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Influences of variations of the amount of compressed material on compressibility, tabletability and compactability

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ABSTRACT

Compression analysis is essential for the investigation of materials and processes in the manufacturing of pharmaceutical tablets. In the past, the influence of various process parameters on compression analysis has been investigated. The strength of these influences can significantly depend on the properties of the compressed material. One example is the effect of tablet compression speed on tabletability. The impact of tablet geometry has also been studied. However, what is still missing in the literature is the investigation of the influence of the quantity of the compressed material. This publication provides a starting point for understanding the effect of material quantity in compression analysis. In addition to the material quantity, two different tablet diameters were also investigated. The study demonstrates that the extent to which material quantity has an influence on compression analysis highly depends on the material properties. It clearly shows that the tabletability and even the compactability of materials can vary significantly depending on the amount of material compressed.

Introduction

In tablet manufacturing, the critical quality attributes of tablets are influenced by both the properties of the compressed materials and the process conditions, as well as the interactions between these factors. Material properties can be broadly categorized into chemical properties, which stem from the molecular composition of the materials, and physical particle properties. Together, these properties govern the deformation behavior of the bulk solid during compression. Process conditions, on the other hand, can be classified into controllable factors, such as punch geometry, punch velocity profile, room temperature, and air humidity at the manufacturing site, and uncontrollable factors, such as the die temperature increases during operation, which is influenced by material properties and the speed of the tableting press.[1,2] Understanding the interplay between material properties and process parameters is essential for compression analysis, as it directly impacts tablet quality.

Among the physical properties of tablets, mechanical resistance and solid fraction (*SF*) are particularly critical. Mechanical resistance affects the durability of tablets during post-processing and patient handling. This property is commonly evaluated using diametrical compression tests, where a crushing force is applied to the tablet until fracture occurs. The resulting force is used to calculate the tensile strength (σ), which accounts for the tablet's geometry. The tensile strength equation for flat-faced tablets is derived from the stress distribution within cylindrical bodies[3] and was refined by Fell and Newton.[4] Despite its widespread use in research, the validity of the test conditions has been a subject of debate since its inception. Solid fraction, which determines tablet porosity, plays a pivotal role in the disintegration and dissolution of active pharmaceutical ingredients.[5–8] It is often used as a surrogate parameter for predicting these properties due to its ease of measurement. Both tensile strength and solid fraction are influenced by the maximum compression pressure (P_{max}) during the tableting process, with these relationships referred to as compressibility ($SF \sim P_{max}$), tabletability ($\sigma \sim P_{max}$), and compactability ($\sigma \sim SF$) .[9] Each material can be represented by a curve within this three-dimensional space. The trajectory of this curve, however, can be influenced and altered by additional process parameters.

The influence of process parameters on compressibility, tabletability, and compactability has been extensively studied. For instance, tableting speed significantly affects tablet properties due to its impact on material deformation during compression.[10,11] At higher speeds, the shorter

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duration of pressure application can reduce tabletability, depending on material properties, while compactability remains relatively unchanged. Additionally, the tableting speed also influences the filling behavior of the dies.[12] Variations between different tableting machines[13] and the inclusion of a precompression step have been shown to enhance tabletability and mitigate defects caused by trapped air expansion.[14–16] Feed frame design and settings also affect die-filling homogeneity and the risk of overlubrication.[17] The geometry of punches influences tablet strength,[18] material deformation behavior,[19] and the stress distribution[20] as well as the density distribution within tablets.[21–23] Furthermore, punch displacement profiles, determined by roller geometry and punch head design, play a key role in the duration of the compaction process on rotary presses.[24] Lastly, changes in temperature during the tableting process can impact the deformation behavior of certain materials, altering tablet properties.[25,26] This enumeration of the influences of process parameters is certainly not exhaustive but demonstrates that a wide range of different parameters has already been investigated in published literature.

While the literature has extensively explored these named variables, limited attention has been given to the effect of tablet weight and thickness on tablet properties like tensile strength. Mazel et al. investigated the lamination of tablet of varying thicknesses under increasing pressures.[27] Newton et al. investigated elongated beam-like tablets with varying thicknesses but did not observe significant differences in tensile strength or solid fraction.[28] Diarra et al. concluded a Drucker Drucker–Prager Cap simulation study on the effect of tablet thickness on the density distribution within the tablet by the estimation that found variations may have an impact in the tensile strength of tablets.[21] A study on the multivariate decomposition of tableting data did not identify a significant effect of tablet mass.[29] However, the publication did not analyze raw data directly but rather assessed the clustering of >60 parameters. Within this clustering, tablet mass appeared to have a minimal influence. These findings are counterintuitive, given the known non-uniform distribution of solid fraction within tablets.[30–32] Variations in thickness could reasonably be expected to influence the distribution patterns of solid fraction and, consequently, the mechanical properties of tablets.

The present study aims to systematically address this gap. The focus lies on investigating whether a correlation exists between the tablet mass and the measured tensile strength. Initially, parts of the database from Berkenkemper et al. were re-evaluated.[29] These results were then reproduced to enhance the reliability of the findings. Furthermore, a new database was created, focusing on single-component systems to keep the complexity of the investigation appropriately aligned with the research question. In addition to varying tablet mass, tablets were produced using punches with two different diameters and at two distinct tableting speeds. The objective was not to explain the observed effects mechanistically but to provide an exploratory analysis of influences on tablet properties, such as tensile strength, which have been largely overlooked in existing literature.

Materials and methods

Reevaluation of database of Berkenkemper et al

The database compiled by Berkenkemper et al. comprises tablet manufacturing data for 12 pharmaceutically utilized excipients. The materials were compressed under varying compression pressures, punch velocities, and punch geometries. Tablet mass was adjusted to 150 mg, 200 mg, and 250 mg. For each parameter setting, at least three tablets were compressed. A detailed description of the dataset can be found in the original publication.[29]

In the present study, the data of 8 mm tablets from the database were re-evaluated. The analysis of the tabletability of these tablets is detailed in Section ↱2.2.

Tableting

The compression experiments were performed using a compaction simulator (STYL'One Evo, Medelpharm, France). The machine was equipped with EU-B 8 mm and 11.28 mm round, flat-faced punches. Prior every tableting process, the punches and the die were externally lubricated with magnesium stearate (Ligamed MF-2-V, Peter Greven Nederland CV, Netherlands) using a brush. Subsequently, the die was filled manually. The weight of the tablets was adjusted by the change of the position of the lower punch during the filling phase of the die. For every material at least 6 different tablets weights were investigated. During the compression phase, the punches were driven at a constant speed of 3 mm s^{-1} or 15 mm s^{-1} in thickness mode of the machine. The minimum of the in-die thickness was adjusted to cover the range from approximative 50 to 1000 MPa for the compression pressure in 10 factor levels. At every setting 10 tablets were produced. Limitations of the machine, such as excessively high ejection forces or a too low minimum thickness, occurred at the edges of the experimental range. Consequently, variations between the minimum and maximum values of individual settings were occasionally encountered. In total 9241 individual tablets were produced and tested. The data of the compaction simulator, including the position of the punches, the compaction pressure and the process time was gathered in a frequency of 10 kHz. The data of the punch positions was corrected for the deformation of the punches and machine parts using the Analis Software of Medelpharm. The whole database will be made available on request.

An overview over the materials and settings included in the investigations is provided in Table 1. Fujicalin® and DiCaFos® A60 were selected to enable the comparison of the effects of significant differences in particle shape. The particle size of both grades is quite similar, with the dx_{50} in a range of 60 – 80 µm.[29] For similar reasons, the spherical spray-agglomerated grade Tablettose® 70 and the coarse milled GranuLac® 200 were included in the study. HPC SL FP serves as an example of a mostly elastically and plastically deformable material. Vivapur® 102 is included to cover a typical grade of microcrystalline cellulose for compression while PROSOLV® HD 90 and PROSOLV® ODT serves as examples for co-processed excipients. Polyglycol 20000 P was investigated to include a material of an exotic deformation behavior.

Determination of the helium pycnometry density

The particle density of the starting materials was measured using helium pycnometry (AccuPyc 1330 pycnometer, Micromeritics®, Germany). The triplicated measurements were performed at 25 °C in a chamber volume of 3.5 cm^3. The pressure of the helium during the measurements was in a range of 1.4 to 1.6 bar.

Tablet characterization

The produced tablets were tested using an automated tablet strength tester (SmartTest50, Sotax AG, Switzerland) in a testing speed of 0.35 mm s^{-1}. The device was used to measure the weight, diameter (d), height (h), and crushing force (F_c) of the respective tablets. According to Fell and Newton, the tensile strength σ of the tablets was calculated (Eq. (1)).

$$\sigma = \frac{2F_c}{\pi dh} \tag{1}$$

Eq. (1) is typically used to calculate the tensile strength of flat-faced tablets. It is derived from considerations of the contact mechanics of elastic cylindrical bodies within the framework of photoelasticity.[3] The validity of this equation requires homogeneous material density, a large difference in the elastic moduli between the jaws and the tablet, and diametral failure of the material in tension. Within the scope of the present investigations, no atypical deviations from these conditions were observed.

When considering the tablet diameter, the following aspect must be

Table 1
Materials and settings and helium pycnometry density.

Trade name	Material	Supplier	Tablet weight / mg	Punch speed / mm s^{-1}	Punch diameter / mm	He density / mg mm^{-3}
DiCaFos® A60	anhydrous dibasic calcium phosphate	Budenheim (Germany)	140 – 300 mg	3	8	2.828 ± 0.002
Fujicalin®	anhydrous dibasic calcium phosphate	Fuji Chemical Industries Co., LTD. (Japan)	110 – 470 mg	3 & 15	8 & 11.28	2.780 ± 0.003
HPC SL FP	hydroxypropyl cellulose	Nippon Soda (Japan)	120 – 270 mg	3	8	1.200 ± 0.001
Vivapur® 102	microcrystalline cellulose	JRS Pharma (Germany)	110 – 470 mg	3 & 15	8 & 11.28	1.535 ± 0.001
PROSOLV® HD 90	microcrystalline cellulose, colloidal anhydrous silica	JRS Pharma (Germany)	110 – 300 mg	3	8	1.550 ± 0.002
PROSOLV® ODT	microcrystalline cellulose, colloidal anhydrous silica, mannitol, fructose, crospovidone	JRS Pharma (Germany)	120 – 300 mg	3	8	1.483 ± 0.002
Polyglycol 20000 P	polyethylene glycol	Clariant (Switzerland)	100 – 260 mg	3	8	1.213 ± 0.002
Tablettose® 70	α-lactose monohydrate	Meggle (Deutschland)	100 – 470 mg	3 & 15	8 & 11.28	1.524 ± 0.001
GranuLac® 200	α-lactose monohydrate	Meggle (Deutschland)	110 – 310 mg	3	8	1.523 ± 0.006

taken into account: After compression, the tablet undergoes elastic recovery, which can cause the actual tablet diameter to differ from the diameter of the punch. The tablet diameter is measured using the SmartTest device. During the measurement of the breaking force, the diameter is determined as the distance between the jaws at the point where a force exceeding a specific threshold of 1 N is detected. However, the material may undergo deformation even before this minimal force is reached, potentially leading to inaccuracies in the measured diameter. These errors in diameter measurement are, in turn, dependent on the deformation properties of the material. Thus, the measured tablet diameter is likely influenced not only by the punch diameter and elastic recovery but also by material deformation during the test. Determining the extent to which elastic recovery or deformation during the test contributes to the measured tablet diameter would require an orthogonal measurement method.

Since the diameter is used in the calculation of tensile strength, it is essential to investigate whether differences in tensile strength can be attributed to variations in the measured tablet diameter. The results of this analysis are presented in Section ↱2.2. This section presents an investigation into the impact of calculating tensile strength using either the measured tablet diameter or the punch diameter.

The testing of the tablets was conducted 24–48 hours after production. During this period the tablets were stored under climate-controlled conditions at 21 °C, 45 % r.h.

Compressibility regression model

To enhance the identification of trends and improve data interpretability, the relationships of compressibility, tabletability, and compactibility were modeled using regression approaches that are well-established in the literature.

The course of the out-of-die compressibility data was described using a rearranged form of the Eq. (2) according to Kuentz and Leuenberger[33] and Sun.[34] The regression coefficients of the models are the deformability constant C, the critical porosity ε_c and the estimated density ρ_{sun}. The equation aims to describe the change of the maximum compression pressure P_{max} over the change of the tablet density ρ.

$$f(\rho) = P_{max} = \frac{1}{C}\left((1-\varepsilon_c) - \frac{\rho}{\rho_{sun}} - \varepsilon_c \ln\left(\frac{1-\frac{\rho}{\rho_{sun}}}{\varepsilon_c}\right)\right) \quad (2)$$

The rearrangement of $f(\rho)$ results in Eq. (3), with W as the Lambert W function.

$$f(P_{max}) = \rho = \left|\rho_{sun}\left(\varepsilon_c W\left(-e^{-\frac{P_{max}C-\varepsilon_c}{\varepsilon_c}}\right)+1\right)\right| \quad (3)$$

For the regression of the equations the least-square regression procedure was chosen. Least-square regression aims to minimize the sum of the squared residuals, with the residuals defined as the deviations of the model's predictions from the measured values.

In the compression of various materials, the out-of-die tablet density is asymptotic to a certain limit with an increase of the maximum compression pressure. An example of this phenomenon is given in Fig. 1. In addition to the measured values, represented by the black error bars, the figure displays the results of the regressions of equations $f(\rho)$ in blue and $f(P)$ in red.

As evident in the figure, the regressions of both equations yield different results. $f(P_{max})$ fits the data significantly better in comparison to $f(\rho)$. Both regressions indeed yield different results for the regression coefficients C, ε_c, and ρ_{sun}. Since the equations are just rearranged forms of each other, both sets of regression coefficients can be inserted into both equations interchangeably. This enables the calculation of $\sum (P_{max} - \widehat{P}_{max})^2$ when inserted into $f(\rho)$ and $\sum (\rho - \widehat{\rho})^2$ when inserted into $f(P_{max})$. The sum of the squared differences $\sum (\rho - \widehat{\rho})^2$ and $\sum (P_{max} - \widehat{P}_{max})^2$ of both model equations and both sets of regression coefficients are listed in Table 2.

While for the regression of $f(\rho)$, a certain set of regression coefficients corresponds to the minimum of the sum of squared residuals, a different set results in the minimum for the regression of $f(P_{max})$. The explanation for the differences in the results of the least-square regression is the weighting of the respective residuals of the models. While $f(\rho)$ approaches infinity for higher values of ρ, with the increase of P_{max} $f(P_{max})$ converges to a certain limit. Therefore, small differences in P_{max} or ρ can have a significant impact on $\sum (P_{max} - \widehat{P}_{max})^2$ in high-pressure ranges.

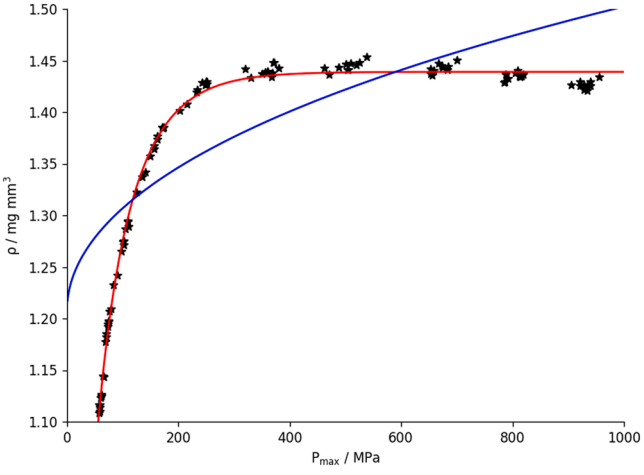

Fig. 1. Compressibility of 8 mm Vivapur® 102 tablets of 300 mg weight compressed at 3 mm s^{-1}, blue line: regression result of $\mathbf{f(\rho)}$, red line: regression result of $\mathbf{f(P_{max})}$.

Table 2
Sums of the squared differences for both regression models in Fig. 1.

Regression model	C / MPa^{-1}	ε_c / -	ρ_{sun} / $g\ cm^{-3}$	$\sum(\rho-\widehat{\rho})^2$ / $g^2\ cm^{-6}$	$\sum(P_{max}-\widehat{P}_{max})^2$ / MPa^2
$f(\rho)$	$1.95{\cdot}10^{-05}$	$4.88{\cdot}10^{-01}$	2.36	0.514	$3.9{\cdot}10^{6}$
f(P)	$1.65{\cdot}10^{-02}$	1.16	1.44	0.005	$6.3{\cdot}10^{6}$

In contrast, $\sum(\rho-\widehat{\rho})^2$ is less sensitive to these deviations. To counteract this misweighting, $f(P_{max})$ was applied for regression of the out-of-die compressibility in the subsequent analyses. Considering the true density of the particles in $f(P_{max})$ leads to Eq. (4), which describes the change in solid fraction SF within the tablet. This model equation is denoted in the following as $Sun^{-1}{}_{comp}$.

$$\mathbf{Sun^{-1}{}_{comp}} = \mathbf{SF} = \frac{\left|\boldsymbol{\rho_{sun}}\left(\boldsymbol{\varepsilon_c}\mathbf{W}\left(-\mathbf{e}^{-\frac{\boldsymbol{P_{max}}\mathbf{C}-\boldsymbol{\varepsilon_c}}{\boldsymbol{\varepsilon_c}}}\right)+1\right)\right|}{\boldsymbol{\rho_{true}}} \tag{4}$$

The regression of $Sun^{-1}{}_{comp}$ was calculated using the optimize.curve_fit algorithm of the SciPy 1.11.4 Python package on the raw data. In this context, the trust region reflective (TRF) algorithm was chosen for the minimization of the residuals. The initial coefficients of the model were set as follows: $C = 10^{-3}MPa^{-1}$, $\varepsilon_c = 0.5$, $\rho_{sun} = 1.5\ g\ cm^{-3}$. The lower bounds for all coefficients were set to 0. Both C and ρ_{sun} had no upper bounds, while the upper bound for ε_c was set to 2. Values of $\varepsilon_c > 1$ were not avoided in the regression as for in-die data a density above the true density of particles is described in literature. The regression was computed over 10^4 iterations.

Tabletability regression model

For the regression of the change of the tensile strength σ over the maximum compression pressure P_{max} the model equation according to Vreeman and Sun[35] was applicated (Eq. (5)).

$$\boldsymbol{\sigma} = \boldsymbol{\sigma_{max}}\mathbf{e}^{\boldsymbol{\alpha}\mathbf{W}\left(-\mathbf{e}^{-\frac{\boldsymbol{P_{max}}}{\boldsymbol{\beta}}-1}\right)} \tag{5}$$

The tensile strength at an infinite maximum compression pressure σ_{max}, the α parameter derived from the Ryshkewitch equation and the β parameter defined as $\frac{C}{\varepsilon_c}$ are the coefficients of the regression model. The model for the tabletability is abbreviated as Sun_{tabl} in the following sections. The regression was calculated via the optimize.curve_fit algorithm of SciPy 1.11.4 in Python 3.9 applying the TRF algorithm. The initial guesses for the coefficients of the model were set as: $\sigma_{max} = 1$ MPa, $\alpha = 1$, $\beta = 500$ MPa. The regression was calculated in 10^4 iterations with the lower bound of 0, and without an upper bound for any of the three coefficients.

Compactability regression model

The compactability expressed as the change of the tensile strength σ over the change of the solid fraction SF was regressed using the equation according to Ryshkewitch[36] (Eq. (6)).

$$\boldsymbol{\sigma} = \boldsymbol{\sigma_{max}}\mathbf{e}^{-\mathbf{b}(1-\mathbf{SF})} \tag{6}$$

The empirical decay constant b and the tensile strength at an infinite maximum compression pressure σ_{max} are the coefficients of this regression model. In the regression of this equation as well, the optimize.curve_fit function of SciPy 1.11.4 was utilized. The initial value for both coefficients was set to 1. Both coefficients were optimized in 10^4 iterations with a lower limit of 0 and without an upper limit.

Generation of graphics of compressibility, tabletability and compactability

For the generation of the graphics, Matplotlib 3.7.2 was utilized. The data was filtered according to the target weight of the tablets and subsequently batched means and standard deviations were calculated over the compression pressure in a step size of 50 MPa. Therefore, the data density of the mean values is not a constant but 10 samples per group in average. The coloring of the markers and lines was done in correspondence to the mean measured weights of the batches of tablets. Individual markers are color-coded according to their respective measured mass.

Multiple linear regression modeling to describe the effect of the surface area to volume ratio

To assess whether variations in tablet weight and diameter could be accounted for by changes in the surface area-to-volume ratio AV^{-1}, data obtained from formulations compressed using different punch geometries were analyzed by multiple linear regression using the least squares method. The models incorporated both linear and quadratic terms for compaction pressure and AV^{-1}, as well as their interaction, to predict tensile strength and solid fraction. Regression residuals were subsequently evaluated separately for each punch geometry to identify systematic deviations and assess systematic trends within the residuals.

Results and discussion

Re-evaluation of results of Berkenkemper et al. and test of reproducibility

Although the authors of the database concluded, based on a principal component analysis, that the influence of the compacted material mass on the compression analysis is minor, the raw tabletability data clearly indicate that this statement holds true only for certain materials (Fig. 2). Despite the relatively low data density of this dataset, it is evident that the tabletability of various grades of dibasic calcium phosphate (DiCaFos® A7, A60, A150, and Fujicalin®) exhibits a pronounced dependence on the compacted mass. Among the materials studied, Fujicalin® exhibits this behavior most prominently. In contrast, both lactose grades, as well as kappa-carrageenan and cornstarch, show a weaker or even none dependency. Tablets made from the investigated grade of microcrystalline cellulose Vivapur® 102, however, display a notable dependence of tensile strength on tablet mass, particularly at higher compression pressures exceeding 150 MPa. To verify and further investigate this mass depended variations, the database presented in this study was generated.

To evaluate the reliability of the data, the two databases were compared. Fig. 3 illustrates the comparison of the measured tensile strength of tablets produced using Fujicalin®, as recorded in the database by Berkenkemper et al., and in the newly generated database, plotted against compression pressure. The figure clearly demonstrates that the data pattern observed in the published data is confirmed in the new database.

Owing to the higher data density and broader range of the new dataset, the dependence of measured tensile strength on tablet mass is even more pronounced. The overall data trends are highly consistent across both datasets, with only minor systematic deviations observed for tablets weighing 250 mg. These deviations, however, are negligible and do certainly not impact the conclusions drawn from this study. Fig. 3 reveals an additional detail. While a separation of the tabletability

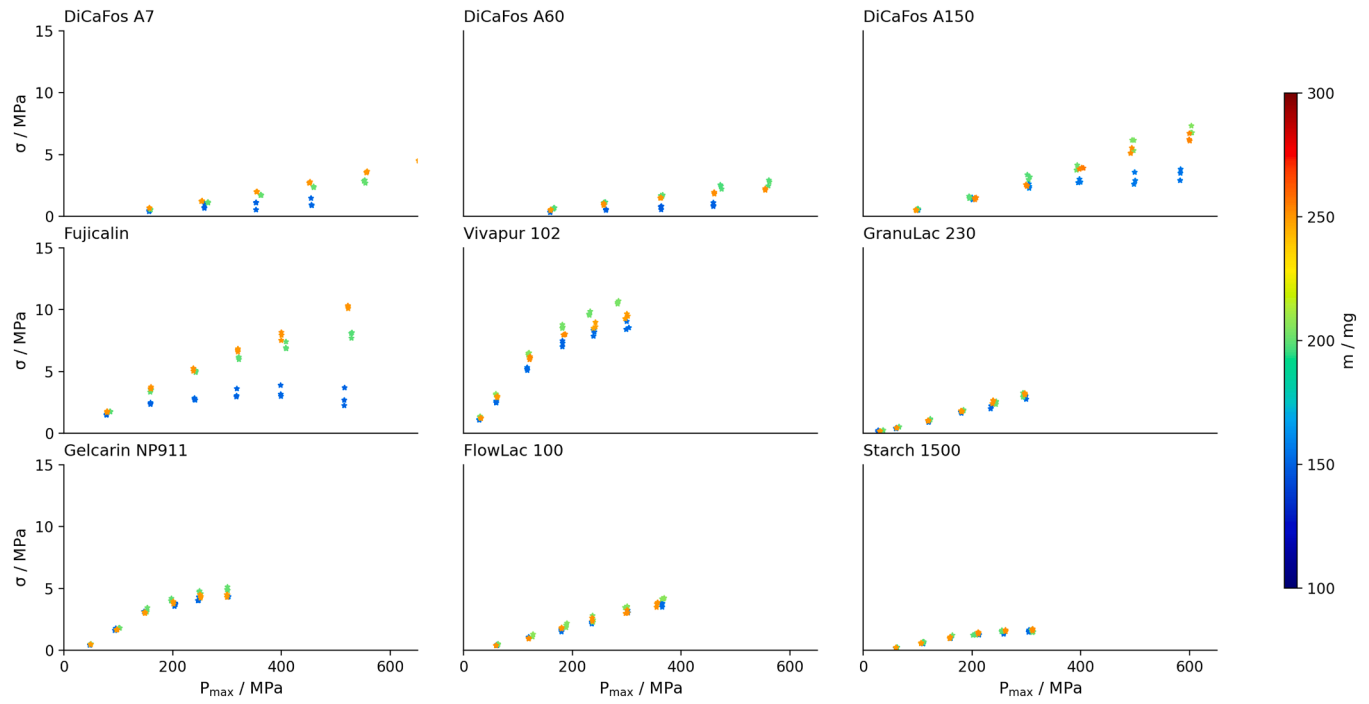

Fig. 2. Tabletability plot of a selection of materials of the data base according to Berkenkemper et al. for 8 mm tablets, at a compression speed of 3 mm s^{-1} for weights of 150, 200 and 250 mg.

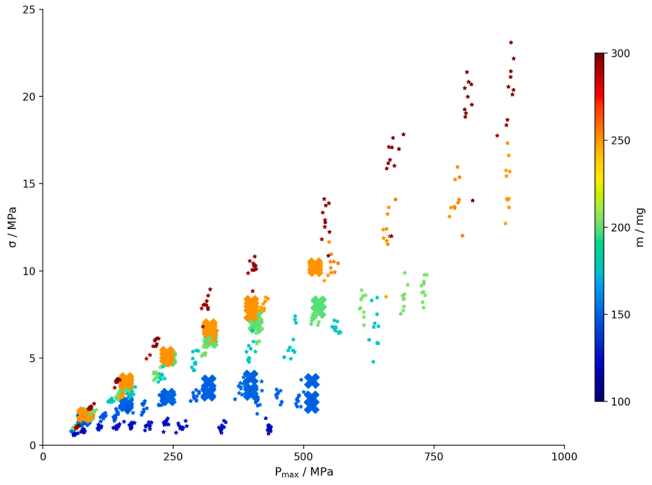

Fig. 3. Comparison of Fujicalin® in the Berkenkemper et al. dataset (bold crosses) to the results in this study (small stars), for 8 mm tablets, at a compression speed of 3 mm s^{-1}.

profiles for tablets of different masses is evident, considering the variability of the values leads to overlaps in between profiles of different masses. The variations in tensile strength within a tabletability profile, therefore, cannot be fully explained by fluctuations in tablet mass.

The mass effects of the tablets presented and analyzed in this study do not appear to arise from experimental errors. Moreover, the reproducibility of the findings from Berkenkemper et al. has been confirmed through validation by an independent experimenter.

Influences of the tablet diameter on the tensile strength

It is evident that the dataset contains erroneous measurements of tablet diameters for the materials DiCaFos® A60 and HPC SL FP (Fig. 4a). These erroneous data points were removed from the dataset prior to all shown analyses by introducing a minimum diameter limit of 7.8 mm for all tablets. However, even upon examining the remaining data (Fig. 4b), it becomes apparent that the measured diameter significantly deviates from the punch diameter depending on the material. For example, tablets made from HPC SL FP are measured to be >100 µm smaller than the diameter of the die. Similar to the trend observed in 8 mm tablets, the data for 11.28 mm tablets show a comparable pattern (Fig. 4c). Tablets made from Fujicalin® and Tablettose® 70 are measured as slightly wider than the punch diameter, whereas Vivapur® 102 tablets are measured as slightly smaller. However, these potential errors in the determination of tablet thickness can only account for effects up to 0.1 MPa. Therefore, they cannot be considered as plausible explanations for the observed effects in this study.

Distance between punches velocity profiles

It is well known that the punch speed profile can influence compression analysis.[11,37] This influence is dependent, both on the deformation properties of the compressed material as well as on the particle shape and particle size distribution. For the sake of completeness, the set punch speed was reviewed based on the collected data. It was found that the compaction simulator showed significant deviations from the set target values depending on the individual materials. Fig. 5 displays the temporal derivatives of the distance between the punches. It can be observed that the compression profiles vary depending on the material. As expected, the duration of compression is individual for each of the material-setting combinations. The higher the dosing high, and the smaller the minimum thickness during compression, the longer is the compression process. However, the velocity profiles of the distance between punches indicate that the change in the velocity depends highly on the material and the machine settings. While for some materials the target value of 6 mm s^{-1} (Fig. 5a) can be maintained for a certain period, the profiles of other substances deviate instantly from the set value. Nevertheless, for the present study, the influence of material- and dosing-height-dependent punch movements is considered small. Investigations into different punch speeds (3 and 15 mm s^{-1}, Fig. 5b) clearly show that only minor differences occur across all materials

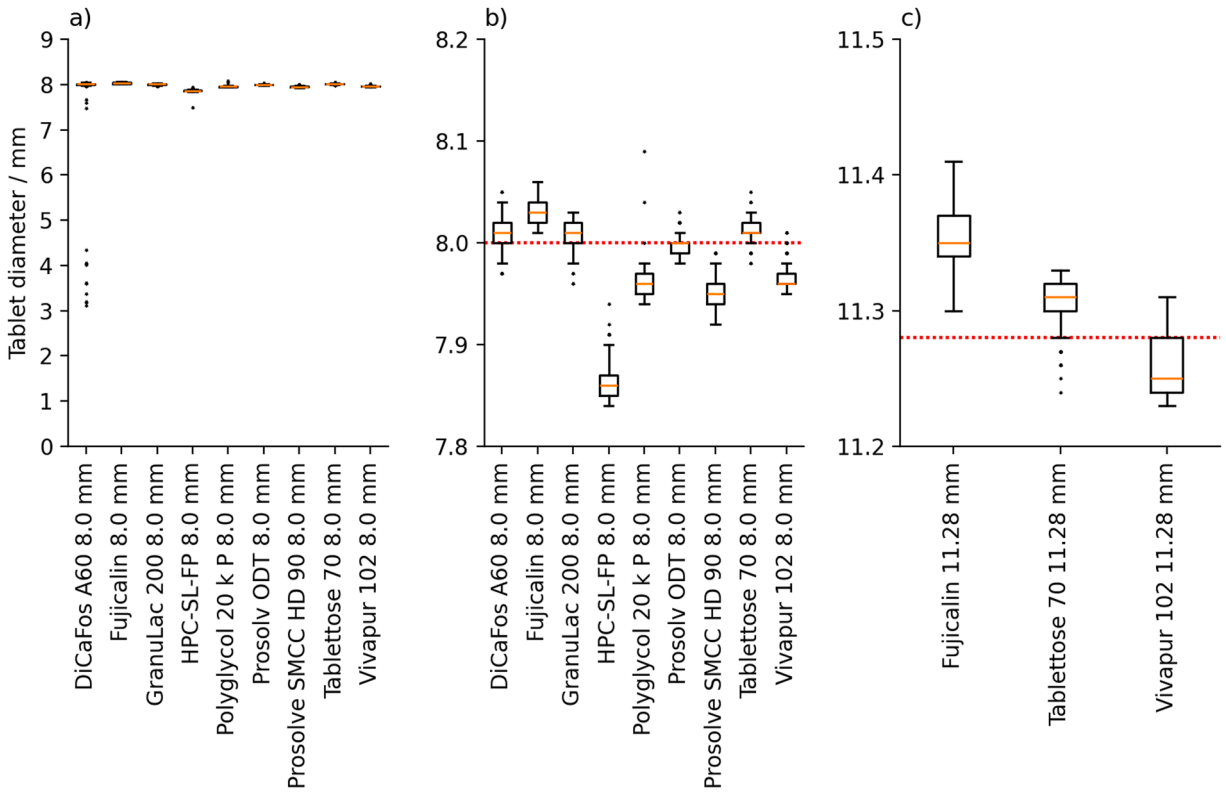

Fig. 4. Measured diameter of the tablets using the SmartTest50, a): 8 mm punch diameter, b): 8 mm punch diameter zoomed, c): 11.28 mm punch diameter, whiskers: 1.5 interquartile range, orange lines: median, red dotted line: die diameter.

(Fig. 9). The material- and dosing-height-dependent variations in the compression profiles are significantly smaller in magnitude than the differences between the two settings of the punch speeds of 3 and 15 mm s^{-1}. Therefore, the effects resulting from the errors in the velocity profile seem to be neglectable. However, it should be noted that such types of variations may need to be considered when working with compaction simulators, depending on the respective study. Furthermore, the differences in punch movements, due to their material- and dosing-height specificity, also seem suitable for enabling investigations into the respective material properties and machine settings. Particularly for transfer studies using compaction simulators, it could be of interest whether material-dependent differences in the punch speed profiles also occur during the simulation of rotary tablet presses.

Mass correlated compressibility

The investigation of the out-of-die compressibility of the substances (Fig. 6) indicates that, for most materials, the tablet mass appears to have minimal influence. The curves of solid fraction versus maximum compression pressure generally form a family of curves.

However, there seems to exist a slight trend where tablets with higher mass exhibit a slightly higher solid fraction at the same compression pressure. This trend is particularly evident in PROSOLV® ODT, PROSOLV® HD 90, and Vivapur® 102. Nevertheless, a weakened version of this trend can also be observed in GranuLac® 200, Tablettose® 70, and Fujicalin®.

This phenomenon can be partially explained by findings regarding the distribution of material density within the tablets. Studies using discrete element methods and μ-CT have shown that material densification within tablets is not uniform. Edge regions, as well as the top and bottom surfaces, experience different compression compared to the tablet core. For instance, in the compression of pH 102 (FMC, USA), a grade of microcrystalline cellulose, into flat-faced tablets of 25 mm at a pressure of 92.7 MPa, it was observed that the density was highest in the "top corner" and "middle bottom half" of the tablets, while the "top center" and "bottom corners" exhibited the lowest density within the compacts.[22] Similarly, flat-faced compacts of various geometries made from anhydrous dibasic calcium phosphate (ATAB®, Rhodia, France) or microcrystalline cellulose (Avicel® PH-200, FMC, USA) showed regions of higher bulk density at the tablet edges.[21] In another example, changes in the density over the height of tablets made from microcrystalline cellulose (Vivapur® 102, JRS Pharma, Germany) were investigated.[23] Besides tablet diameter, the tablet height influences AV^{-1}. The ratio of regions with high material density to those with low material density is expected to correlate roughly with the tablet's AV^{-1}. As suggested by material-dependent differences in these studies, the density distribution within tablets strongly depends on the properties of the compressed materials.

An increase in tablet mass, while maintaining the same average solid fraction within the tablet, leads to an increase in thickness. This might explain why the measured solid fraction of the tablet appears to depend on its mass. The authors hypothesize that investigations using discrete element method, μ-CT, or similar methods might reveal differences in the density distribution within the tablets, depending on whether a material shows a mass-dependent solid fraction or not.

However, it appears evident that differences in the density distribution within a tablet can also lead to variations in adhesion forces. As a result, denser regions contribute differently to the overall bonding within the tablet compared to the core volume. A correlated measure to the bonding forces is the tensile strength, which is examined in the following sections.

Mass correlated tabletability and compactability

Fig. 7 demonstrates over almost all materials a significant correlation of the strength of the 8 mm flat-faced tablets with amount of compressed material. For all influenced materials the tensile strength increases for

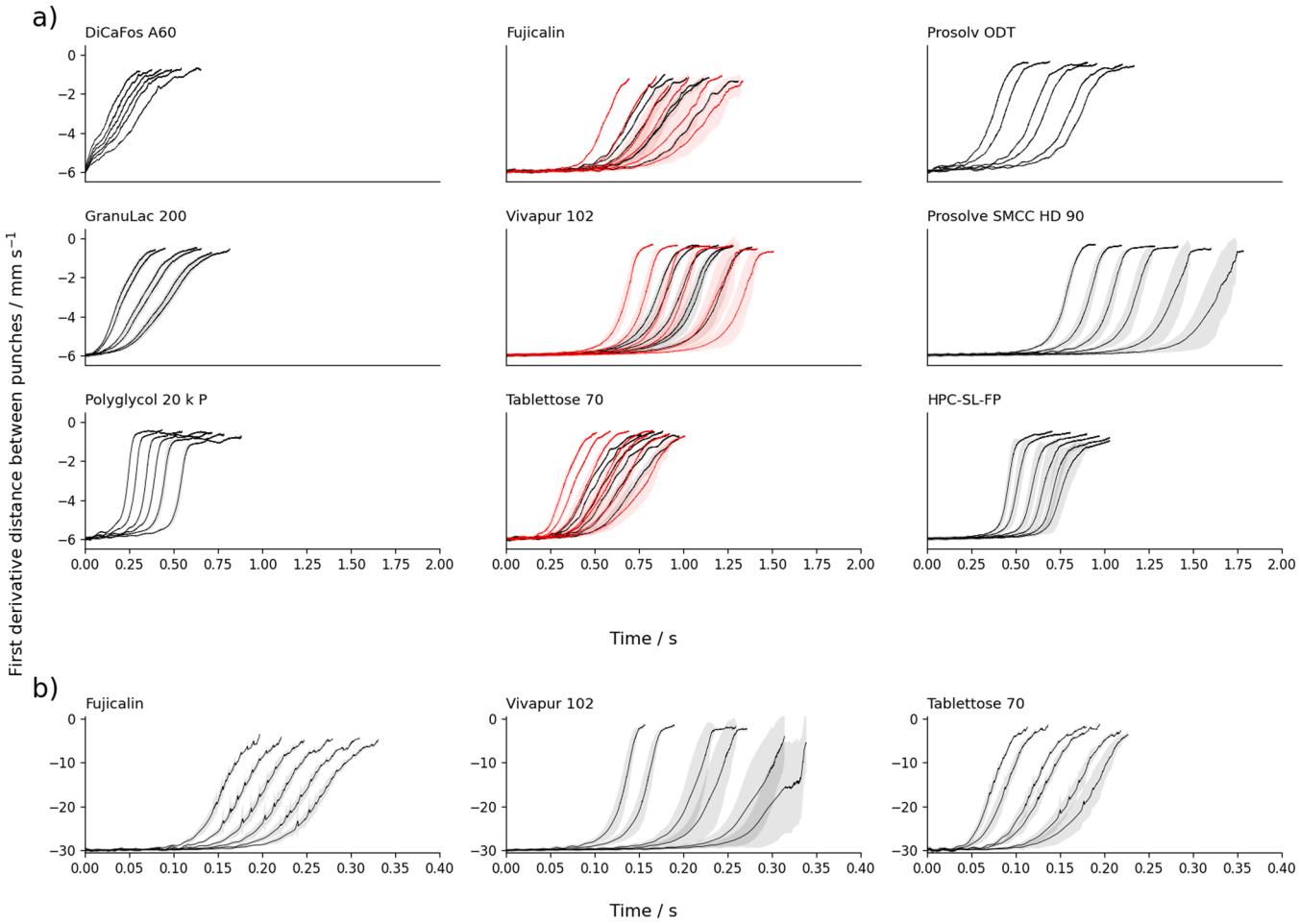

Fig. 5. First derivative of the distance between punches for compressions at a): 3 mm s^{-1} and b): 15 mm s^{-1} punch speed, black: 8 mm punch, red: 11.28 mm punch, solid lines: $\bar{x}$, shaded areas: $\bar{x} \pm s$, all curves are filtered based on mean filters in a width of 73 values and averaged over interpolations.

higher tablet masses. Thereby, the increase in the tensile strength is non-linear in correspondence to the compression pressure. In the comparison of Vivapur® 102 and PROSOLV® HD 90 the differences in both grades of microcrystalline cellulose are striking. While the tabletability of Vivapur® 102 is steadily increasing depending on the weight of the tablets, PROSOLV® HD 90 shows a capping tendency of the tensile strength around the 200 mg tablets. Beyond this point increases in the amount of compressed material were not resulting in an increase of the tensile strength. Additionally, the tensile strength at around 200 MPa reaches a maximum for 200 mg tablets of PROSOLV® HD 90. Both, lower and higher masses yielded in a reduction of the strength of the tablets in this pressure range. The tablets made of the co-processed excipient PROSOLV® ODT behaves comparable to PROSOLV® HD 90, with a clear dependency up to around 200 mg followed by a plateau. For all materials containing microcrystalline cellulose as well as for HPC SL FP and Polyglycol 20000 P, at high pressures the tensile strength approaches a plateau. This well-known phenomenon is often referred to as over-compression. A new finding of this study is that the influence of the tablet weight on the tensile strength in this range seems to be constant in respective to changes of the compression pressure. Both investigated grades of lactose seem to behave comparable to each another. The tensile strength of tablets composed of Tablettose® 70 or GranuLac® 200 increased with an increase in the weights of the tablets. Only a slightly higher dependency of GranuLac® 200 on the amount of compressed material in ranges above 150 mg can be detected. Hardly any change in the tabletability is visible for HPC SL FP and Polyglycol 20000 P HPC SL FP reaches a plateau in tensile strength already at low compaction pressures. The height of this plateau does not appear to depend on the amount of material compressed. The data for Polyglycol 20000 P indicate a change in the course of tabletability, although the observed trend is not consistent. At the same time, clear deviations of the data from the regression lines are evident.

As already suggested by the data of Berkenkemper et all., the highest effect of the tablet weight on the strength of the tablets is within the data of Fujicalin®. The differences in the tensile strength at similar compression pressures is up to 10 MPa. In direct contrast is DiCaFos® A60, which's tablets hardly show any effect resulting from the increase in tablet weight. The comparisons clearly demonstrate that the particle architecture must be considered to estimate the impact of tablet weight on the strength of tablets. The results indicate that the interdependency of material properties, tablet weight and geometry seem to be complex and highly depending on the respective factor combinations.

Influences of process parameters are commonly known in the literature. Here the most prominent example is the impact of the tableting speed and/or dwell time on the tabletability profile.[11] In dependence on the material properties this effect is of varying prominence. However, the authors of former studies were able to demonstrate that the correlation of the solid fraction and the tablet strength, the compactability, is hardly influenced by the tableting speed. In the present study, considering the compactability of the 8 mm tablets at 3 mm s^{-1}, most of the differences in the tabletability resulting from the changes of the amount of material are equalized (Fig. 8). As already observed for tabletability, the data for materials HPC SL FP and Polyglycol 20000 P show no interpretable trend and exhibit very high scattering. Small variations

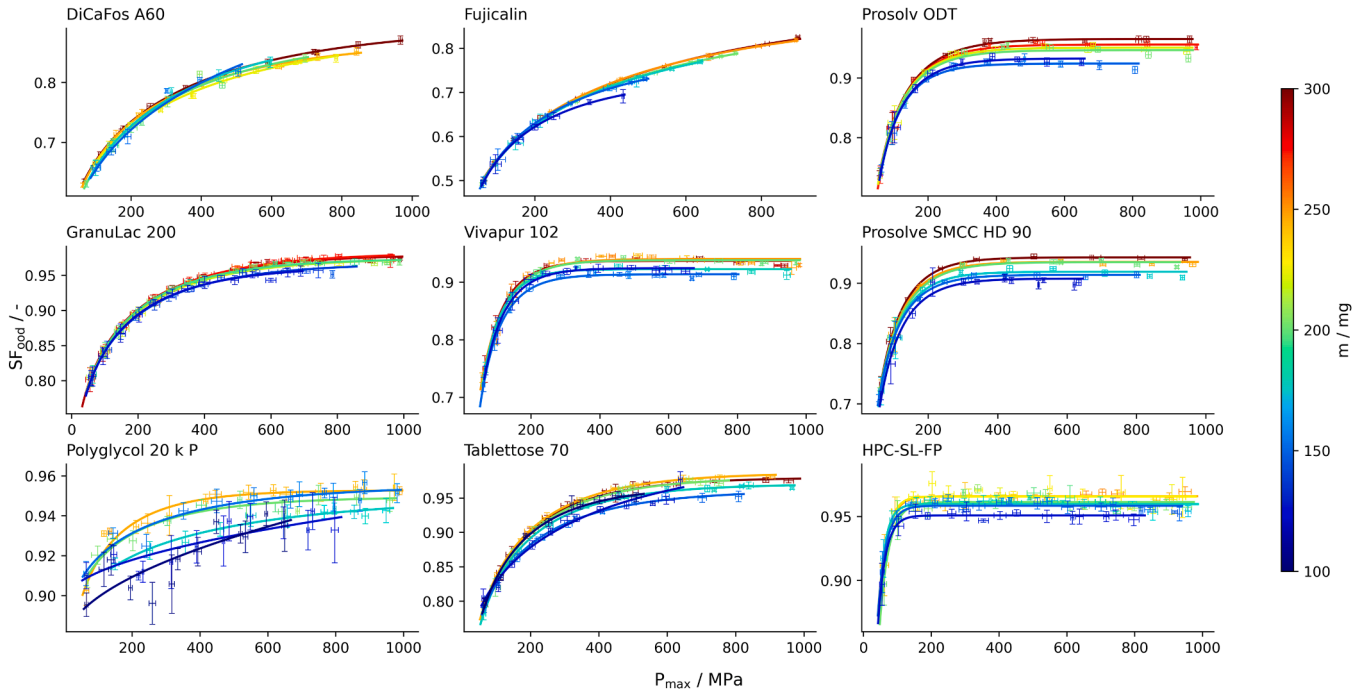

Fig. 6. Influence of tablet weight on the out-of-die compressibility of the materials within the database for 8 mm tablets at a punch speed of 3 mm s^{-1}, markers and error bars: $\bar{\mathbf{x}} \pm \mathbf{s}$, $\bar{\mathbf{n}} = 10$, solid lines: regression of the $\mathbf{Sun}^{-1}_{\mathbf{comp}}$ model.

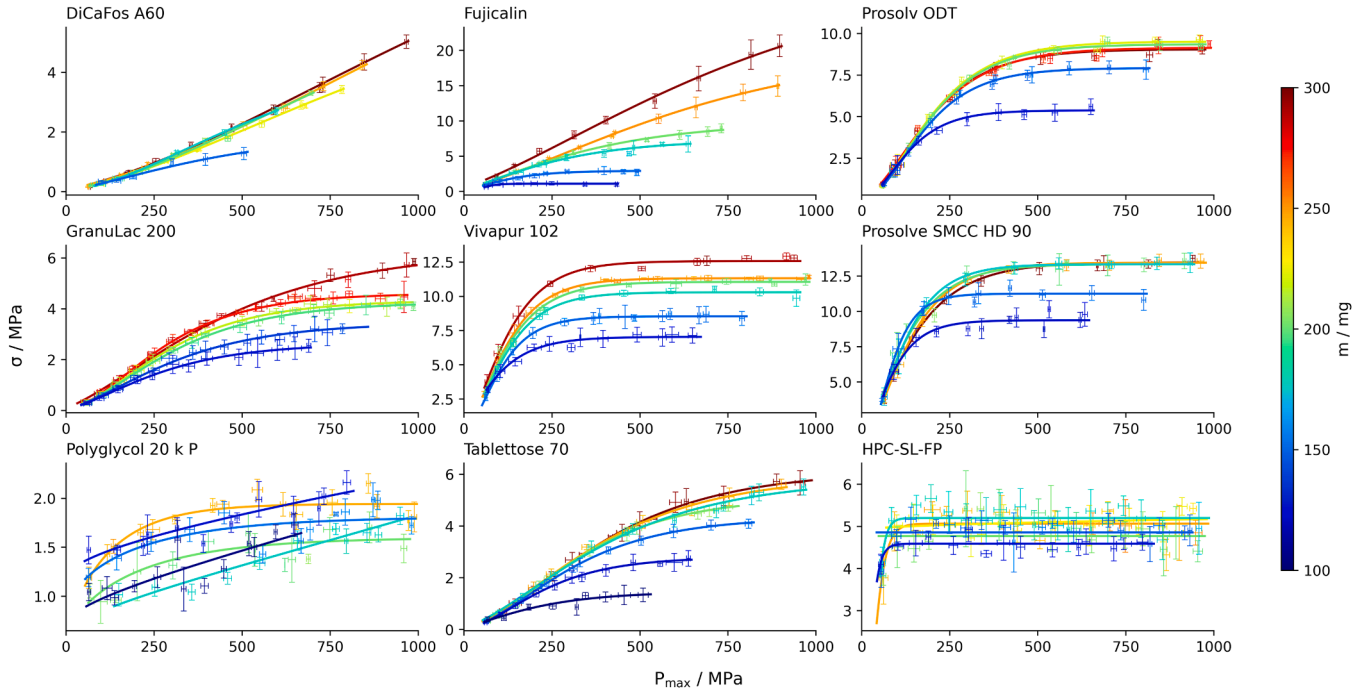

Fig. 7. Influence of tablet weight on the tabletability of the materials within the database for 8 mm tablets at a compression speed of 3 mm s^{-1}, markers and error bars: $\bar{\mathbf{x}} \pm \mathbf{s}$, $\bar{\mathbf{n}} = 10$, solid lines: regression of the $\mathbf{Sun}_{\mathbf{tabl}}$ model.

clearly can be identified in the data of DiCaFos® A60, GranuLac® 200, PROSOLV® ODT, and PROSOLV® HD 90. In sharp contrast, tablets of Fujicalin®, Tablettose® 70, or Vivapur® 102, exhibit even in the compactability a high dependency on the tablet weight. In the case of Tablettose® 70, the influence of the amount of compressed material on compactability is primarily observed for masses below 150 mg. Above this threshold, the effect becomes negligible. For Vivapur® 102, the influence is also most pronounced at lower masses but continues to persist at higher masses. In the case of Fujicalin®, the dependence can be traced in a manner similar to that observed for tabletability. Here, a clear relationship between compactability and the amount of compressed material is evident over the full mass range. Again, a direct comparison of Fujicalin® with DiCaFos® A60 indicates that this behavior is influenced not only by the chemical properties of the material but also by its particle characteristics.

DiCaFos A60 is a roundish milled grade of dibasic calcium

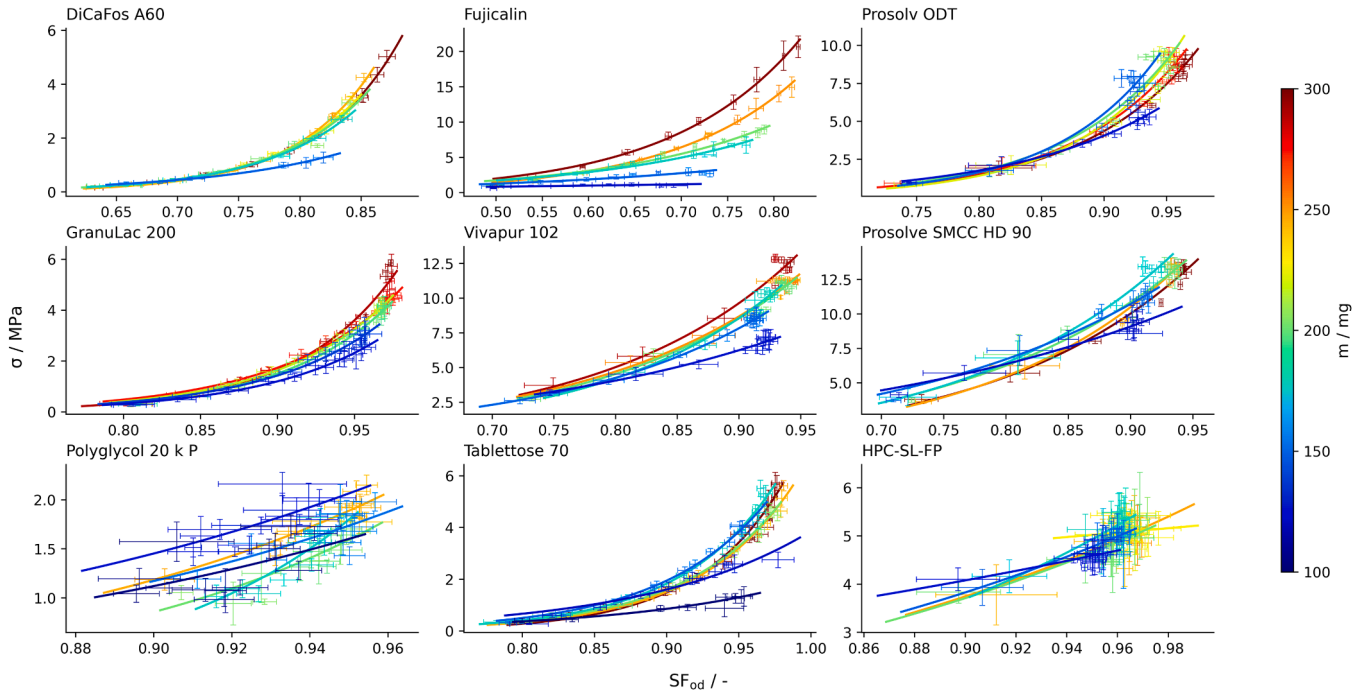

Fig. 8. Influence of tablet weight on the compactability of the materials within the database for 8 mm tablets at a compression speed of 3 mm s^{-1}, markers and error bars: $\bar{\mathbf{x}} \pm \mathbf{s}$, $\bar{\mathbf{n}} = 10$, solid lines: regression of the Ryshkewitch model.

phosphate. In comparison, Fujicalin® is manufactured via spray-drying. Both grades are of a similar particle size with dx$_{50}$ in between 60 and 80 µm. The hollow and spherical particles of Fujicalin® however, are described to provide a plastically-like deformation behavior to dibasic calcium phosphate.[38] The particles easily fragmentate during the compression what results in an increase of the total binding area.

The plasticity of the materials cannot be identified as the factor to consider in the evaluation of the impact of tablet weight on the strength of tablets as plastically deformable materials in the database based on microcrystalline cellulose or hydroxypropyl cellulose behave differently. Also, spherical particle architecture cannot be fully responsible for the behavior of Fujicalin® as the spray agglomerated grade of α-lactose monohydrate, Tablettose® 70, shows to be much less influenced in direct comparison with GranuLac® 200. At this point it can be stated that the impact of the amount of compressed material on the properties of the tablet depends on material attributes ranging over particle

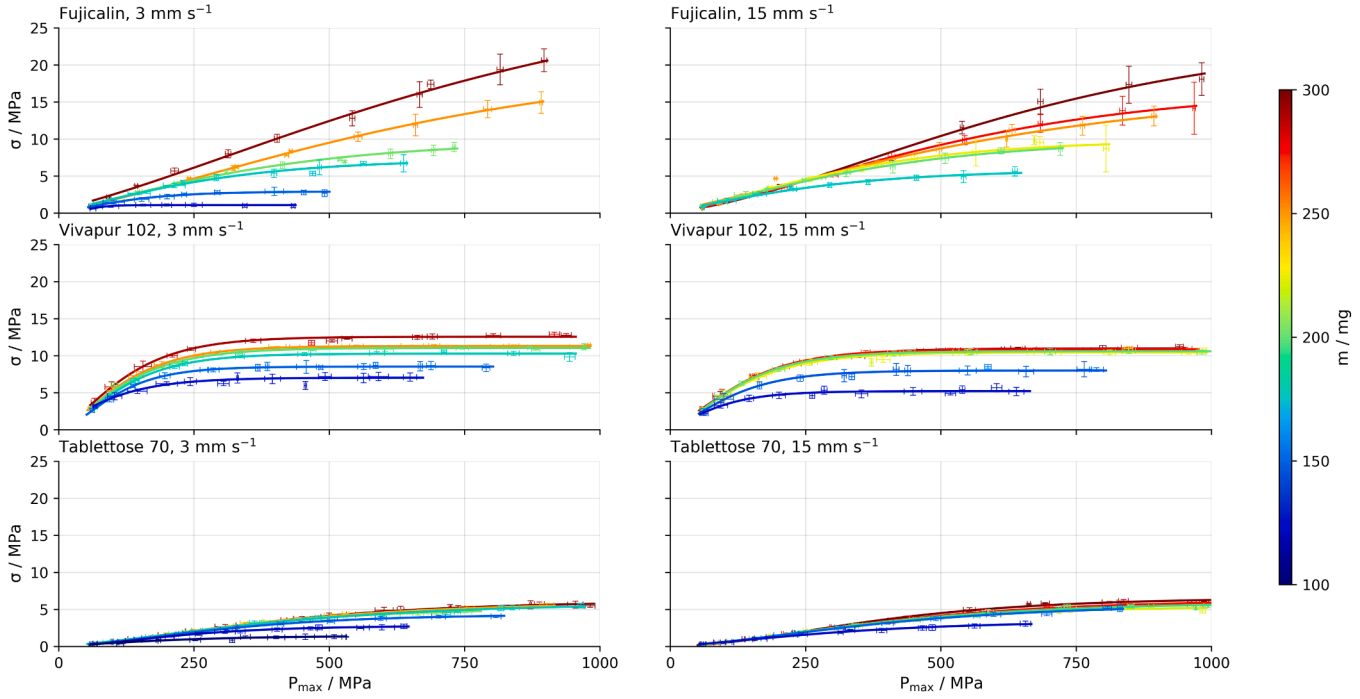

Fig. 9. Influence of tablet weight on the tabletability of the materials within the database for 8 mm tablets at compression speeds of 3 and 15 mm s^{-1}, markers and error bars: $\bar{\mathbf{x}} \pm \mathbf{s}$, $\bar{\mathbf{n}} = 10$, solid lines: regression of the $\mathbf{Sun}_{\mathbf{tabl}}$ model.

architecture and deformation behavior. Even the compactability of some materials is influenced by changes in the tablet weight.

Influences of the tableting speed and the punch diameter

When considering the influence of process parameters, the question always arises whether there are interactions with other parameters. For this reason, investigations were conducted at two different compression speeds for three of the materials. The comparison of the three materials regarding the factor of the tableting speed interacting with the changes in the weights of tablets can be assessed in Fig. 9. As expected, the tabletability is reduced by the increase in the tableting speed. Reproducing former knowledge, this seems to be most prominent in Vivapur® 102 while the tabletability profiles of Tablettose® 70 are almost not influenced. The effect of the amount of compressed material is hardly influenced by the tableting speed for any of the materials. However, the differences in the punch speeds examined were quite small. Larger interactions may potentially be observed at higher speeds.

In contrast the influence on the punch diameter on the effect of amount of compressed material is more striking. While the effect of the tablets weight in 8 mm tablets is as significant as described previously, for 11.28 mm tablets the impact is highly reduced. It must be mentioned here that the comparability between 8 mm and 11.28 mm tablets is influenced by the fact that the larger tablets had to be manufactured in a different range of tablet weights and archived compression pressures. To achieve the similarly weighting tablets with diameters of 8 mm and 11.28 mm, their dosing height must differ by a factor of 1.99. The same applies to the compression pressure. With a maximum punch load of around 50 kN, approximately 1000 MPa can be achieved using 8 mm punches, while only 500 MPa can be reached with 11.28 mm punches. Due to machine limitations, this further hinders the investigation of similar ranges of settings. However, the prominence of the effect on the tabletability of Fujicalin® is lost in the tablets of the larger diameter. Only smaller differences can be observed here with a difference in the tensile strength in between the maximum and the minimum weight of around 3 MPa. This appears to be primarily influenced by the fact that the tabletability of the 11.28 mm tablets is dramatically lower compared to the 8 mm tablets. The tabletability of Tablettose® 70 remains mostly unaffected by the amount of compressed material, when the tablet diameter is changed from 8 mm to 11.28 mm. Contrary, the tabletability of Vivapur® 102 is still highly influenced by the weight of the 11.28 mm tablets. The overall tabletability of both Tablettose® 70 and Vivapur® 102 is considerably less affected by changes in tablet diameter compared to that of Fujicalin®. Again, it remains unclear what material properties results in the dependency of the properties of the tablets on the tablet's weights. The behavior of the materials of different properties seem to indicate that the mechanistical explanation of this phenomenon cannot be made up based on simple correlations with material properties.

This study is not the first published to investigate the dependency of tensile strength on tablet size. Previous studies examining tablets of varying diameters in context of the investigations of mini-tablets have already demonstrated that diameter can influence the compactability profile of materials.[39] In the cited study, the authors maintained a constant fill height during tableting, resulting in an investigation of tablets with diameters ranging from 1 mm to 11.28 mm across distinct and non-overlapping weight ranges. The magnitude of the effect on tensile strength was shown to be material-dependent. The data collected in the present study clearly indicate that not only the diameter but also the height of the tablets can affect the tabletability and compactability of a material. This underscores the complexity of comparing tablets of different diameters. Tablets with the same fill height but varying diameters differ in weight. Simultaneously, they may exhibit differences in tensile strength. When considering which geometry to choose, maintaining a constant mass for smaller tablets would require a greater fill height. As shown in Fig. 10, this would result in an increase in tabletability. For instance, 300 mg tablets with an 8 mm diameter achieve a higher tensile strength compared to 300 mg tablets with an 11.28 mm diameter, given the same mass and compaction pressure. The following section examines whether AV^{-1} can serve as a geometric factor to describe this effect.

MLR results

Variation in the amount of compressed material results in different

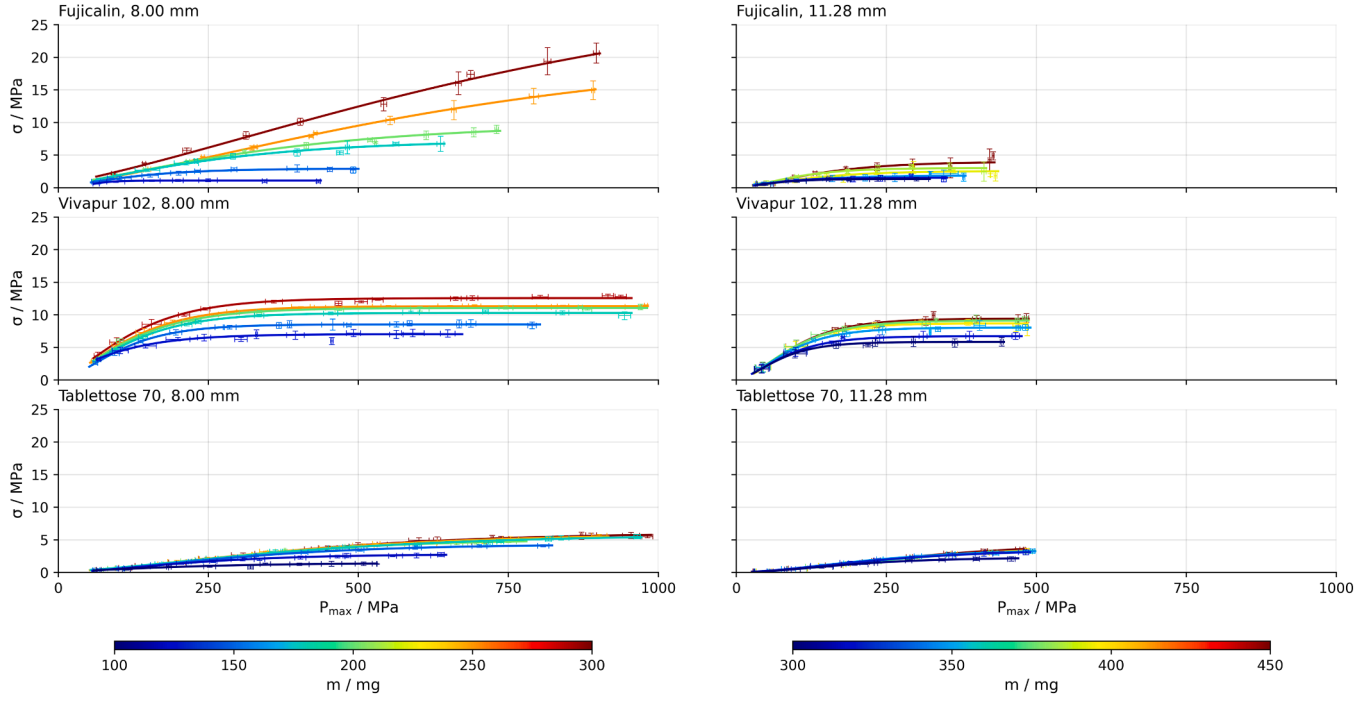

Fig. 10. Influence of tablet weight on the tabletability of the materials within the database for 8 and 11.28 mm tablets at compression speeds of 3 mm s^{-1}, markers and error bars: $\bar{x} \pm s$, $\bar{n} = 10$, solid lines: regression of the $\mathbf{Sun}_{\mathbf{tabl}}$ model.

tablet heights at constant compaction pressure. Conversely, changes in tablet diameter at a fixed tablet mass lead to changes in tablet thickness. To address this geometric factor, AV^{-1} appears to be a suitable descriptor. The central question is whether changes in AV^{-1} - whether caused by variations in the amount of compressed material or by changes in tablet diameter - have the same effect on the responses tensile strength and solid fraction. If this is the case, the residuals of regression models based on data from tablets of different diameters should exhibit similar distributions.

To assess the subsequent models, the factor spaces of the different materials were examined (Fig. 11a). It was found that the investigated ranges of AV^{-1} of tablets with both diameters overlap. However, significant confounding was observed in the respective correlation plots. Consequently, in the following analyses, it must be considered that, for example, the interaction effect PAV^{-1} and the linear effect AV^{-1} cannot be clearly separated. The corresponding magnitudes of the Pearson correlation coefficients reach up to 0.8. The models for tensile strength exhibit coefficients of determination ranging from 0.83 (Vivapur® 102) to 0.96 (Tablettose® 70). Similar values are achieved for the models of solid fraction, ranging from 0.82 (Vivapur® 102) to 0.96 (Fujicalin®).

Fig. 11 presents the coefficient plots of the multiple linear regression models for tensile strength (Fig. 11b) and solid fraction (Fig. 11d). As expected from previous analyses, all three materials investigated in this study exhibit significant coefficients for AV^{-1} regarding its effect on tensile strength. An increase in AV^{-1} has a nonlinear negative effect on tensile strength. This observation accounts for both effects described earlier. An increase in tablet diameter, at constant mass, leads to a reduction in tablet height and consequently to an increase in AV^{-1}, resulting in a decrease in tensile strength. At the same time, increasing the amount of compressed material leads to a decrease in AV^{-1} and, accordingly, to an increase in tensile strength. Moreover, the negative interaction term reflects that the effects of changes in material quantity become more pronounced at higher compaction pressures.

An examination of the residuals of tensile strength (Fig. 11c) reveals a systematic trend: the tensile strength of tablets with larger diameters tends to be overestimated by the models, whereas that of smaller tablets tends to be underestimated. The models for the solid fraction of the tablets show a smaller, yet significant, influence of AV^{-1}, as well as its interaction with compaction pressure. Here too, a subtle systematic pattern in the residuals across different tablet geometries can be discerned (Fig. 11e).

In addition to AV^{-1}, there thus appears to be another geometric effect, which, however, cannot be further resolved at this point. To investigate this, detailed studies focusing on incremental variations in tablet diameter would be required.

Conclusion

This publication highlights that tablet weight and corresponding thickness can influence compression characteristics and tablet strength. At this stage, it remains unclear whether the observed effects are driven by changes in the surface area-to-volume ratio, variations in density distribution within the tablets, alterations in tablet geometry, or other contributing factors. Nevertheless, the results clearly indicate that the amount of compressed material may significantly impact the tabletability of the produced tablets. The magnitude of this correlation depends on the properties of the compressed materials and the pressure range of interest. Notably, materials with fragile particle architectures appear particularly sensitive to the amount of compressed material.

While compactability is less affected overall, one of the investigated

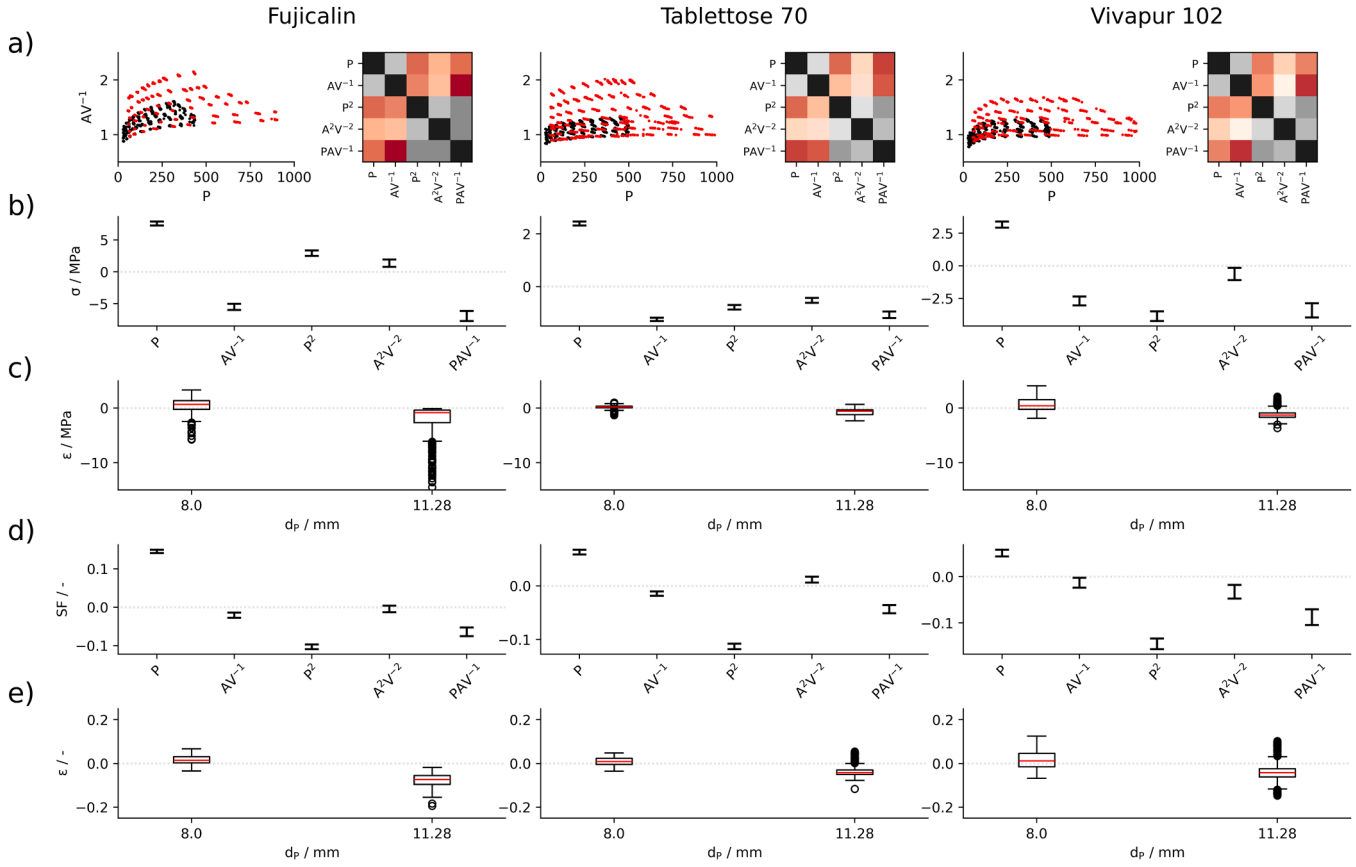

Fig. 11. Multiple linear regression results, a): factor spaces and correlation plots of the coefficients, black markers: 11.28 mm tablets, red markers: 8 mm tablets, b): coefficient plot for tensile strength, c): residuals of tensile strength, d): coefficient plot for solid fraction, e): residuals of solid fraction, all whiskers in boxplots in range of 1.5 IQR.

materials still showed a strong dependency on tablet weight. These findings have potential implications for formulation development and the selection of punch geometries for the final product. However, it is important to note that the pressure ranges investigated in this study significantly exceed those typically employed in industrial tablet production. Furthermore, the question arises as to whether similar effects can also be observed in multicomponent mixtures. Future studies will need to assess whether these findings have practical relevance or remain primarily of academic interest. Additionally, the underlying causes of the observed changes in tensile strength must be further explored. This could involve investigating tablets of varying shapes and weights using advanced imaging techniques such as μ-CT or NMR to evaluate density distributions. Furthermore, other parameters of mechanical strength should be analysed to confirm the observed differences in mechanical resistance.

This study makes it unequivocally clear that tensile strength must be critically reconsidered as a parameter for comparisons of tablets with differing geometries, thicknesses, or diameters, even though it is commonly used for this purpose in the literature.

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the authors used ChatGPT 4o and o1-preview in order to generate code snippets and to improve the writing style. After using this tool, the authors reviewed and edited the content as needed and take full responsibility for the content of the published article.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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