Lubricant sensitivity in function of paddle movement in the forced feeder of a high-speed tablet press

Elisabeth Peeters, Valérie Vanhoorne, Chris Vervaet, Jean-Paul Remon

-Elisabeth Peeters; PhD. Student, Laboratory of Pharmaceutical Technology, Ghent University, Ottergemsesteenweg 460, 9000 Ghent, Belgium

-Valérie Vanhoorne; PhD. Student, Laboratory of Pharmaceutical Technology, Ghent University, Ottergemsesteenweg 460, 9000 Ghent, Belgium

-Chris Vervaet; Professor, Laboratory of Pharmaceutical Technology, Ghent University, Ottergemsesteenweg 460, 9000 Ghent, Belgium

-Jean-Paul Remon; Professor, Laboratory of Pharmaceutical Technology, Ghent University, Ottergemsesteenweg 460, 9000 Ghent, Belgium

Corresponding Author: Chris Vervaet

Ghent University

Laboratory of Pharmaceutical Technology

Ottergemsesteenweg 460

9000 Ghent

Belgium

Tel: +32 9 264 80 69

Fax: +32 9 222 82 36

E-mail: Chris.Vervaet@UGent.be

KEYWORDS: Tableting; Microcrystalline cellulose; Magnesium stearate; Shear; Tensile strength; Blending.

Abstract

Context: The negative impact of magnesium stearate on the hardness of tablets is a well-known phenomenon, but the influence of paddle movement in the forced feeder on the lubricant effect during tablet compression is often neglected.

Objective: The purpose of this research was to investigate the influence of paddle speed in the forced feeder on tablet tensile strength.

Materials and methods: Mixtures of microcrystalline cellulose and magnesium stearate (0.5%) were blended using different methods (low & high shear). After blending, the formulations were compressed into tablets. All parameters of the tableting cycle were kept constant except the speed of the paddles in the forced feeder.

Results and discussion: The blending technique affected the sensitivity of the formulation to the paddle speed. The tensile strength of pure microcrystalline cellulose tablets didn't change in function of paddle speed, while tablets prepared by low shear mixing became softer at higher paddle speed. The tensile strength of tablets manufactured using the high-shear mixed blend was low and didn't vary in function of paddle speed, suggesting that overlubrication already occurred during the initial blending step. Furthermore, analysis of the machine parameters allowed evaluation of the influence of the paddles on the flowability, initial packing and compactability of the powder mixtures.

Conclusion: The results elucidated that during manufacturing of tablets using magnesium stearate-containing blends care should not only be taken during the blending step prior to tableting, but also during the tableting process itself, as paddle speed can affect tablet tensile strength, a critical quality attribute.

1. Introduction

The negative impact of magnesium stearate as a tablet lubricant on the hardness of tablets containing components with a plastic deforming behavior is a well-known phenomenon.[1-6] The extent of this effect mainly depends on the magnesium stearate concentration, mixing time and mixing intensity.[2,7-9] During tablet manufacturing, the lubricant concentration and the mixing procedure (type of mixer, mixing time and intensity, mixing order) is mostly well defined, taking into account the possible negative effects of magnesium stearate.[10-13] However, the paddle speed in the forced feeder influences the shear rate and material residence time inside the forced feeder of the tablet press, but its influence on the lubricant effect during tablet compression is often neglected.[14-17] This study highlights the influence of the paddle speed in the forced feeder of a high speed rotary tablet press on the tensile strength of microcrystalline cellulose (MCC) tablets containing magnesium stearate (MgSt). Furthermore, as machine parameters were set to obtain an equal tablet weight and compression force for all formulations, analysis of the obtained results for these settings allowed evaluation of the influence of the paddles on the flowability, initial packing in the die and compactability of the powder mixtures.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (Avicel® PH-102, FMC Biopolymer, Cork, Ireland) was selected as model for materials exhibiting plastic deformation during compression. Magnesium stearate was purchased from Fagron (Waregem, Belgium).

2.2. Preparation of powder mixtures

An overview of the formulations and mixing method is provided in Table 1. Four kg of each blend was prepared. Prior to blending, the MCC was manually sieved through a 3000 µm mesh to break up large agglomerates which might have been formed during storage. MgSt was placed on a 100 µm sieve and shaken at an amplitude of 2 mm for 30 min, using a sieve shaker (Retsch VE 1000, Haan, Germany).

Low shear mixing was performed using a 20 l tumbling mixer (Inversina, Bioengineering, Wald, Switzerland). A 10 l high shear mixer (Gral10, GEA Pharma Systems - Collette™, Wommelgem, Belgium) was used for the high shear mixing of the powder blend. The low shear mixer was run for 3 or 15 minutes, depending on the formulation (Table 1), at 25 rotations per minute (rpm) with a filling degree of approximately 60 %. The high shear blending was performed at 400 rpm. In order to also obtain a filling degree of 60 % of the high shear mixer, the powder was processed in 2 subbatches of 2 kg. After blending, the powder blend was allowed to settle for 5 minutes before unloading the mixer, in order to reduce material loss due to airborne particles. Room temperature and relative humidity were logged.

2.3. Powder characterization

Particle size analysis was done by sieve analysis (n = 3), using a sieve shaker (Retsch VE 1000, Haan, Germany). 30 g of powder was placed on a nest of sieves (50, 100, 125, 150 and 250 µm) and shaken at an amplitude of 2 mm for 2 min. The amount of powder retained on each sieve was determined.

The bulk (ρ_{bulk}) and tapped density (ρ_{tapped}) of 30 g of powder was determined in a 100 ml graduated cylinder (n = 3). The powder was poured from a height of 40 cm through a stainless steel funnel with a 10 mm orifice into the graduated cylinder, mounted on a tapping device (J. Engelsmann, Ludwigshafen am Rhein, Germany). The powder was allowed to settle loosely under the influence of gravity and the initial volume (V_0) was recorded. The sample was tapped

for 1250 times and the final volume (V_{1250}) was determined. Bulk and tapped densities were calculated as 30 (g)/V_0 and 30 (g)/V_{1250}, respectively. These values were used to calculate the compressibility index (CI) in order to assess the tendency of a powder to consolidate (Equation (1)).[18]

$$\mathrm{CI}\ (\%) = \left(\frac{\rho_{tapped} - \rho_{bulk}}{\rho_{tapped}}\right) \times 100 \qquad (1)$$

Scanning electron microscopy (SEM) was used to study the shape and size distribution of the powder particles. A small amount of powder was mounted on metal stubs with carbon tape and coated with gold by means of a sputter coater (Emitech SC7620, Quorum Technologies, East Grinstead, UK). Photomicrographs were taken with a scanning electron microscope (FEI Quanta™ 200F, FEI, Hillsboro, USA) operated at an acceleration voltage of 20 kV. The powders were observed at a magnification of 100 x.

2.4. Preparation of tablets

All tablets were prepared using a MODUL™ P tablet press (GEA Process Engineering - Courtoy™, Halle, Belgium) equipped with an overfill cam of 10 mm. As the die table (turret) rotates, powder is fed from the forced feeder into the dies at the overfilling station. After weight adjustment at the filling station, the punches (*n* = 10, diameter 8 mm, flat faced bevel edge) move further through the pre- and main compression station to the ejection cam, where they are removed from the die table by a tablet stripper.[19] Tablets were prepared by double compression (i.e. a precompression (P) and main compression step (M)). At the precompression station the punches apply an initial force on the powder, and subsequently, under the main compression rollers the final compression takes place, usually at a higher load compared to the precompression phase.[20-22]

Most rotary presses operate by maintaining the upper roller in a fixed position during compression. By adjusting the position of the lower roller (prebot, mbot), the compression force (PCF, MCF) is determined and hence, the thickness of the compact under compression. In contrast, the MODUL™ P high-speed rotary tablet press is equipped with an air compensator which allows displacement of the upper compression rollers (PCD, MCD). The upper rollers are attached to an air piston, which allows vertical movement in an air cylinder. During a compression run the air pressure in the cylinder (PCF_r, MCF_r) is set at a constant value due to a control system of pressure valves and expansion vessels. The piston, and consequently the upper roller, is pushed downwards by the air pressure against a fixed stop, being the bottom of the air cylinder. The adjustable position of the lower roller is controlled similar to a conventional tablet press with fixed rollers. During compression, the upper punch initially moves downwards into the die when in contact with the upper roller. As the lower punch is pushed upwards by the lower roller, the powder bed in the die consolidates and the compression force increases. When the reaction force exerted by the powder on the upper punch exceeds the force exerted by the counter pressure (i.e. the air pressure on the piston), upward movement of the upper compression roller is possible. The distance by which the upper roller is displaced is referred to as 'displacement'. If, however, a higher air pressure than the force exerted by the powder is set in the cylinder of the air compensator, the upper roller does not move, and the system behaves as a set-up with fixed rollers.[23-24]

2.4.1. Tabletability

A preliminary study with pure MCC was performed to determine the main compression force (MCF) for further experiments. Tabletability is examined by plotting tensile strength (TS) against the main compression pressure (MCP).[15,25,26] As the obtained correlation is not an intrinsic material characteristic and the profile depends upon the press, tooling and settings

used (e.g. tableting speed, paddle speed in the forced feeder, fill depth), the same machine and tooling were used throughout the study.[15,27-29]

The fill depth was adjusted to obtain tablets of 150 mg, in accordance with the subsequent experiments. Tableting speed was set at 400 tablets per minute (tpm) and force feeder speeds were kept constant at 25 rpm – 40 rpm. Precompression force (PCF) was controlled at 2 kN and precompression displacement (PCD) at 0.2 mm. Main compression displacement (MCD) was kept at 0.0 mm for all experiments and MCF was varied from 3 to 31 kN. For each experiment the machine was run for 2 minutes, with sampling during the second minute. Room temperature (21.0 ± 2.0 °C) and relative humidity (RH) (30.0 ± 2.0 %) were controlled. Prior to analysis tablets were stored overnight in open tablet trays in a sealed container at 23.1 ± 1.0 °C and 30.0 ± 2.0 % RH.

2.4.2. Evaluation of the effect of paddle speeds

For the evaluation of the effect of the paddle speeds, the different formulations (Table 1) were compressed into tablets. A feed frame equipped with 2 paddle wheels, as described by Peeters et al., was utilized.[30] The first paddle wheel, the feeding wheel (further referred to as 'Paddle 1') is composed of eight curved paddles and is located above the overfilling station. The second paddle wheel, the metering wheel (further referred to as 'Paddle 2'), has twelve curved paddles and is located at the filling station. Both wheels are motor driven and rotate in opposite directions. Their speed can be adjusted independently from one another and from the turret speed.

Paddle speeds were varied according to Table 2. All other machine settings were kept constant during an experiment ('set machine settings' in Table 3). The fill depth was adjusted to obtain tablets of 150 mg. Tableting speed was set at 400 tpm. PCF was controlled at 2 kN and PCD at 0.2 mm. MCD was 0.0 mm for all experiments and MCF was controlled at 9 kN,

based on the results of the preliminary tabletability test. When starting an experimental run, the hopper and feeder were filled with the powder blend. For every experiment the machine was run for 1 minute before adjusting fill depth and parameters controlling the compression force and displacement. Subsequently, the machine was run for another five minutes with sampling during the last minute. Experiments were conducted from the lowest to the highest paddle speed (Table 2, from experiment 1 to 4) and vice versa. Room temperature (21.0 ± 2.0 °C) and RH (30.0 ± 2.0 %) were controlled. Tablets were also stored overnight before analysis.

2.5. Monitoring of set and dependent machine parameters

The machine settings which were kept constant ('set machine settings' in Table 3) were logged during each experiment. Fill depth was set to obtain a tablet weight of 150 mg. Although this value is set at the beginning of each experimental run and kept constant, its absolute value is dependent on the flow properties of the formulation. Consequently, it is actually a response factor, and monitoring this value provides insight in the lubrication effect of the paddles. Similarly, the position of the bottom punch (prebot, mbot) and the pressure in the air-compensator (PCF_r, MCF_r) are also response factors, since these parameters in combination with the powder characteristics determine the compression force (PCF, MCF) and the compression displacement (PCD, MCD) at pre- and main compression. As PCF (2 kN), MCF (9 kN), PCD (0.2 mm) and MCD (0.0 mm) were maintained at a fixed value, the pressure in the air-compensator and position of the bottom punch had to be adapted for each run to reach these values.

Since PCF, MCF, PCD and MCD are dependent on the above machine settings, they were identified as dependent process parameters. These values, together with the ejection force (EF), were logged with a customized data acquisition and analyzing system. The maximum values of ten successive signals for each parameter were determined and the mean value and

standard deviation calculated. An overview of these dependent machine settings is also provided in Table 3.

2.6. Tablet evaluation

Tablets (*n* = 20) were weighed and their hardness, thickness and diameter were determined (Sotax HT 10, Basel, Switzerland). The tablet tensile strength (TS) was calculated using Equation (2).[31]

$$\mathrm{TS} = \frac{2F}{\pi dt} \qquad (2)$$

where *F*, *d* and *t* denote the diametral crushing force (N), the tablet diameter (mm) and the tablet thickness (mm), respectively.

Tablet friability was determined (*n* = 3) on forty-three tablets using a friabilator described in the European Pharmacopeia (Pharma Test PTF-E, Hainburg, Germany), at a speed of 25 rpm for 4 min. Tablets were dedusted and weighed prior to and after the test. Tablet friability was expressed as the percentage weight loss.

3. Results and discussion

3.1. Tabletability

Figure 1 depicts the tabletability curve obtained when compressing pure MCC into tablets, by plotting TS against MCP. Based on these data 9 kN, which corresponds to 180 MPa of compression pressure, was selected as MCF to perform further experiments. While the tabletability curve is linear below compression pressures of 180 MPa, from 250 MPa onwards

a further increase in the compaction pressure does not contribute to a higher tensile strength as the higher energy put in the system is not used for additional bond formation. The preferred compression force from a manufacturing point of view is the lowest force (i.e. the least energy input) at which tablets complying with quality- and bioavailability requirements can be produced. Although strong MCC tablets are formed at relatively low compression pressures, the variability in TS is significantly larger when a variation (e.g. 10 MPa) in MCP occurs at lower compression pressures (Figure 1).[2] Since this could be a confounding factor in the interpretation of the influence of magnesium stearate on tensile strength, a force closer to the plateau of the curve was chosen.

3.2. Effect of the paddle speeds

As it was the purpose of this study to investigate the influence of the paddle speeds in the forced feeder, the blends were prepared by different mixing methods (Table 1). Low shear mixing was performed in a tumbling mixer. Besides the rotational and translational movement of a conventional tumbling mixer, this particular mixer uses inversional motion which leads to more efficient mixing and decreases the possibility of segregation.[32-34] Tumbling mixers are commonly used for the mixing and blending of granules or free-flowing powders with lubricants, glidants and disintegrants prior to tableting. In industry, intermediate bulk containers (IBCs) are commonly used for both mixing and immediate feeding of the machine. Shear occurs as a velocity gradient is generated by rotation of the mixing container around an axis. As the powder bed tumbles it dilates, allowing diffusive mixing to occur. The operational speed, size and filling degree of these low shear blenders are all process factors influencing the mixing pattern inside the container. In a high shear mixer, the components mix owing to high shear forces (arising from the high impeller velocity) and the expansion in bed volume that allows diffusive mixing. In pharmaceutical product manufacturing, this type of mixer is used for the mixing of cohesive powders or more commonly for single-pot processing.[34-36] Because of the high-speed movement within the mixer-granulator which can fracture material

easily and the problems associated with overmixing of lubricants, this type of mixer is usually not used for blending lubricants.[34] However, its use in this research is justified, as it was the intention to obtain an overlubricated blend.

A schematic overview of the tableting machine parameters, both set and dependent, the tablet characteristics and their relation to each other is outlined in Table 4. Since water content has a major influence on the mechanical properties of MCC and to avoid moisture content as a confounding factor, all samples (including pure MCC) were exposed to the same conditions during storage, blending and powder characterization (20.1 ± 2.0 °C and 54.0 ± 5.4 % RH) as well as during tableting, storage and analysis of tablets (21.5 ± 2.0 °C and 30.0 ± 2.0 % RH).[2,3,37-39]

The influence of the paddle speed on the tensile strength is depicted in Figure 2. The tensile strength of tablets without MgSt was not affected by the paddle speed (Formulation A). Following low shear blending of MCC and MgSt the tensile strength decreased using a higher paddle speed (Formulation B). The higher mixing intensity in the forced feeder increased the lubricant effect on the plastically deforming MCC. The effect of paddle speed was less pronounced using a longer low shear mixing time (Formulation C), but the tensile strength of the tablets was lower due to increased coating of the MCC fibers during blending. Following high shear blending of MCC and MgSt no effect of the paddle speed was observed, indicating that the powder mixture was already overblended during the mixing step (Formulation D). Overall, irrespective of the paddle speeds, the influence of MgSt on the tensile strength is pronounced, as the tensile strength of the tablets containing MgSt is lower than the tablets lacking lubricant. When taking the structure of MCC into account, it could be argued that the observed results are not solely dependent on the presence of MgSt, but on a combination of the influence of the blending step (prior to and during tableting) on the particle size distribution of MCC and the distribution of MgSt. MCC consists of porous microfibrilles, which are easily broken down during the blending step, when shear is introduced in the powder bed.[3,9] At higher

shear rates, either by altering the blending step prior to tableting (by increasing the mixing time or intensity) or during tableting by increasing the paddle speed, particles will fracture more extensively. This is supported by the particle size distribution of the different blends, as presented in Table 5. Also the SEM-pictures (Figure 3) illustrate the difference in particle size distribution.

However, as reported in literature, tablets prepared from different size fractions of pure MCC did not differ in disintegration time or tensile strength.[3,9] This indicates that, even when MCC particles are broken down during the blending step or in the forced feeder, this does not contribute to the differences observed in TS. Moreover, due to their small size, MCC microfibrilles have a relatively large surface-to-volume ratio.[40] Consequently, when the concentration of MgSt and the blending conditions remain the same, the smaller the lubricating effect on smaller host particles will be.[2] When the influence of MgSt on different sieve-fractions was compared, all results in literature report an increase in TS for smaller particle sizes. This demonstrates that in this experiment the observed (negative) results of TS can be mainly attributed to the difference in the blending step of magnesium stearate, and not to a change in particle size of MCC.[2,3,9,12]

An overview of the obtained values of set and dependent machine parameters and tablet characteristics is presented in Table 6. Regardless the paddle speed, the friability for all tablets was low. The tablets prepared from the high shear blended mixture (Formulation D) had a somewhat higher friability. These results show that the resistance to crushing, expressed by the tensile strength (Figure 2), and the susceptibility to abrasion, represented by the friability (‘Friability (%)’ in Table 6), are not completely interdependent and care should be taken not to generalize results obtained by determining only one characteristic.

Based on the weight and weight variability, it is evident that for all experiments tablets with the required weight could be obtained. All powders possessed sufficient flow, regardless of the

paddle speed. This is supported by the compressibility index (Table 5), which classified all powder blends as fairly flowing powders. The fill depth necessary to obtain the desired weight provided info about the fill density and was ranked as Formulation A > B > D > C. As bulk density is dependent on particle size, the higher fill depth of formulation D compared to C is somewhat surprising, since the results of powder flow (Table 5) indicate otherwise. Moreover, smaller particles commonly exhibit worse flow properties and this opposes the observed results.[2,3] However, both effects can be explained by the glidant properties of MgSt, as lower friction between particles results in a higher bulk density.[10,41-43]

The formulation without MgSt (Formulation A) has a poor flowability, shown by the large fill depth and its dependence on paddle speed, as fill depth gradually decreases with higher paddle speeds.[30] Also the flow of the mixture subjected for a short period to low shear (Formulation B) depended on the paddle movement. But since the overall fill depth is lower compared to formulation A, the flow can be considered to be improved, due to the presence of MgSt. The flow of the other two formulations (C and D) was not affected by the paddle speed, indicating that these materials are free-flowing. The higher fill depth of formulation D compared to C is linked to the specific surface of the MCC particles. In Formulation D the powder particles were exposed to more shear, and more particles are broken down into their primary particles (Table 5). Hence, the MgSt concentration is insufficient to completely cover the free surface area, herewith contributing less to an improvement of the flowability.[3] The flow properties determined via bulk and tapped density and via the parameter settings of the tablet press did not match with each other, especially for Formulations C and D. Although the former method is useful to obtain an initial indication about the flow performance, these determinations are static measurements, whereas the powder flow in a forced feeder is a dynamic process. Different mechanisms act simultaneously on the powder bed, which cannot be captured by the existing conventional techniques to measure and quantify powder flow.[30,44-46] Since the capacity of a glidant is mainly expressed in moving material, it is possible that this

property is more pronounced in the forced feeder, during actual die filling, then it is during the static flow measurements.

As PCF and PCD for all tablets were similar, the PCF_r and position of the lower punch (prebot) provide information about the effect of MgSt on the initial densification of the powders under compression. The position of the bottom punch mainly provides information about the interparticulate voids. As this value was the largest for the formulation lacking the lubricant, it was indicative of more space between the particles which can be linked to the larger particle size of the non-lubricated MCC particles. For formulations B and C, a smaller particle size and the presence of MgSt were translated in a denser packing, due to the ability of MgSt-coated particles to more easily slip by one another and pack into a denser formation.[10] Since the glidant ability of MgSt in blend D is hampered due to the large specific surface of the individual MCC particles, the initial packing is not as dense as with formulation C.

PCF_r gives information about the ability of MgSt to reduce die-wall friction. As die-wall friction is reduced, the net energy introduced in the process will be more efficiently used. Since the difference between PCF_r and PCF is smaller for MgSt-containing formulations (B-D) compared to A, this means less energy is lost when MgSt is used, which is attributed to its lubricating potential.[47] Another contributing factor to the observed effect is the ability of MgSt to reduce air entrapment.[48] The initial volume of formulation A is larger for the same weight than for the other formulations (i.e. more void spaces, more air entrapment and a less dense packing of the particles). Hence, for the same displacement (PCD) more air will be expelled from the powder bed for formulation A compared to MgSt/MCC blends. A lower PCF_r value when reaching a similar displacement (PCD) under an equal load (PCF), implies less densification of the particles. These results showed that during precompression of formulation A mainly release of entrapped air and particle rearrangement takes place, whereas for the other mixtures already bond formation and deformation of particles occurred.

Finally, some researchers reported the ability of MgSt to reduce elasticity and/or to promote plastic behavior.[6,7,49] This might also have contributed to the lower PCF_r values for an equal displacement under an equal load. In accordance to the findings of other researchers, this mechanism was not affected by the particle size of MCC based on similar values of PCF_r for formulations B, C and D.[2] Compared to the MgSt/MCC mixtures, the PCF_r values of formulation A are lower, i.e. indicative of a higher elasticity. However, results obtained by other researchers are not always consistent and straightforward, nor a full explanation for these observations is given. Therefore, no clear statement about this effect can be made.

The results of the main compression should be interpreted with a different rationale compared to the precompression data. Since no displacement is generated, the MCF_r has no added value in the interpretation of the results as this parameter is set at a high value to inhibit roller displacement. Hence, the determining factor is the position of the bottom punch: a change of this parameter, while the force exerted on the powder bed (MCF) remains constant, indicates a change in compactability. Since the particle size of MCC does not influence this factor, an observed effect is mainly caused by the presence of MgSt.[7] As the difference between pure MCC (formulation A) and MgSt/MCC blends (formulations B-D) are small, the reduction of die-wall friction in the presence of MgSt was the main cause of this effect, rather than a change in compactability, as was also reported by other authors.[6,50]

Finally, the effect of MgSt on the ejection force revealed the impact of the lubricating properties of MgSt.[51] The reduction in EF induced by MgSt was similar for all formulations and all paddle speeds. The desired effect (i.e. lowering the die-wall friction at ejection) is already reached after only 3 minutes of blending in a low shear mixer.[52]

From a manufacturing point of view, formulation B is the closest one related to a real life setting. This mixture is the most susceptible to changes in paddle speed of the forced feeder. Since MCC has a good compression behavior and forms strong tablets at relatively low

compression forces, it is likely that the negative effect of MgSt on TS will be even more pronounced when adding active pharmaceutical ingredients which deform plastically to the formulation. Furthermore, next to the reduction of TS, MgSt is also known to increase the disintegration and dissolution time and to reduce the adhesion of film-coatings to tablet surfaces.[52-54] Instead of incorporating the lubricant into the formulation, external lubrication by spraying MgSt immediately on the punch tips and dies could decrease its detrimental effects.[55-57] However, some challenges arise to incorporate this system into existing tableting machines currently lacking the system.

4. Conclusion

Based on the data collected during compression of MgSt/MCC blends on a high-speed tablet press, it was shown that the paddle speed of the forced feeder had a limited effect (except at the filling station) on the tableting process (packing, compactability, lubrication). However, the rotational speeds of the paddle wheels affected the shear rate and material residence time inside the forced feeder, inducing an effect on the flowability of the powders and on the tensile strength of the tablets.

This study illustrates that the paddles not only aid to force powder into a die, but that the passage of the material through the forced feeder must be considered as an additional blending step. As its impact on the quality of tablets manufactured using plastically deforming material can be significant it is essential to take this factor into account when optimizing a tableting process.

Declaration of interest

The authors report no declarations of interest.

References

[1] Bolhuis GK, Lerk CF, Zijlstra HT, De Boer AH. Film formation by magnesium stearate during mixing and its effect on tabletting. Pharm Weekbl 1975;110:517-60.

[2] Doelker E. Comparative compaction properties of various microcrystalline cellulose types and generic products. Drug Dev Ind Pharm 1993;19:2399-471.

[3] Doelker E, Massuell D, Vueillez F, Humbert-Droz P. Morphological, packing, flow and tableting properties of new avicel types. Drug Dev Ind Pharm 1995;21:643-61.

[4] Jarosz PJ, Parrott EL. Effect of lubricants on tensile strengths of tablets. Drug Dev Ind Pharm 1984;10:259-73.

[5] Lakio S, Vajna B, Farkas I, Salokangas H, Marosi G, Yliruusi J. Challenges in detecting magnesium stearate distribution in tablets. AAPS PharmSciTech 2013;14:435-44.

[6] Zuurman K, Van der Voort Maarschalk K, Bolhuis GK. Effect of magnesium stearate on bonding and porosity expansion produced from materials with different consolidation properties. Int J Pharm 1999;179:107-15.

[7] Haware RV, Bauer-Brandl A, Tho I. Comparative evaluation of the powder and compression properties of various grades and brands of microcrystalline cellulose by multivariate methods. Pharm Dev Technol 2010;15:394-404.

[8] Jarosz PJ, Parrott EL. Effect of lubricants on axial and radial work of failure. Drug Dev Ind Pharm 1982;8:445-53.

[9] van der Watt JG. The effect of the particle size of microcrystalline cellulose on tablet properties in mixtures with magnesium stearate. Int J Pharm 1987;36:51-54.

[10] Kushner J, Moore F. Scale-up model describing the impact of lubrication on tablet tensile strength. Int J Pharm 2010;399:19-30.

[11] Kushner J. Incorporating Turbula mixers into a blending scale-up model for evaluating the effect of magnesium stearta on tabelt tensile strenth and bulk specific volume. Int J Pharm 2012;429:1-11.

[12] Pingali K, Mendez R, Lewis D, Michniak-Kohn B, Cuitino A, Muzzio F. Mixing order of glidant and lubricant – influence on powder and tablet properties. Int J Pharm 2011;409:269-77.

[13] van der Watt JG, de Villiers MM, The effect of V-mixer scale-up on the mixing of magnesium stearate with direct compression microcrystalline cellulose. Int J Pharm Biopharm 1997;43:91-94.

[14] Mendez R, Muzzio F, Velazquez C. Study of the effects of feed frames on powder blend properties during the filling of tablet press dies. Powder Technol 2010;200:105-16.

[15] Narang AS, Rao VM, Guo H, Lu JA, Desai DS. Effect of force feeder on tablet strength during compression. Int J Pharm 2010;401:7-15.

[16] Pingali K, Mendez R, Lewis D, Michniak-Kohn B, Cuitino A, Muzzio F. Evaluation of strain-induced hydrophobicity of pharmaceutical blends and its effect on drug release rate under multiple compression conditions. Drug Dev Ind Pharm 2011;37:428-35.

[17] Wang J, Wen H, Desai D. Lubrication in tablet formulations. Eur J Pharm Biopharm 2010;75:1-15.

[18] Carr RL. Evaluating flow properties of solids. Chem Eng 1965;72:163-68.

[19] Sinka IC, Motazedian F, Cocks ACF, Pitt KG. The effect of processing parameters on pharmaceutical tablet properties. Powder Technol 2009;189:276-84.

[20] Akande OF, Ford JL, Rowe PH, Rubinstein MH. The effects of lag-time and dwell-time on the comaction properties of 1:1 paracetamol/microcrystalline cellulose tablets prepared by pre-compression and main compression. J Pharm Pharmacol 1998;50:19-28.

[21] Bogda MJ. Tablet compression: Machine theory, design, and process troubleshooting. In: Swarbrick J, ed. Encyclopedia of pharmaceutical technology. New York: Informa Healthcare USA Inc., 2007:3611-3629.

[22] Ruegger CE, Celik M. The influence of varying precompaction and main compaction profile parameters on the mechanical stength of compacts. Pharm Dev Technol 2000;5:495-505.

[23] Van Evelghem J. Improving tablet quality with compression to equal force technology. Pharm Technol: Tableting and Granulation (Suppl.) 2008;32:26-29.

[24] Vogeleer J. Rotary tablet press. Eur Pharm Manuf 2008:1.

[25] Sun CC, Grant DJW. Influence of crystal structure on the tableting properties of sulfamerazine polymorphs. Pharm Res 2001;18:274-80.

[26] Joiris E, Di Martino P, Berneron C, Guyot-Hermann AM, Guyot JC. Compression behavior of orthorhombic paracetamol. Pharm Res 1998;15:1122-30.

[27] Tye CK, Sun C, Amidon GE. Evaluation of the effects of tableting speed on the relationships between compaction pressure, tablet tensile strenght, and tablet solid fraction. J Pharm Sci 2005;94:465-72.

[28] Cantor SL, Hoag SW, Augsburger LL. Evaluation of the mechanical properties of extrusion-spheronized beads and multiparticulate systems. Drug Dev Ind Pharm 2009;35:683-93.

[29] Ruegger CE, Celik M. The effect of compression and decompression speed on the mechanical strength of compacts. Pharm Dev Technol 2000;5:485-94.

[30] Peeters E, De Beer T, Vervaet C, Remon JP. Reduction of tablet weight variability by optimizing paddle speed in the forced feeder of a high-speed rotary tablet press. Drug Dev Ind Pharm 2015;41:530-39.

[31] Fell JT, Newton JM. Determination of tablet strength by diametral-compression test. J Pharm Sci 1970;59:688-91.

[32] Porion P, Sommier N, Faugere A, Evesqu P. Dynamics of size segregation and mixing of granular materials in a 3D-blender by NMR imaging investigation. Powder Technol 2004;141:55-68.

[33] Sommier N, Porion P, Evesque P, Leclerc B, Tchoreloff P, Couarraze G. Magnetic resonance imaging investigation of the mixing-segregation process in a pharmaceutical blender. Int J Pharm 2001;222:243-58.

[34] Twitchell A. Mixing. In: Aulton ME, ed. Pharmaceutics: The science of dosage form design. London: Churchill Livingstone, 2002:181-96.

[35] Cavinato M, Artoni R, Bresciani M, Canu P, Santomosa AC. Scale-up effects on flow patterns in the high shear mixing of cohesive powders. Chem Eng Sci 2013;102:1-9.

[36] Reynolds GK, Le PK, Nilpawar AM. High shear granulation. In: Salman AD, Hounslow MJ, Sevile JPK, ed. Granulation. Oxford: Elsevier, 2007:3-19.

[37] Crouter A, Briens L. The effect of moisture on the flowability of pharmaceutical excipients. AAPS PharmSciTech 2014;15:65-74.

[38] Sun CC. Mechanism of moisture induced variations in true density and compaction properties of microcrystalline cellulose. Int J Pharm 2008;346:93-101.

[39] Sun CC. True density of microcrystalline cellulose. J Pharm Sci 2005;94:2132-34.

[40] Iijima H, Takeo K. Microcrystalline cellulose: an overview. In: Phillips GO, Williams PA, ed. Handbook of hydrocolloids. Cambridge: Woodhead Publishing Ltd., 2000:331-46.

[41] Abdullah EC, Geldart D. The use of bulk density measurements as flowability indicators. Powder Technol 1999:102:151-65.

[42] Podczeck F, Miah Y. The influence of particle size and shape on the angle of internal friction and the flow factor of unlubricated and lubricated powders. Int J Pharm 1996;144:187-94.

[43] Velasco MV, Munoz-Ruiz A, Monedero MC, Jimenez-Castellanos MR. Study of flowability of powders. Effect of the addition of lubricants. Drug Dev Ind Pharm 1995;21:2385-91.

[44] Li Q, Rudolph C, Weigl B, Earl A. Interparticle van der Waals force in powder flowability and compactibility. Int J Pharm 2004;280:77-93.

[45] Xie X, Puri VM. Uniformity of powder die filling using a feed shoe: a review. Part Sci Technol 2006;24:411-26.

[46] Yaginuma Y, Ozeki Y, Kakizawa M, Gomi SI, Watanabe Y. Effects of powder flowability on die-fill properties in rotary compression. J Drug Deliv Sci Technol 2007;17:205-10.

[47] Hwang RC, Parrott EL. Effect of lubricant on wear rate of tablets. Drug Dev Ind Pharm 1993;19:1379-91.

[48] Ebba F, Piccerelle P, Prinderre P, Opota D, Joachim J. Stress relaxation studies of granules as a function of different lubricants. Eur J Pharm Biopharm 2001;52:211-20.

[49] Wurster DE, Likitlersuang S, Chen Y. The influence of magnesium stearate on the Hiestand tableting indices and other related mechanical properties of maltodextrines. Pharm Dev Technol 2005;10:461-66.

[50] van Veen B, Bolhuis GK, Xu YS, Zuurman K, Frijlink HW. Compaction mechanism and tablet strenth of unlubricated and lubricated (silicified) microcrystalline cellulose. Eur J Pharm Biopharm 2005;59:133-38.

[51] Patel S, Kaushal AM, Bansal AK. Lubrication potential of magnesium stearate studied on instrumented rotary tablet press. AAPS PharmSciTech 2007;8:E1-E8.

[52] Kikuta J, Kitamori N. Effect of mixing time on the lubricating properties of magnesium stearate and the final charactersitics of the compressed tablets. Drug Dev Ind Pharm 1994;20:343-55.

[53] Lethola VM, Heinamaki JT, Nikupaavo P, Yliruusi JK. Effect of some excipients and compression pressure on the adhesion of aqueous-based hydroxypropyl methylcellulose film coatings to tablet sufraces. Drug Dev Ind Pharm 1995;21:1365-75.

[54] Sheskey PJ, Robb RT, Moore RD, Boyce BM. Effect of lubricant level, method of mixing, and duration of mixing on a controlled-release matrix tablet containing hydroxypropyl methylcellulose. Drug Dev Ind Pharm 1995;21:2151-65.

[55] Jahn T, Steffens KJ. Press chamber coating as external lubrication for high speed rotary presses: lubricant spray rate optimization. Drug Dev Ind Pharm 2005;31:951-57.

[56] Otsuka M, Sato M, Matsuda M. Comparative evaluation of tableting compression behaviors by methods of internal and external lubricant addition: inhibition of enzymic

activity of trypsin reparation by using external lubricant addition during the tableting compression process. AAPS PharmSci 2001;3:1-11.

[57] Yamamura T, Ohta T, Taira T, Ogawa Y, Sakai Y, Moribe K, Yamamoto K. Effect of automated external lubrication on tablet properties and the stabilitity of eprazinone hydrochloride. Int J Pharm 2009;370:1-7.

Figures

Figure 1: Tabletability curve of pure MCC. The arrows indicate the range over which tensile strength (TS) changes when compression pressure varies by 10 MPa.

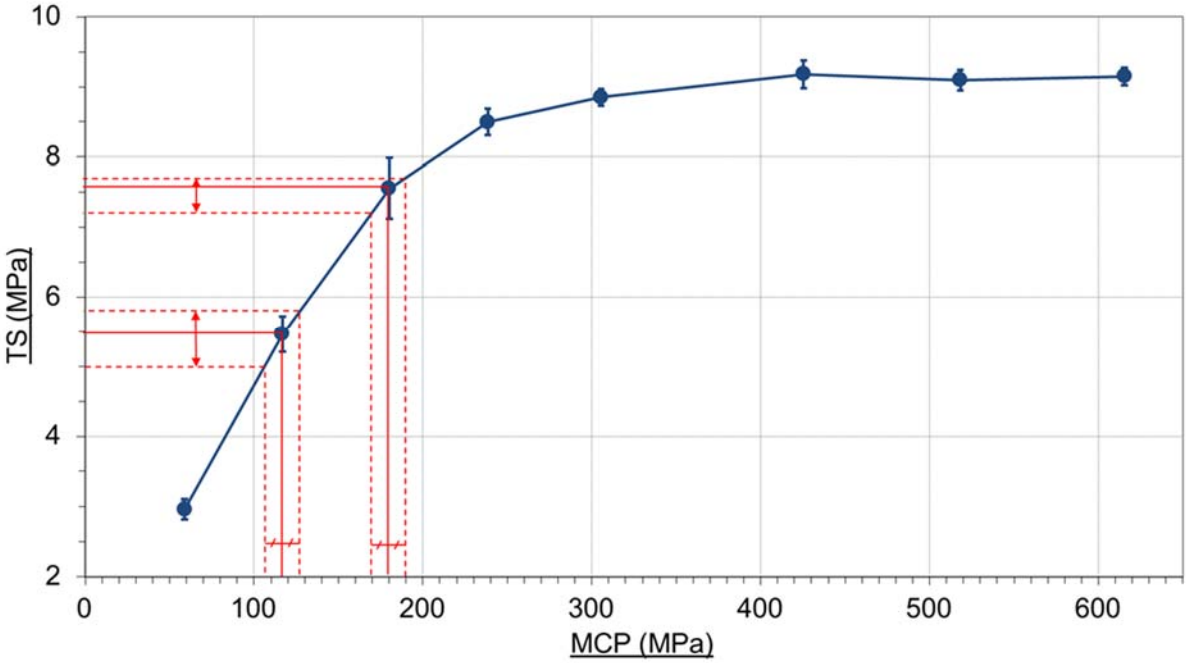

Figure 2: Influence of the paddle speed on the tensile strength of tablets.

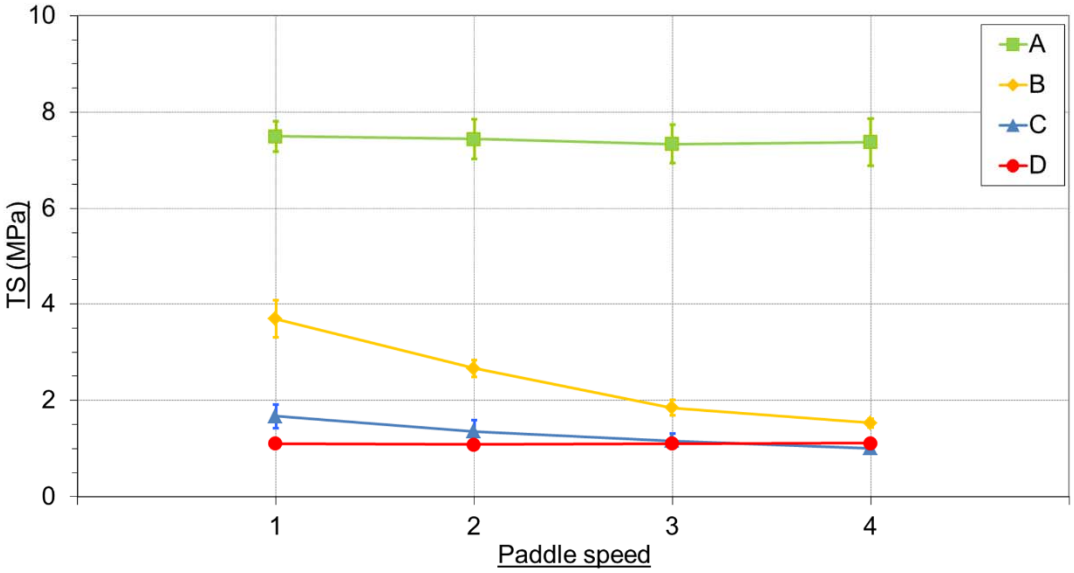

Figure 3: SEM-pictures (magnification 100 x) illustrating the difference in particle size distribution: (a) Formulation A, (b) Formulation C.

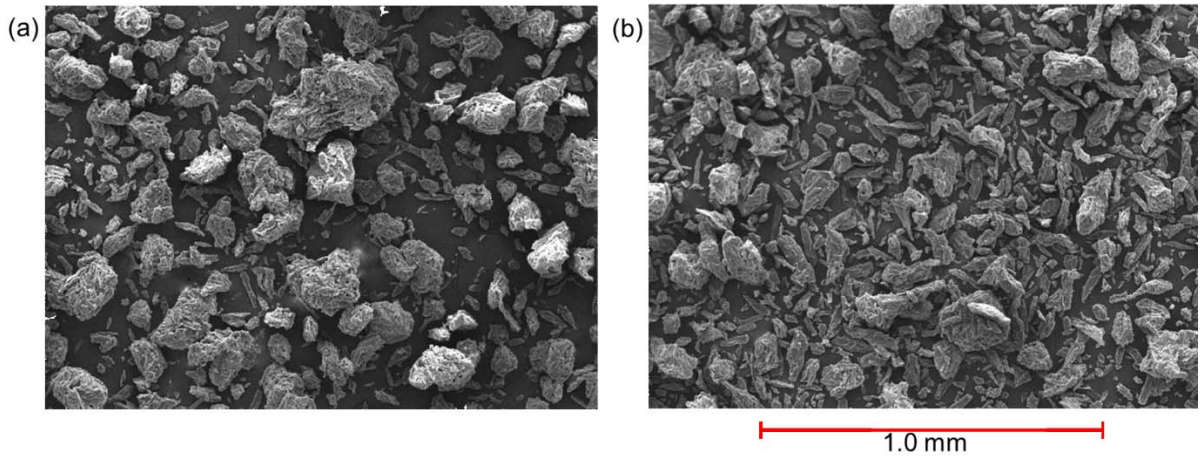

Table 1: Composition and mixing method of the formulations.

Formulation	A	B	C	D
Microcrystalline cellulose (%)	100.0	99.5	99.5	99.5
Magnesium stearate (%)	-	0.5	0.5	0.5
Mixing method	-	Low shear	Low shear	High shear
Mixing time (min)	-	3	15	5

Table 2: Combination of paddle speeds used for the different experiments.

Paddle speed (rpm)	1	2	3	4
Paddle 1	10	25	40	60
Paddle 2	20	40	70	100

Table 3: Overview of the set and dependent machine settings included in the data analysis.

Key	Meaning
	Set machine settings
speed (tpm)	Tableting speed
pad1 (rpm)	Speed of paddle 1 in the forced feeder
pad2 (rpm)	Speed of paddle 2 in the forced feeder
fill (mm)	Fill depth, which determines the weight
PCF_r (kN)	Air pressure in the air-compensator of the upper roller at precompression
MCF_r (kN)	Air pressure in the air-compensator of the upper roller at main
prebot (mm)	Position of bottom roller at precompression
mbot (mm)	Position of bottom roller at main compression
	Dependent machine settings
PCF (kN)	Maximum precompression force exerted on powder under compression
MCF (kN)	Maximum main compression force exerted on powder under compression
PCD (mm)	Maximum displacement of the upper roller during precompression
MCD (mm)	Maximum displacement of the upper roller during main compression
EF (kN)	Maximum ejection force measured during the ejection phase

Table 4: Schematic overview of the set and dependent machine parameters, the tablet characteristics and their relation to each other. The preset factors are highlighted with grey background.

Tablet characteristics	Dependent machine parameters		Set machine parameters	Relation
			speed (tpm)	
TS (MPa) Friability (%)			pad1 (rpm) – pad2 (rpm)	Influence of the lubricating properties of the paddles Affects
Weight (mg)		Depends on	fill (mm)	Influence of MgSt on flowability of the powder
	PCF (kN) PCD (mm)		PCF_r (kN) prebot (mm)	Influence of MgSt on initial packing of the powder
	MCF (kN) MCD (mm)		MCF_r (kN) mbot (mm)	Influence of MgSt on compactibility of the powder
	EF (kN)			Influence of MgSt on lubrication of the powder

Table 5: Flow properties and particle size distribution of the formulations.

Formulation	A	B	C	D
V_0 (ml)	89.7 ± 0.6	81.8 ± 0.3	75.3 ± 0.6	65.8 ± 0.3
V_{1250} (ml)	71.0 ± 0.9	65.8 ± 0.3	61.8 ± 0.3	55.0 ± 0.0
ρ_{bulk} (g/cm^3)	0.33 ± 0.00	0.37 ± 0.00	0.40 ± 0.00	0.46 ± 0.00
ρ_{tapped} (g/cm^3)	0.42 ± 0.01	0.46 ± 0.00	0.49 ± 0.00	0.55 ± 0.00
Compressibility index (CI) (%)	20.82 ± 0.46	19.55 ± 0.07	17.92 ± 0.55	16.45 ± 0.37
Particle size distribution				
d10 (µm)	54.7 ± 3.2	50.8 ± 7.3	37.5 ± 7.1	31.7 ± 0.6
d50 (µm)	154.7 ± 2.9	148.2 ± 14.8	122.5 ± 13.6	117.5 ± 0.5
d90 (µm)	232.5 ± 2.0	232.0 ± 2.0	227.8 ± 2.8	227.0 ± 0.5

Table 6: Overview of the obtained values of set and dependent machine parameters and the tablet characteristics.

Formulation	Paddle speed	Friability (%)	Flowability		Initial packing				Compactibility				Lubrication
			Fill (mm)	Weight (mg)	PCF_r (kN)	prebot (mm)	PCF (kN)	PCD (mm)	MCF_r (kN)	mbot (mm)	MCF (kN)	MCD (mm)	EF (kN)
A	1	0.25 ± 0.02	7.72	151.59 ± 0.85	1.56	4.87	2.16 ± 0.19	0.19 ± 0.01	25.15	4.62	9.29 ± 0.39	0.00	0.26 ± 0.02
	2	0.23 ± 0.01	7.56	151.70 ± 0.75	1.56	4.87	2.11 ± 0.13	0.20 ± 0.01	25.15	4.63	9.28 ± 0.35	0.00	0.26 ± 0.02
	3	0.24 ± 0.01	7.54	151.45 ± 0.70	1.56	4.87	2.08 ± 0.10	0.19 ± 0.01	25.15	4.62	9.40 ± 0.48	0.00	0.25 ± 0.01
	4	0.17 ± 0.04	7.54	151.23 ± 0.66	1.56	4.87	2.19 ± 0.14	0.19 ± 0.01	25.15	4.62	9.32 ± 0.32	0.00	0.26 ± 0.02
B	1	0.05 ± 0.00	6.88	150.07 ± 0.52	1.80	4.85	2.06 ± 0.09	0.19 ± 0.01	25.21	4.59	8.97 ± 0.39	0.00	0.08 ± 0.01
	2	0.11 ± 0.01	6.71	151.12 ± 0.95	1.80	4.85	2.07 ± 0.14	0.19 ± 0.01	25.21	4.60	8.99 ± 0.49	0.00	0.08 ± 0.01
	3	0.20 ± 0.02	6.60	150.75 ± 0.69	1.80	4.86	2.11 ± 0.15	0.20 ± 0.01	25.23	4.60	8.98 ± 0.43	0.00	0.09 ± 0.01
	4	0.28 ± 0.01	6.59	151.23 ± 0.99	1.80	4.86	2.17 ± 0.19	0.19 ± 0.01	25.23	4.60	9.01 ± 0.53	0.00	0.08 ± 0.00
C	1	0.13 ± 0.01	6.25	150.74 ± 0.77	1.80	4.77	2.10 ± 0.15	0.18 ± 0.01	25.38	4.59	9.12 ± 0.35	0.00	0.09 ± 0.01
	2	0.21 ± 0.01	6.17	150.15 ± 0.74	1.80	4.76	2.14 ± 0.14	0.19 ± 0.01	25.38	4.59	8.96 ± 0.40	0.00	0.08 ± 0.01
	3	0.22 ± 0.03	6.14	149.74 ± 1.24	1.80	4.75	2.10 ± 0.16	0.18 ± 0.01	25.37	4.59	9.13 ± 0.50	0.00	0.08 ± 0.00
	4	0.10 ± 0.05	6.15	150.29 ± 1.09	1.80	4.76	2.18 ± 0.14	0.18 ± 0.01	25.36	4.59	9.14 ± 0.44	0.00	0.09 ± 0.00
D	1	0.39 ± 0.01	6.27	150.32 ± 0.63	1.80	4.81	2.11 ± 0.15	0.20 ± 0.01	25.21	4.60	9.15 ± 0.58	0.00	0.09 ± 0.00
	2	0.40 ± 0.01	6.26	150.17 ± 0.89	1.80	4.80	2.02 ± 0.17	0.19 ± 0.01	25.21	4.60	9.24 ± 0.54	0.00	0.09 ± 0.00
	3	0.34 ± 0.03	6.29	150.83 ± 0.88	1.80	4.80	2.12 ± 0.18	0.19 ± 0.01	25.21	4.59	8.91 ± 0.52	0.00	0.08 ± 0.00
	4	0.35 ± 0.02	6.30	150.42 ± 1.09	1.80	4.80	2.12 ± 0.13	0.19 ± 0.01	25.21	4.59	8.94 ± 0.52	0.00	0.08 ± 0.00