight (w), the speed of turret (s) and the number of punches (n') are considered. Accordingly, the shear number is the mechanical stress over a certain period of time. However, the residence time is constant as all variables were kept constant during the experiments, except for the feed frame speed. This results in a direct correlation between feed frame speed and shear number. This model was chosen due to the insufficient availability of models to describe particle systems, even if the properties are transferred from a fluid to the particle system. Nevertheless, this model provides information about the shear in the feed frame and by using the shear number, a dimensionless consideration of the shear enables the transfer of the method to other feed frames.

2.5. Porosity

The tablet porosity (ε) (Eq. (3)) was calculated by relating the tablet density (ρ_t) obtained by geometry and weight measurements (ST50, Sotax, Aesch, Switzerland) with the solid density (ρ_s) obtained by helium pycnometry measurements according to European Pharmacopoeia 11 (chapter 2.9.23).

$$\varepsilon = \left(1 - \frac{\rho_t}{\rho_s}\right)*100 \tag{3}$$

2.6. Tensile strength

For each set point, 20 tablets were randomly chosen as a representative sample, and analysis of hardness, diameter, height and weight were performed with a diametrical compression test (ST50, Sotax, Aesch, Switzerland). The tensile strength was calculated according to United States Pharmacopoeia 351,217 (Eq. (4)), whereby the extended version for convex-faced tablets based on the equation for flat-faced tablets was used [37,38]. Within the tensile strength (σ_{TS}), breaking force (*F*), tablet diameter (*d*), tablet thickness (*h*), and central cylinder thickness (*t*) are considered.

$$\sigma_{TS} = \left(\frac{10F}{\pi d^2}\right)\left[\left(\frac{2.84h}{d}\right) - \left(\frac{0.126h}{t}\right) + \left(\frac{3.15t}{d}\right) + 0.01\right]^{-1} \tag{4}$$

2.7. Disintegration time

Disintegration times were evaluated according to the European Pharmacopoeia 11 (chapter 2.9.1) with apparatus A (DisiTest50 Master, Sotax, Aesch, Switzerland) [39]. For each lubrication method, six randomly chosen tablets were investigated, and the time until the tablets disintegrated without leaving any residue in 1 l water at 37 ± 2 °C was measured.

2.8. Contact angle

The wettability of the tablet surface was characterized by the contact angle (θ). Here, water was used as the liquid for determination [40]. The sessile drop method was applied according to European Pharmacopoeia 11 (chapter 2.9.45) and the contact angle was determined with an optical contact angle meter (OCA 15EC, DataPhysics Instruments, Filderstadt, Germany) [39].

2.9. Ejection force

The ejection force was recorded for one minute during sampling in the steady state and the average value was calculated accordingly.

3. Results and discussion

3.1. Concept of feed frame lubrication

The concept of feed frame lubrication (Fig. 1) follows the findings of Zimmermann et al. regarding the blending capacity of the tablet press feed frame [14]. Drug and excipients (microcrystalline cellulose and lactose) are initially blended. Afterwards, this pre-blend and the lubricant are fed separately into the feed frame hopper at a constant mass flow (Fig. 1). For this purpose, a twin-screw feeder (KT-20, Cooperion, Niederlenz, Switzerland) and a micro-screw feeder (MT-12, Cooperion, Niederlenz, Switzerland) were used depending on the required mass flow. This is the main difference from the method of internal lubrication, where a second blending of the components is needed.

In both cases, the powder is fed into the three-chamber feed frame (Fig. 2). Each chamber consists of a paddle wheel. Here the powder from the hopper flows into the chamber of the distribution wheel, which then conveys the powder to the filling and dosing chamber. The filling paddle wheel overfills the dies. Afterwards, excess powder is ejected by an upward movement of the lower punch. This is removed by the dosing wheel before reaching the scraper and is conveyed back into the feed frame. The powder circulates in the feed frame and is further blended in this way [12,14].

3.2. Performance of feed frame lubrication

The performance of the feed frame lubrication was compared with internal lubrication using model coefficients. With respect to the study design, the coefficients represent the feed frame speed in terms of shear number, lubricant content and the combination term of these. A backward stepwise regression was performed to optimize the model (Eq. (5)) [41].

$$Y = \beta_0 + \beta_{S_N} x_{S_N} + \beta_{lub} x_{lub} + \beta_{S_N*lub} x_{S_N} x_{lub} \tag{5}$$

Y represents the responses (tensile strength, disintegration time and contact angle). The shear number is given by factors x_{S_N} and the lubricant content by x_{lub}. The regression coefficients are given by the term β. Since internal lubrication and feed frame lubrication were expected to exhibit differences in blending characteristics, separate parameters were derived and compared (Table 2).

Coefficient of determination (R^2), coefficient of prediction Q^2, lack of fit (p-value) and reproducibility were considered for model quality evaluation. For both lubrication methods, quality was sufficient for investigated responses according to [41]. Contour plots (Fig. 3–5) resulting from the model were utilized to investigate the influence of feed frame speed in terms of shear number and lubricant content on the target property, respectively. (Table 3).

3.3. Tensile strength

Significant coefficients for both lubrication types in terms of tensile

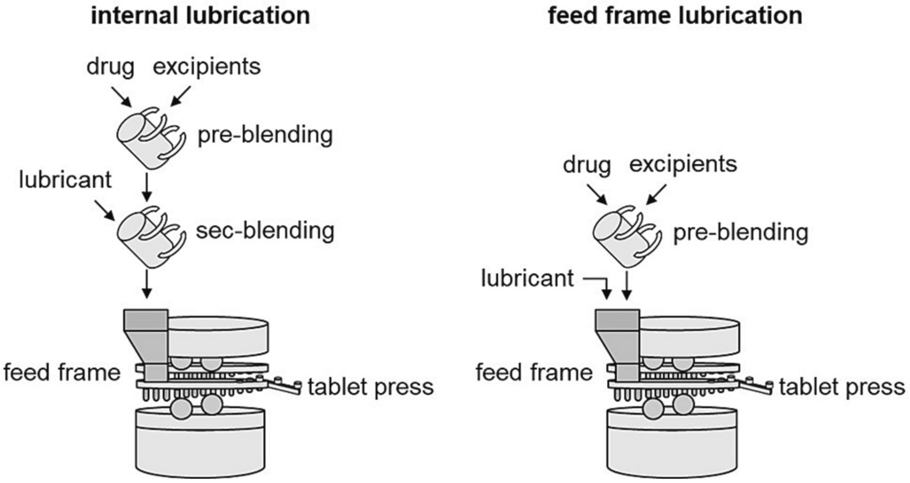

Fig. 1. Schematic illustration of internal lubrication (left) with pre- and second-blending (sec-blending) and feed frame lubrication (right) with pre-blending.

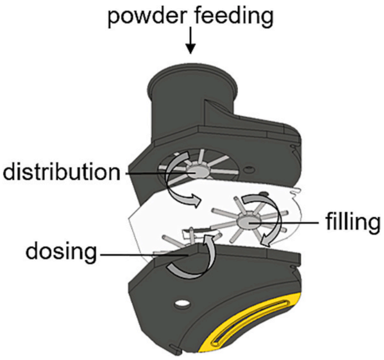

Fig. 2. Schematic illustration of the feed frame with distribution chamber, filling chamber and dosing chamber.

strength were shear number and lubricant content. The interaction term was not significant and consequently was removed in the course of backward stepwise regression (Table 3). With increasing shear number, the tensile strength decreases for both lubrication types (Fig. 3). The same effect is related to an enhanced lubricant content, which corresponds to the negative model coefficients. These are quite similar for both lubrication types. The coefficients for feed frame lubrication imply a higher sensitivity (S_N -0.17 ± 0.05) for changes in shear number than those for internal lubrication (S_N -0.07 ± 0.04). Apparently, in feed frame lubrication, the particles are less covered with lubricant (higher tensile strength), while the feed frame speed in terms of shear number influences the degree of lubrication, leading to higher differences in tensile strength. Under equal process parameters, feed frame lubrication results in harder tablets (0.92 ± 0.02 MPa) than internal lubrication (0.76 ± 0.02 MPa) for the centre point experiments. This agrees with expectations, since feed frame lubrication avoids a second blending phase, in which high shear forces are applied to the particles by rapid inversion and tumbling of the powder bed. This may lead to surface coverage of particles with lubricant. According to the literature, a reduction of the cohesive forces occurs, since existing bond valences are no longer available for the formation between particles. This leads to a decrease in tensile strength with increasing lubricant content and feed frame speed [26,42]. The influence of the porosity on the tensile strength can be excluded here, as the porosities do not vary significantly (porosity feed frame lubrication 12.19 ± 0.41%; porosity internal lubrication 12.21 ± 0.47%).

3.4. *Disintegration time*

For internal lubrication as well as feed frame lubrication, both the higher lubricant content and the higher shear number enhance the disintegration time (Table 3). These effects are related to the surface coverage as described previously. The hydrophobic lubricant consequently forms a physical barrier around the particles, which needs to be overcome in order to come into contact with water and dissolve. This leads to an increase in the disintegration time [24,25]. As described in 3.3, the influence of porosity on the disintegration time can also be excluded here, as these do not differ. Furthermore, a strong interaction of both process variables was recognized, which is attributed to the process of surface coverage with lubricant. For a high lubricant content, less shear energy input by the applied feed frame speed in terms of shear number is required in order to obtain a high particle surface coverage leading to higher disintegration times. For a low lubricant content, more shear energy input is necessary to result in similar surface coverage and disintegration time. Thereby, internal lubrication in general tends toward higher disintegration times compared to feed frame lubrication, especially using high lubrication content and/or shear number (Fig. 4). This leads to a more robust process for feed frame lubrication, since factor changes tend to have less influence on the disintegration time. It is likely, that a high degree of lubrication is already generated in the second blending during internal lubrication (Fig. 1).

Table 2
Power of model for internal lubrication and feed frame lubrication after backwards stepwise regression with coefficient of determination (R^2), coefficient of prediction (Q^2), lack of fit (*p*-value) and reproducibility for the investigated responses tensile strength, disintegration time and contact angle.

	Internal lubrication			Feed frame lubrication		
	Tensile strength	Disintegration time	Contact angle	Tensile strength	Disintegration time	Contact angle
R^2	0.97	0.99	0.92	0.98	1.00	0.98
Q^2	0.88	0.56	0.83	0.86	1.00	0.88
p-value	1.83*10–7	9.82*10–5	1.74*10–7	1.88*10–7	2.59*10–6	2.15*10–7
reproducibility	0.97	0.99	0.93	0.99	0.99	1.00

Table 3

Model equations and shear number (S_N), lubricant content (lub) and combination term (S_N*lub) as scaled and centered coefficients (β) with confidence intervals for tensile strength, disintegration time and contact angle as responses for internal and feed frame lubrication.

Internal lubrication

	Model equation	β_{S_N}	β_{lub}	β_{S_N*lub}
tensile strength [MPa]	$Y = \beta_0 + \beta_{S_N}x_{S_N} + \beta_{lub}x_{lub}$	−0.07 ± 0.04	−0.14 ± 0.04	/
disintegration time [s]	$Y = \beta_0 + \beta_{S_N}x_{S_N} + \beta_{lub}x_{lub} + \beta_{S_N*lub}x_{S_N}x_{lub}$	13.69 ± 4.59	17.00 ± 4.59	8.5 ± 4.59
contact angle [°]	$Y = \beta_0 + \beta_{lub}x_{lub}$	/	12.03 ± 4.04	/

Feed frame lubrication

	Model equation	β_{S_N}	β_{lub}	β_{S_N*lub}
tensile strength [MPa]	$Y = \beta_0 + \beta_{S_N}x_{S_N} + \beta_{lub}x_{lub}$	−0.17 ± 0.05	−0.15 ± 0.05	/
disintegration time [s]	$Y = \beta_0 + \beta_{S_N}x_{S_N} + \beta_{lub}x_{lub} + \beta_{S_N*lub}x_{S_N}x_{lub}$	7.01 ± 1.30	10.50 ± 1.30	4.0 ± 1.30
contact angle [°]	$Y = \beta_0 + \beta_{S_N}x_{S_N} + \beta_{lub}x_{lub}$	2.36 ± 2.23	9.78 ± 2.23	/

3.5. Contact angle

Contact angle measurements were performed to quantify the degree of surface coverage with lubricant in order to interpret the impact of lubricant content, feed frame speed in terms of shear number and type of lubrication on the tensile strength and disintegration time. Thus, pure magnesium stearate and the powder formulation without magnesium stearate were analysed individually with respect to the contact angle. For this purpose, single punch compression was carried out for pure magnesium stearate and powder formulation without magnesium stearate on a Fette 102i rotary tablet press. Here, the tablets were manufactured using the same compression and test conditions as the DoE test points. Values of about 130° for pure magnesium stearate and 20° for the unlubricated powder formulation were observed. The measured contact angles for the tablet formulations were within this range with an increase of the lubrication content leading to higher contact angles. This was attributed to an enhanced fraction of magnesium stearate at the surface (Fig. 5). Overall, lower contact angles were determined for feed frame lubrication, which is consistent with tensile strength and disintegration time data. At the centre point experiments, the contact angle is 46.90 ± 2.71° for internal lubrication and 43.70 ± 0.45° for feed frame lubrication. A reduction of the contact angles corresponds to an increase of the shear number, with the more intensive blending resulting in an enhanced surface coverage with magnesium stearate. This effect is not considered for internal lubrication in the model, which was related to the not significant slope and model optimization in terms of the backwards regression. Nevertheless, the measured values of the DoE imply an impact of feed frame speed for internal lubrication. The absolute values in terms of contact angles indicate a higher surface coverage with magnesium stearate for the powder formulation.

3.6. Ejection force

The maximum ejection force possible with this rotary tablet press is 2000 N. All the ejection forces achieved are significantly below this limit, reaching a maximum of 13% of it. In general, higher ejection forces are obtained with feed frame lubrication than with internal lubrication. On average, the ejection forces are 11% higher. For internal lubrication, the ejection force reaches values of up to 243.3 N and for feed frame lubrication up to 257.8 N. It can be further observed that lubricant content and feed frame speed in terms of shear number are not significant factors, with p-values above 0.05. These results are consistent with those previously obtained from the tensile strength, disintegration time and contact angle studies. The extent of surface coverage with lubricant is comparatively lower in tablets produced by feed frame lubrication than in tablets produced by internal lubrication. This increases the friction within the system, resulting in an increased ejection force. However, the lubrication and associated reduction in ejection force is sufficient for feed frame lubrication.

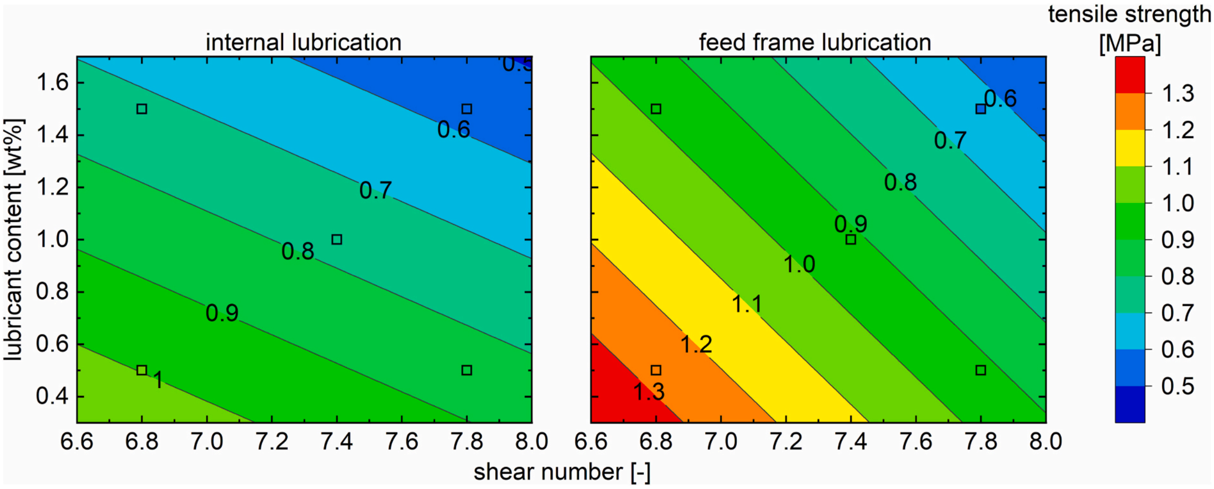

Fig. 3. Contour plots of tensile strength as a function of shear number and lubricant content for internal lubrication (left) and feed frame lubrication (right). 20 tablets were randomly chosen for each DoE set point.

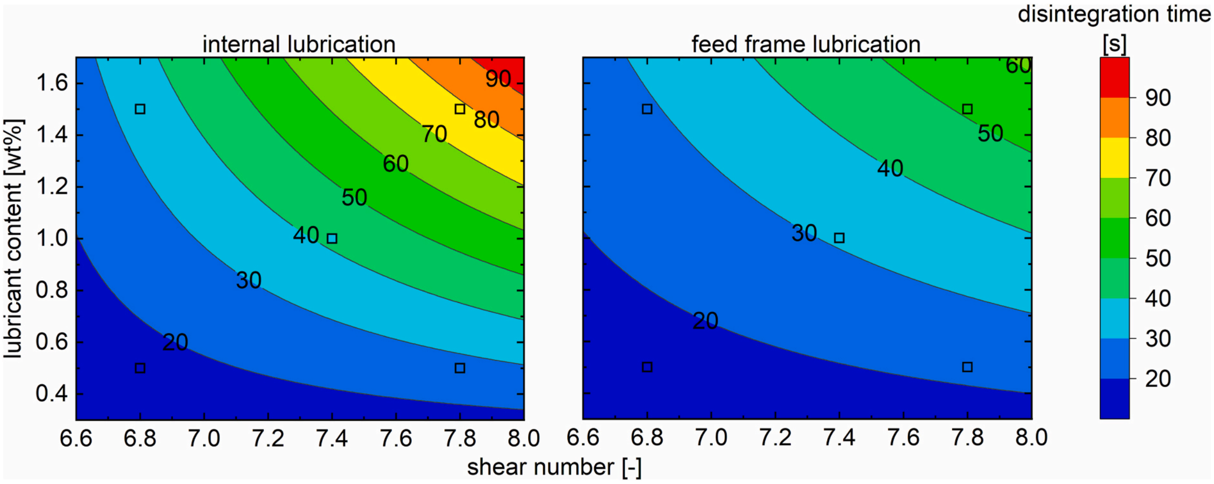

Fig. 4. Contour plots of disintegration time as function of shear number and lubricant content for internal lubrication (left) and feed frame lubrication (right). Six tablets were analysed for each DoE set point.

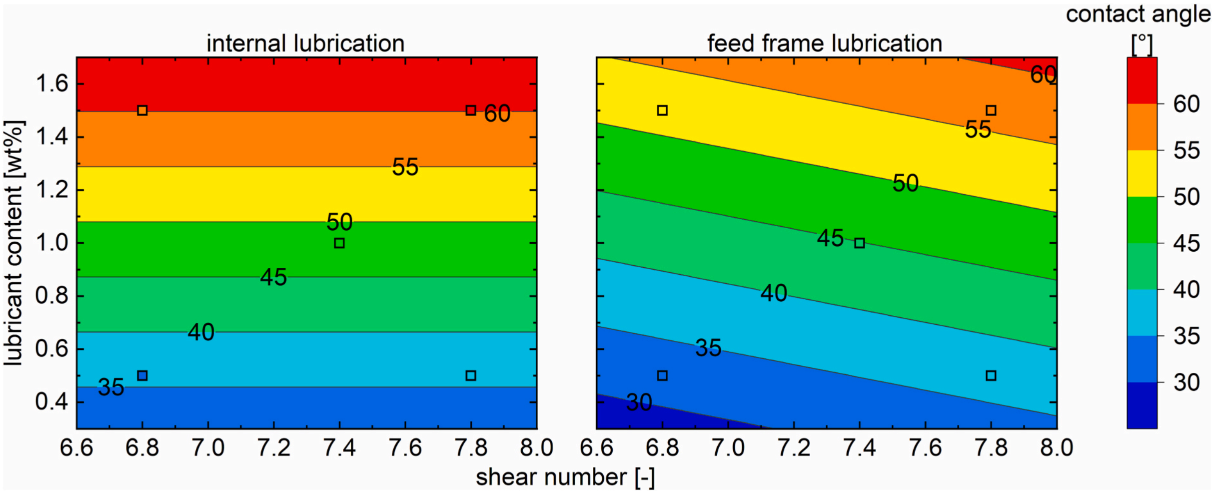

Fig. 5. Contour plots obtained by plotting contact angle of water as function of shear number and lubricant content for internal lubrication (left), feed frame lubrication (right). A sample of six tablets was tested for each set point of the DoE.

4. Conclusion

In this study, a new method for lubrication in powder compression on rotary tablet presses, referred to as feed frame lubrication, was developed. In this method, the inherent blending capacity of the feed frame was utilized to replace an additional powder blending step.

Then feed frame lubrication was systematically compared to internal lubrication with respect to tablet quality properties including tensile strength, disintegration time and contact angle. For this, a parameter study on lubricant content and feed frame speed in terms of shear number was performed and evaluated via variance analysis. Overall, feed frame lubrication resulted in tablets with less lubricant impact. The evaluated tablets were harder and showed shorter disintegration times compared to those manufactured using the internal lubrication process. Additionally, feed frame lubrication exhibited lower contact angles compared to internal lubrication. However, the achieved ejection forces are sufficient for both lubrication types.

In conclusion, the blending capacity in the feed frame is sufficient to disperse the lubricant and reduces the risk of over-lubrication. Furthermore, feed frame lubrication reduces the need for an additional blending step.

List of symbols

c	clearance between spokes and base [cm]
d	tablet diameter [m]
d_s	spokes diameter [cm]
F	breaking force [N]
h	tablet thickness [m]
k	number of spokes [−]
m	mass of powder in feed frame [g]
n′	number of punches [−]
n	feed frame speed [rpm]
s	turret speed [rpm]
t	central wall thickness [m]
TS	tensile strength [Pa]
w	tablet weight [g]
ε	tablet porosity [%]
ρ_t	tablet density [g/cm^3]
ρ_s	solid density [g/cm^3]

Funding

The work was supported by the German Research Foundation [Grant SPP2364].

CRediT authorship contribution statement

René Brands: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Christopher Mathias:** Methodology, Investigation. **Jens Bartsch:** Writing – review & editing, Supervision, Conceptualization. **Markus Thommes:** Writing – review & editing, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare no conflict of interest.

Data availability

Research data is linked as CSV

Acknowledgments

The authors thank Merck for providing lactose and Peter Greven for providing magnesium stearate.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.powtec.2024.119369.

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