



Mean yield pressure from the in-die Heckel analysis is a reliable plasticity parameter

Gerrit Vreeman, Changquan Calvin Sun*

Pharmaceutical Materials Science and Engineering Laboratory, Department of Pharmaceutics, College of Pharmacy, University of Minnesota, Minneapolis, MN 55455, United States

ARTICLE INFO

Keywords:

Compaction
Plasticity
Powder
Heckel analysis
In-die

ABSTRACT

Despite the ability to characterize the plasticity of powders in a material-sparing and expedited manner, the in-die Heckel analysis has been widely criticized for its sensitivity to several factors, such as particle elastic deformation, tooling size, lubrication, and speed. Using materials exhibiting a wide range of mechanical properties, we show that the in-die P_y correlates strongly with three established plasticity parameters obtained from the out-of-die Heckel analysis, Kuentz-Leuenberger analysis, and macroindentation. Thus, the in-die P_y is a reliable parameter for quantifying powder plasticity in a material-sparing and expedited manner.

1. Introduction

The plasticity of powdered materials plays a major role in handling and manufacturing of solids. For example, materials with high plasticity are more difficult to fracture under impact than hard materials, rendering particle size reduction by milling less effective (Taylor et al., 2004). During tablet manufacturing, plastic deformation is a prerequisite for particles to develop and maintain a sufficiently large interparticulate bonding area with neighboring particles to attain an adequate tablet strength (Sun, 2011). Higher plasticity of active pharmaceutical ingredients (APIs) has also been correlated with an increased punch sticking tendency (Paul et al., 2019; Paul et al., 2017c; Paul et al., 2017b). Hence, a clear understanding of the plasticity of a powder or a powder mixture is critical to the efficient development of tablets by enabling reliable predictions of powder performance during various manufacturing steps.

Powder plasticity can be quantified by plasticity parameters obtained from analyzing pressure–porosity data using a mathematical model, e.g., the Heckel (Heckel, 1961a, 1961b), Kawakita (Kawakita and Lüdde, 1971), Kuentz and Leuenberger (KL) (Kuentz and Leuenberger, 1999), and Walker (Walker, 1923) equations. Macroindentation hardness of a compact at zero porosity, obtained by extrapolating hardness–porosity data, can also quantify material plasticity (Patel and Sun, 2016). Historically, out-of-die (zero-pressure) tablet porosity has been preferred to in-die (at-pressure) porosity in all these analyses for two main reasons, 1) the access to accurate force and punch

displacement data during the course of compaction was limited; 2) the elastic deformation of powders under stress, exerted by both the punches and die wall, obscures the relationship between tablet porosity and pressure (Denny, 2002; Krycer et al., 1982; Sun and Grant, 2001).

However, the application of out-of-die analysis methods is limited for the following reasons: 1) it requires a large amount of material; 2) it requires a significant amount of time to collect sufficient tablet porosity data over a wide range of compaction pressures for reliable analysis; 3) it may not be possible to obtain intact tablets for some materials due to tablet capping or lamination (Paul and Sun, 2017a); 4) punch sticking (Chattoraj et al., 2018; Paul et al., 2017b) and tablet flashing (Paul et al., 2017a) can influence the accuracy of the measured out-of-die tablet porosity. These limitations are particularly problematic in the context of drug development for a number of reasons: 1) APIs are usually not available in large quantities in the early stages of drug development due to the high synthesis cost; 2) most APIs exhibit compression problems, such as capping, lamination, and punch sticking; 3) the laborious characterization methods are incompatible with the desire to develop drug products quickly; 4) the accuracy of out-of-die tablet porosity is limited by the accuracy of user-measured tablet dimensions using a caliper (usually 10 μm accuracy). In this regard, in-die methods for quantifying powder plasticity of pharmaceutical ingredients hold many advantages compared to out-of-die methods. For example, user measurement errors are eliminated since all pressure–porosity data during compression is collected directly by the instrument, and, more importantly, all materials can be studied regardless of whether or not they can

* Corresponding author at: 9-127B Weaver-Densford Hall, 308 Harvard Street S.E., Minneapolis, MN 55455, United States.

E-mail address: sunx0053@umn.edu (C.C. Sun).

<https://doi.org/10.1016/j.ijpx.2021.100094>

Received 15 May 2021; Received in revised form 23 July 2021; Accepted 10 August 2021

Available online 14 August 2021

2590-1567/© 2021 The Author(s).

Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license

(<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

form intact tablets. Thus, it is appropriate to systematically examine the potential use of in-die analysis for quantifying powder plasticity. Of the methods available for quantifying powder plasticity, the Heckel analysis is by far the most commonly employed (Ilkka and Paronen, 1993; Paronen, 1986; Paul and Sun, 2017b; Roberts and Rowe, 1987). The mean yield pressure, P_y , derived from the Heckel analysis has been shown to correlate with yield strength for some metals (Heckel, 1961b) and indentation hardness of certain pharmaceutical powders (Roberts and Rowe, 1987).

The broad adoption of in-die analysis requires the following two conditions to be met: 1) accurate in-die porosity–pressure data can be obtained, and 2) the impact of pressure-induced elastic deformation on derived plasticity parameters does not affect their ability to quantify plasticity. Modern compaction simulators, which are now more broadly available, can capture highly accurate force–displacement data, with an accuracy of $\sim 1 \mu\text{m}$ for displacement, which allows for the calculation of pressure and in-die tablet porosity throughout the entire tableting process. Thus, the main barrier for the adoption of the in-die Heckel analysis is the robustness and reliability of P_y for quantifying powder plasticity. This work aims to systematically evaluate the suitability of in-die P_y for quantifying powder plasticity using a large set of powders exhibiting a wide range of mechanical properties.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (MCC; Avicel PH102, FMC Biopolymer, Philadelphia, PA), lactose monohydrate (LM; #316 Fastflo® NF, Foremost Farms, Clayton, WI), mannitol (Mann; Pearlitol® 200SD, Roquette America Inc., Keokuk, IA), dicalcium phosphate anhydrate (DCPA; Anhydrous Emcompress®, JRS Pharma, Patterson, NY), dicalcium phosphate dihydrate (DCPD; Emcompress®, JRS Pharma, Patterson, NY), ibuprofen (IBN; Sigma Aldrich, St. Louis, MO), celecoxib (CEL; Aarti Drugs Pvt Ltd., Mumbai, India), hydroxypropyl cellulose (HPC; Klucel EF-PHARM, Ashland, Wilmington DE), and magnesium stearate (MgSt; non-bovine, HyQual™, Mallinckrodt, St. Louis, MO) were used as received.

2.2. Mixing and tableting

LM, Mann, and DCPA were studied individually and as mixtures in 25% increments with MCC. An additional mixture of 60% DCPA with 40% MCC, 90% DCPA with 10% MCC, and two mixtures of 20% IBN or CEL with 80% MCC were also prepared. All mixtures were blended for 10 min at 49 rpm using a blender (Turbula, Glen Mills, Clifton, NJ). All powders, except pure MCC and HPC, were mixed with 1% (w/w) of MgSt in the Turbula for 2 min at 49 rpm. The 1% MgSt was intended as an internal lubricant to reduce frictional force during compression.

Tablets were prepared with a compaction simulator (Styl'One Evolution; MedelPharm, Beynost, France) using a symmetrical, force-controlled, single compression cycle (2% speed, 2 s compression composed of a 1 s rise and a 1 s fall without holding at the maximum force, followed by 3 s relaxation, and a 2 s ejection step). Round, flat-faced tooling with an 11.28 mm diameter was used to compress tablets (approximately 600 mg) when pressures were under 450 MPa. Round, flat-faced tooling with a diameter of 8 mm was used to make tablets (approximately 250 mg) at higher pressures (450 MPa – 1 GPa). Out-of-die tablet density (ρ) was calculated from tablet dimensions after ejection (measured with calipers, fitted with an attachment to avoid flashing) and tablet mass (measured using an analytical balance). The accuracy of the calipers (model CD-6"AX, Mitutoyo, Kawasaki, Kanagawa, Japan) was 10 μm .

2.3. True density and tablet porosity

The true density (ρ_t) of pure LM, Mann, DCPD, DCPA, IBN, and CEL was determined using helium pycnometry (Quantachrome Instruments, Ultracycrometer 1000e, Byonton Beach, Florida) with 1–2 g of an accurately weighed sample that filled about $\frac{3}{4}$ of the volume of the sample cell. An analytical balance (Mettler Toledo, Columbus, Ohio, model AG204) was used for weighing. The experiment was stopped when the variation between five consecutive measurements was below 0.005% and the mean of the last five measurements was taken as the sample true density. The ρ_t of pure MCC and HPC was determined by fitting pressure (P) – ρ data to the Sun equation (Eq. 1) to avoid gross errors in true density measurements due to the release of water during helium pycnometry (Sun, 2004).

$$P = \frac{1}{C} \left[(1 - \epsilon_c) - \frac{\rho}{\rho_t} - \epsilon_c \ln \left(\frac{1 - \frac{\rho}{\rho_t}}{\epsilon_c} \right) \right] \quad (1)$$

This non-linear regression of $P - \rho$ data was performed on a batch of 24 tablets at pressures ranging from 25 to 350 MPa for MCC and 42 tablets at pressures ranging from 10 to 120 MPa for HPC. HPC tablets formed above 120 MPa were not included in the regression because ρ plateaued at these pressures (Fig. S1). True density values for individual materials used in this study are summarized in Table S1.

The true density of each binary mixture ($\rho_{1,2}$) was calculated from the true density values of constituent powders (ρ_1 and ρ_2) and their corresponding weight fractions (x_1 and x_2) according to Eq. 2.

$$\frac{1}{\rho_{1,2}} = \frac{x_1}{\rho_1} + \frac{x_2}{\rho_2} \quad (2)$$

Tablet porosity (ϵ) was calculated according to Eq. 3.

$$\epsilon = 1 - \frac{\rho}{\rho_t} \quad (3)$$

2.4. In-die P_y analysis

In-die ϵ data was calculated from tablet thickness measured with the compaction simulator (accuracy of 1 μm) and tablet weight determined after ejection. P_y was obtained from a linear regression of the linear portion of the Heckel plot (negative natural log of ϵ versus pressure), according to Eq. 4 (Heckel, 1961a, 1961b).

$$-\ln(\epsilon) = \frac{1}{P_y} P + A \quad (4)$$

A typical in-die Heckel plot is characterized by two curved portions in the low and high-pressure regions separated by a linear portion in the intermediate pressure range (Sun and Grant, 2001). All in-die P_y values were determined using compression data obtained with the 11.28 mm tooling with a maximum pressure of 450 MPa. For hard materials, the non-linear high-pressure region of the Heckel plot could not be unambiguously identified within 450 MPa. Therefore, 8 mm tooling was used to attain a maximum pressure of 1 GPa, which includes the high-pressure, non-linear region, to aid the unambiguous determination of the linear portion of the Heckel plot. The data obtained using the 11.28 mm tooling in the same pressure range was used for linear regression to determine P_y . All measurements were triplicated.

2.5. Out-of-die P_y analysis

Out-of-die P_y values were obtained from the literature for all powders except MCC, HPC, DCPD, and DCPA blends (Paul and Sun, 2017b). The out-of-die P_y value of HPC was determined in this work since it was not available in the literature. The out-of-die P_y values of MCC, DCPD, and DCPA mixtures were redetermined because their reported values were based on regression of points that do not follow a strong linear

relationship (Paul and Sun, 2017b). In these cases, the out-of-die P_y values were obtained by making tablets at a range of compaction pressures, measuring the out-of-die tablet porosity, and fitting the Heckel equation to the linear region of the out-of-die Heckel plots. The pressure range for out-of-die regression was chosen to match the linear region identified from the corresponding in-die Heckel plot (Fig. S2). This was especially important when the linear portion of the out-of-die Heckel plot was difficult to identify, e.g., due to curvature as a result of tablet defects induced by excessive elastic recovery during decompression.

2.6. Kuentz-Leuenberger analysis

The value of the plasticity parameter $1/C$ was obtained from the literature for all powders except MCC, HPC, DCPD, and DCPA blends, which were either determined if they were not available in the literature or were redetermined if there was clear evidence suggesting errors in the literature values (Paul and Sun, 2017b). The $1/C$ values of MCC and HPC were extracted from the Sun fitting described earlier. The $1/C$ values of DCPD and DCPA blends were determined from a non-linear fitting of $P - \epsilon$ data to the KL equation (Eq. 5) (Fig. S3).

$$P = \frac{1}{C} \left[(\epsilon - \epsilon_c) - \epsilon_c \ln \left(\frac{\epsilon}{\epsilon_c} \right) \right] \quad (5)$$

where ϵ_c is a constant corresponding to a critical porosity at which the powder bed begins to gain mechanical rigidity (Kuentz and Leuenberger, 1999).

2.7. Curve fitting and data analysis

Non-linear regression was performed using SciPy's orthogonal distance regression (ODR) package (SciPy v1.6.2, Python v3.8.2). Unless otherwise specified, ordinary least squares regression (job = 2) was used, and y standard deviations were included for fitting. For in-die Heckel linear fitting, the `curve_fit` function in SciPy's `optimize` package was utilized for least squares optimization.

Signal derivatives were generated by first applying a Savitzky-Golay filter with a window length of 97 and a polynomial order of 3 to the raw $P - \epsilon$ data using the `savgol_filter` function from SciPy's signal package. The derivative was then taken using Numpy's gradient function.

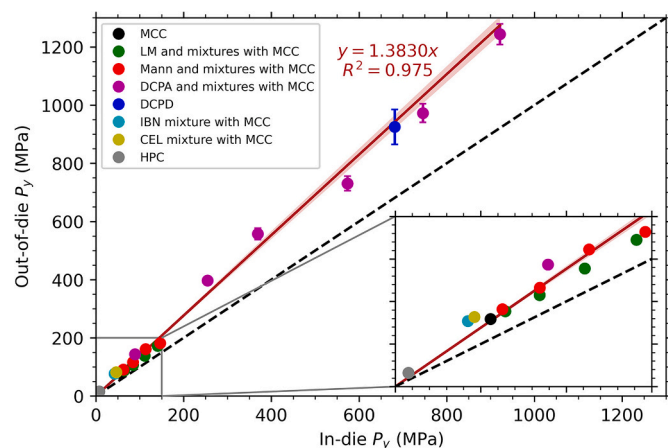


Fig. 1. Out-of-die versus in-die P_y for a variety of pharmaceutical powders. The shaded region corresponds to ± 1 standard error on the fitted line. All markers have error bars in both x and y directions, but some are hidden by the symbols.

3. Results and discussion

3.1. Correlation between in-die and out-of-die P_y

The out-of-die P_y is correlated with the in-die P_y through a strong linear relationship ($R^2 = 0.975$), with a slope of 1.383 (Fig. 1).

This strong linear relationship between in-die and out-of-die P_y suggests that the in-die P_y can quantify material plasticity with the same authority as out-of-die P_y , despite the influence that elastic deformation has on the tablet under pressure. Curiously, the same extent of the influence by elastic deformation on in-die P_y values (out-of-die P_y is $\sim 38\%$ higher than the corresponding in-die P_y) was observed for a set of very different materials, ranging from the highly plastic HPC to the hard DCPA and DCPD. Intuitively, softer materials have lower moduli. Hence, at the same pressure, softer materials undergo more elastic deformation and their in-die P_y values are expected to deviate more from their out-of-die P_y values than harder materials. However, a larger absolute change from a higher slope for a softer material does not lead to a larger relative change. Therefore, the relative difference between in-die and out-of-die P_y remains remarkably constant, with a ratio of ~ 1.38 , among the entire set of diverse materials investigated. However, the robustness and generality of this relative difference remain to be confirmed using more materials. In a previous report, out-of-die P_y values were 10%–170% higher than corresponding in-die P_y values for three powders and their various binary mixtures (Busignies et al., 2006). However, a detailed analysis of that set of data is not possible since no details on the out-of-die Heckel analysis were given. It is useful to point out that their in-die and out-of-die data also exhibits a strong linear relationship ($R^2 = 0.97$) with a slope of 1.13 (Fig. S4). However, the regression line crosses the out-of-die P_y axis at 75 MPa instead of origin, indicating systematic errors in at least one of the values.

3.2. Correlation between in-die P_y and H_0

As further validation of the ability of in-die P_y to quantify material plasticity, the correlation between in-die P_y and H_0 was assessed. Here, the H_0 values were obtained by extrapolating hardness values of compacts experimentally determined by macroindentation (Paul and Sun, 2017b).

The relationship between in-die P_y and H_0 data can be reasonably described with the quadratic equation, $H_0 = 32.1 + 1.28P_y + 0.004P_y^2$, $R^2 = 0.949$ (Fig. 2a). Other relationships, including higher-order polynomial, allometric (power-law), and exponential relationships, were explored but resulted in generally worse fittings. The fitting is poorer at high H_0 values, as suggested by the large residuals (Fig. 2b). This could be due to a combination of fewer data points available for hard materials and lower accuracy of the estimated H_0 values, as suggested by the relatively large error bars (Fig. 2a).

It should be pointed out that the polynomial fitting suggests a small finite H_0 value of 32.1 MPa at a hypothetical in-die P_y value of zero. This impossibility may result from either errors in the data, especially at high H_0 values, or the empirical nature of the fitting equation. In any case, such a strong correlation with H_0 again suggests that in-die P_y can be used to quantify material plasticity.

3.3. Correlation between in-die P_y and $1/C$

To further validate its ability to quantify material plasticity, the in-die P_y was also correlated with another established plasticity parameter, $1/C$. A strong power-law relationship ($y = 0.89x^{1.24}$) is observed (Fig. 3). The relatively lower R^2 value (0.971) is mainly caused by the point in the far left lower region from the trend line, corresponding to the highly plastic HPC. On a log-log scale in this low-value range, even a small error can have a large impact. Unfortunately, errors in $1/C$ are difficult to avoid for very plastic materials due to issues such as tablet flashing and errors in true density. Considering these factors, the overall

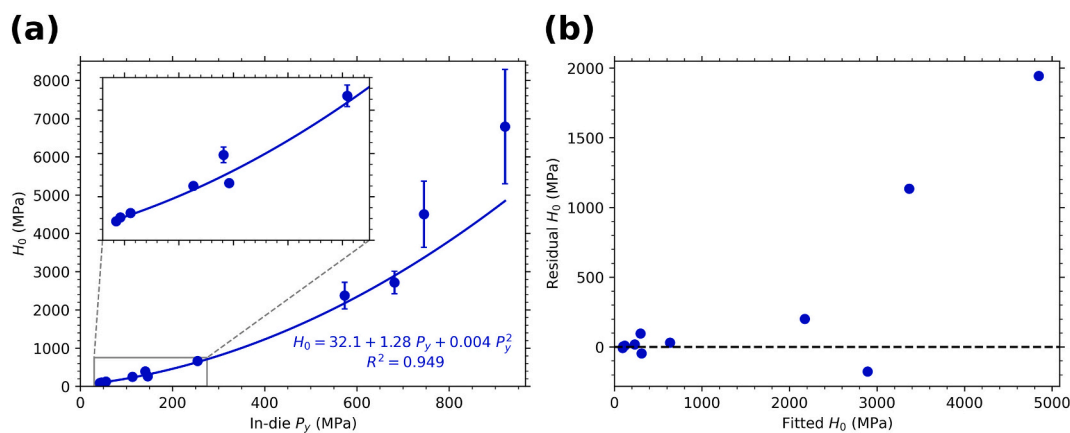


Fig. 2. (a) In-die P_y versus macroindentation hardness, H_0 , and (b) the residuals versus fitted plot.

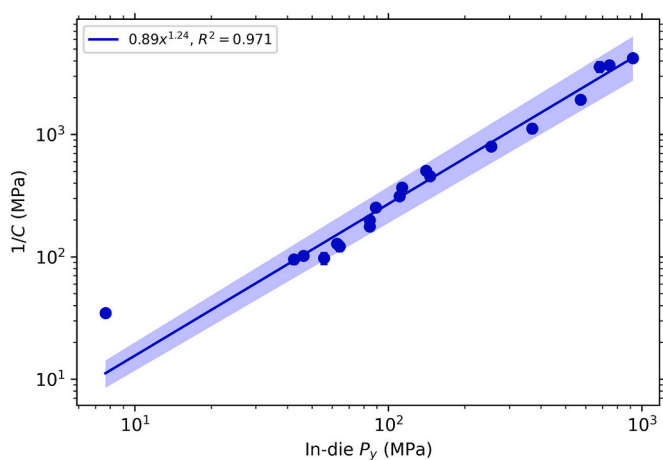


Fig. 3. The relationship between $1/C$ and in-die P_y . The line is the best-fit power-law function. The shaded region is ± 1 standard error on the fitting parameters.

correlation is deemed strong.

Numerical values of all parameters used in Figs. 1–3 are summarized in Table S2.

3.4. Robustness of the observed correlations

It has been suggested that the P_y value is affected by numerous experimental variables, including tooling size, lubrication, compression speed, and peak compaction pressure (Denny, 2002; Gabaude et al., 1999; Hersey et al., 1973; Hooper et al., 2016; Patel and Kaushal, 2010; Patel et al., 2007; Roberts and Rowe, 1985; Sonnergaard, 2021; Sonnergaard, 1999). Since it was not possible in this study to collect in-die data using identical materials and under identical experimental conditions as those in the paper that reported $1/C$ and H_0 values (Paul and Sun, 2017b), we have evaluated the possible impact of these factors on the value of in-die P_y .

The in-die P_y values obtained in this study were highly reproducible, exhibiting very small relative standard deviations ($< 2.5\%$) (Fig. S5). Following the procedure for the Heckel analysis adopted in this work, the P_y value is independent of maximum compaction pressure applied, i. e., there is only one P_y value for a given material under otherwise the same set of compression conditions (Fig. S6). We attribute the earlier observations of pressure dependence of in-die P_y (Hooper et al., 2016; Patel and Kaushal, 2010; Patel et al., 2007; Sonnergaard, 1999) to the incorrect and inconsistent selection of the linear regions of the Heckel profiles for regression in those studies. Based on the shape of a complete

in-die Heckel profile, its first derivative curve should have a “U” shape, corresponding to a rapid decrease of slope transitioning to an approximately linear portion and then a rapidly increasing slope with increasing pressure (Fig. S7). We have found that the linear portion of the Heckel plot determined visually by comparing the fitted line and data points is as reliable as the first derivative approach. The former approach was adopted in this work because it is much more straightforward.

To unambiguously identify the linear portion of the in-die Heckel plot for regression, pressure must be sufficiently high for the Heckel profile to show the non-linear region (Fig. S8). The non-linearity at high pressures due to elastic deformation of the particles (Sun and Grant, 2001) can be easily achieved for soft materials but does not appear until the pressure is very high for harder materials. In those cases, a smaller tooling size (8 mm in diameter) was used to access data in the high-pressure region so that the linear portion can be unambiguously determined. Subsequently, this linear pressure range determined using the smaller tooling was used for regression of data obtained using the 11.28 mm tooling to eliminate the possible introduction of errors in P_y due to different tooling sizes.

In fact, a change in tooling size did slightly influence the in-die P_y for some materials (Fig. S9), as previously suggested (Denny, 2002; Hersey et al., 1973). This effect may be attributed to the greater impact of die wall friction on the consolidation of a powder bed with smaller tooling and thicker tablets. To minimize this effect, we adopted the practice of using larger tooling sizes and thinner compacts to make tablets with a lower thickness/diameter ratio to accurately determine P_y (Denny, 2002). Although the criterion for an optimal compact size may be material-dependent, such a criterion, if established, would prove beneficial when drawing comparisons between data from different labs or users. However, to compare the plasticity of different powders within a given study, it suffices to keep tooling size and tablet thickness comparable. In this work, the minimum in-die tablet thickness ranged from 3 to 4 mm, wherein tablets were prepared using tooling with a diameter of 11.28 mm.

When compaction speed was changed from a 2 s symmetrical compression to a simulated high-speed tablet press, the in-die P_y was relatively unchanged for hard materials, such as LM, Mann, DCPD, and DCPA (Fig. S10). However, P_y increased at a higher speed for pure MCC and HPC, indicating their more prominent viscoelasticity compared to these harder materials. Therefore, compaction speeds should be similar in order to rank-order plasticity of powders based on P_y values obtained from different studies.

While 1% internal lubrication was used when determining in-die P_y for most powders in this work, the out-of-die P_y and H_0 data obtained from the literature used 0.25% internal lubrication (Paul and Sun, 2017b). To study the possible effects of lubrication on in-die P_y , data was collected using either external lubrication or 1% MgSt internal

lubrication for LM, Mann, DCPD, and DCPA. Compared to external lubrication, 1% MgSt internal lubrication slightly reduced the P_y of LM but did not influence the P_y of Mann (Fig. S11). Surprisingly, DCPD and DCPA had higher P_y values when 1% MgSt internal lubrication was used. This was unexpected since the inclusion of 1% MgSt, which is much more plastic than DCPD and DCPA, should reduce P_y . Further examination of the compression data revealed that the ejection forces of 1% MgSt internally lubricated DCPD and DCPA were higher than that of the externally lubricated samples. Thus, the external lubrication mode was more effective at reducing frictional force, which resulted in a more effective transmission of stress from the punches to the tablet interior (Table S3). Consequently, the porosity of the powder bed compressed with external lubrication is lower under the same pressure, resulting in a lower P_y . For LM and Mann, the ejection force of the 1% internally lubricated tablets is similar to the externally lubricated tablets, which is aligned with their similar in-die P_y (Table S3).

Overall, these experimental variables only slightly affect the in-die P_y . Therefore, the extent of the impact of different compression conditions between this and the literature work is unlikely to change the observed strong correlations of in-die P_y with out-of-die P_y , H_0 , and $1/C$. This is also supported since the out-of-die P_y and $1/C$ values of mixtures of MCC with Mann and LM redetermined in this work at experimental conditions identical to that for in-die P_y experiments are described by the same relationships as the literature values that were correctly determined (Paul and Sun, 2017b).

Finally, it is appropriate to describe a material with a higher in-die P_y value as being less plastic, or more resistant to permanent plastic deformation. However, it is inappropriate to describe it as being more brittle. The brittle fracture behavior depends on not only plasticity but also the size of the particles. When particles are sufficiently small, they plastically yield under compressive stress instead of fracture (Kendall, 1978).

4. Conclusion

The strong positive correlations of in-die P_y with three established plasticity parameters, out-of-die P_y , H_0 , and $1/C$, suggest that the in-die P_y is as reliable as these out-of-die parameters for quantifying powder plasticity. However, the in-die P_y can be determined in a much more material- and time-efficient manner. Thus, the in-die Heckel analysis is an excellent approach to evaluate the effects of various factors, such as speed sensitivity, lubrication efficiency, pressure, and tooling size, on material plasticity.

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.

Acknowledgments

Funding from the National Science Foundation through grant number IIP-1919037 is gratefully acknowledged for partially supporting G. V.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.ijpx.2021.100094>.

References

- Busignies, V., Leclerc, B., Porion, P., Evesque, P., Couarraze, G., Tchoreloff, P., 2006. Compaction behaviour and new predictive approach to the compressibility of binary mixtures of pharmaceutical excipients. *Eur. J. Pharm. Biopharm.* 64, 66–74.
- Chatteraj, S., Daugherty, P., McDermott, T., Olsosky, A., Roth, W.J., Tobyn, M., 2018. Sticking and picking in pharmaceutical tablet compression: an IQ consortium review. *J. Pharm. Sci.* 107, 2267–2282.
- Denny, P.J., 2002. Compaction equations: a comparison of the Heckel and Kawakita equations. *Powder Technol.* 127, 162–172.
- Gabaude, C.M.D., Guillot, M., Gautier, J., Saudemon, P., Chulia, D., 1999. Effects of true density, compacted mass, compression speed, and punch deformation on the mean yield pressure. *J. Pharm. Sci.* 88, 725–730.
- Heckel, R.W., 1961a. Density-pressure relationships in powder compaction. *Trans. Metall. Soc. AIME* 221, 671–675.
- Heckel, R.W., 1961b. An analysis of powder compaction phenomena. *Trans. Metall. Soc. AIME* 221, 1001–1008.
- Hersey, J.A., Rees, J.E., Cole, E.T., 1973. Density changes in lactose tablets. *J. Pharm. Sci.* 62, 2060.
- Hooper, D., Clarke, F., Mitchell, J., Snowden, M., 2016. A modern approach to the Heckel equation: the effect of compaction pressure on the yield pressure of ibuprofen and its sodium salt. *J. Nanomedicine Nanotechnol.* 7.
- Ilkka, J., Paronen, P., 1993. Prediction of the compression behaviour of powder mixtures by the Heckel equation. *Int. J. Pharm.* 94, 181–187.
- Kawakita, K., Lüdde, K.-H., 1971. Some considerations on powder compression equations. *Powder Technol.* 4, 61–68.
- Kendall, K., 1978. The impossibility of comminuting small particles by compression. *Nature* 272, 710–711.
- Krycer, I., Pope, D.G., Hersey, J.A., 1982. The interpretation of powder compaction data - a critical review. *Drug Dev. Ind. Pharm.* 8, 307–342.
- Kuentz, M., Leuenberger, H., 1999. Pressure susceptibility of polymer tablets as a critical property: a modified Heckel equation. *J. Pharm. Sci.* 88, 174–179.
- Paronen, P., 1986. Heckel plots as indicators of elastic properties of pharmaceuticals. *Drug Dev. Ind. Pharm.* 12, 1903–1912.
- Patel, S., Kaushal, A.M., Bansal, A.K., 2010. Mechanistic investigation on pressure dependency of Heckel parameter. *Int. J. Pharm.* 389, 66–73.
- Patel, S., Sun, C.C., 2016. Macroindentation hardness measurement—Modernization and applications. *Int. J. Pharm.* 506, 262–267.
- Patel, S., Kaushal, A.M., Bansal, A.K., 2007. Effect of particle size and compression force on compaction behavior and derived mathematical parameters of compressibility. *Pharm. Res.* 24, 111–124.
- Paul, S., Sun, C.C., 2017a. Gaining insight into tablet capping tendency from compaction simulation. *Int. J. Pharm.* 524, 111–120.
- Paul, S., Sun, C.C., 2017b. The suitability of common compressibility equations for characterizing plasticity of diverse powders. *Int. J. Pharm.* 532, 124–130.
- Paul, S., Chang, S.-Y., Sun, C.C., 2017a. The phenomenon of tablet flashing — its impact on tableting data analysis and a method to eliminate it. *Powder Technol.* 305, 117–124.
- Paul, S., Taylor, L.J., Murphy, B., Krzyzaniak, J., Dawson, N., Mullarney, M.P., Meenan, P., Sun, C.C., 2017b. Mechanism and kinetics of punch sticking of pharmaceuticals. *J. Pharm. Sci.* 106, 151–158.
- Paul, S., Wang, K., Taylor, L.J., Murphy, B., Krzyzaniak, J., Dawson, N., Mullarney, M.P., Meenan, P., Sun, C.C., 2017c. Dependence of punch sticking on compaction pressure—Roles of particle deformability and tablet tensile strength. *J. Pharm. Sci.* 106, 2060–2067.
- Paul, S., Wang, C., Wang, K., Sun, C.C., 2019. Reduced punch sticking propensity of aceulfame by salt formation: Role of crystal mechanical property and surface chemistry. *Mol. Pharm.* 16, 2700–2707.
- Roberts, R.J., Rowe, R.C., 1985. The effect of punch velocity on the compaction of a variety of materials. *J. Pharm. Pharmacol.* 37, 377–384.
- Roberts, R.J., Rowe, R.C., 1987. The compaction of pharmaceutical and other model materials - a pragmatic approach. *Chem. Eng. Sci.* 42, 903–911.
- Sonnergaard, J.M., 1999. A critical evaluation of the Heckel equation. *Int. J. Pharm.* 193, 63–71.
- Sonnergaard, J.M., 2021. Ockham's razor applied on pharmaceutical powder compaction models. *J. Pharm. Sci.* 110, 989–996.
- Sun, C.C., 2004. A novel method for deriving true density of pharmaceutical solids including hydrates and water-containing powders. *J. Pharm. Sci.* 93, 646–653.
- Sun, C.C., 2011. Decoding powder tableability: Roles of particle adhesion and plasticity. *J. Adhes. Sci. Technol.* 25, 483–499.
- Sun, C.C., Grant, D.J.W., 2001. Influence of elastic deformation of particles on Heckel analysis. *Pharm. Dev. Technol.* 6, 193–200.
- Taylor, L.J., Papadopoulos, D.G., Dunn, P.J., Bentham, A.C., Dawson, N.J., Mitchell, J.C., Snowden, M.J., 2004. Predictive milling of pharmaceutical materials using nanoindentation of single crystals. *Org. Process. Res. Dev.* 8, 674–679.
- Walker, E.E., 1923. The properties of powders. Part VI. The compressibility of powders. *Trans. Faraday Soc.* 19, 73–82.