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

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Abstract

Despite its 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.

Key words: A. Powder compaction, A. yield condition, B. elastic-plastic material, B. granular materials, Heckel analysis

1 Introduction

The plasticity of powdered materials plays a major role in solids handling and manufacturing. For example, highly plastic materials 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, 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, obfuscates the relationship between tablet porosity and pressure (Denny, 2002; 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 these regards, 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 form intact tablets. Thus, it is timely 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 (Paul and Sun, 2017b). 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 that accurate in-die porosity–pressure data can be obtained and that 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 ~1 µm 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 aimed 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 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 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 using 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 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, Ultrapycnometer 1000e, Byonton Beach, Florida) with 1-2 g of an accurately weighed sample that filled about ¾ of the volume of the sample cell. The experiment was stopped when the variation between five consecutive

97 measurements was below 0.005% and the mean of the last five measurements was taken as the
98 sample true density. The ρ_t of pure MCC and HPC were determined by fitting pressure (P) – ρ
99 data to the Sun equation (Equation 1) to avoid gross errors in true density measurements due to
100 the release of water during helium pycnometry (Sun, 2004).

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

101 This non-linear regression of P – ρ data was performed on a batch of 24 tablets at pressures
102 ranging from 25 to 350 MPa for MCC and a batch of 42 tablets at pressures ranging from 10 to
103 120 MPa for HPC. HPC tablets formed above 120 MPa were not included in the regression
104 because ρ plateaued at these pressures (Figure S1). True densities for individual materials used
105 in this study are summarized in Table S1.
106 The true density of each binary mixture ($\rho_{1,2}$) was calculated from the true density values
107 of constituent powders (ρ_1 and ρ_2) and their corresponding weight fractions (x_1 and x_2)
108 according to Equation 2.

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

109
110 Tablet porosity (ε) was calculated according to Equation 3.

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

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 Equation 4 (Heckel, 1961a, 1961b).

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

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

128 determined in this work since it was not available in the literature. The out-of-die P_y of MCC,

129 DCPD, and DCPA mixtures was redetermined because their reported values were based on
130 regression of points that do not follow a strong linear relationship (Paul and Sun, 2017b). In
131 these cases, the out-of-die P_y values were obtained in this work by making tablets at a range of

132 compaction pressures, measuring the out-of-die tablet porosity, and fitting the Heckel equation to
133 the linear region of the out-of-die Heckel plots. The pressure range for out-of-die regression was
134 chosen to match the linear region identified from the corresponding in-die Heckel plot (Figure
135 S2). This was especially important when the linear portion of the out-of-die Heckel plot was
136 difficult to identify, e.g., due to curvature as a result of tablet defects induced by excessive elastic
137 recovery during decompression.

138 **2.6 Kuentz-Leuenberger analysis**

139 The value of the plasticity parameter $1/C$ was obtained from the literature for all powders

140 except MCC, HPC, DCPD, and DCPA blends, which were either determined if they were not
141 available in the literature or were redetermined if there was clear evidence suggesting errors in
142 the literature values (Paul and Sun, 2017b). The $1/C$ values of MCC and HPC were extracted

143 from the Sun fitting described earlier. The $1/C$ values of DCPD and DCPA blends were

144 determined from a non-linear fitting of $P - \varepsilon$ data to the KL equation (Equation 5) (Figure S3).

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

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

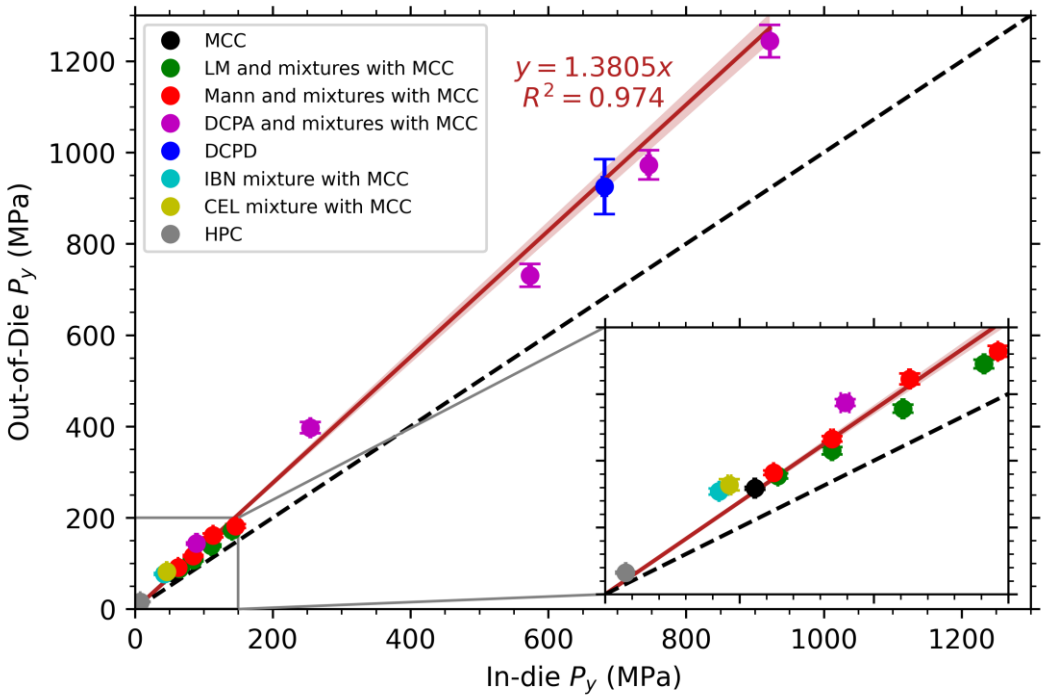
Non-linear regression was performed using SciPy's orthogonal distance regression (ODR) package (SciPy v1.6.2, Python v3.8.2). Unless otherwise specified, ordinary least-squares (job=2) was used, and y standard deviations were included for fitting. For in-die Heckel linear fitting, the curve_fit function 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 $P - \varepsilon$ data using the savgol_filter function from SciPy's signal package. The derivative was then taken using Numpy's gradient function.

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 ($R^2 = 0.974$), with a slope of 1.3805 (Figure 1).



159

160 **Figure 1.** Out-of-die versus in-die P_y for a variety of pharmaceutical powders. The shaded region

161 corresponds to ±1 standard error on the fitted line. All markers have error bars in both x and y

162 directions, but some are hidden by the symbols.

163 This strong linear relationship between in-die and out-of-die P_y suggests that the in-die P_y

164 can quantify material plasticity with the same authority as out-of-die P_y, despite the influence

165 that elastic deformation has on the tablet under pressure. Curiously, the same extent of the

166 influence by elastic deformation on in-die P_y values (~38% higher than the corresponding out-of-

167 die P_y) was observed for a set of very different materials, ranging from the highly plastic HPC to

168 the hard DCPA and DCPD. Intuitively, softer materials are affected by elastic deformation more,

i.e., their in-die P_y values are expected to deviate more from their out-of-die P_y than harder materials are. However, a larger absolute change from a higher slope for a soft 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 1.3805, among the entire set of diverse materials investigated.

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, a 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).

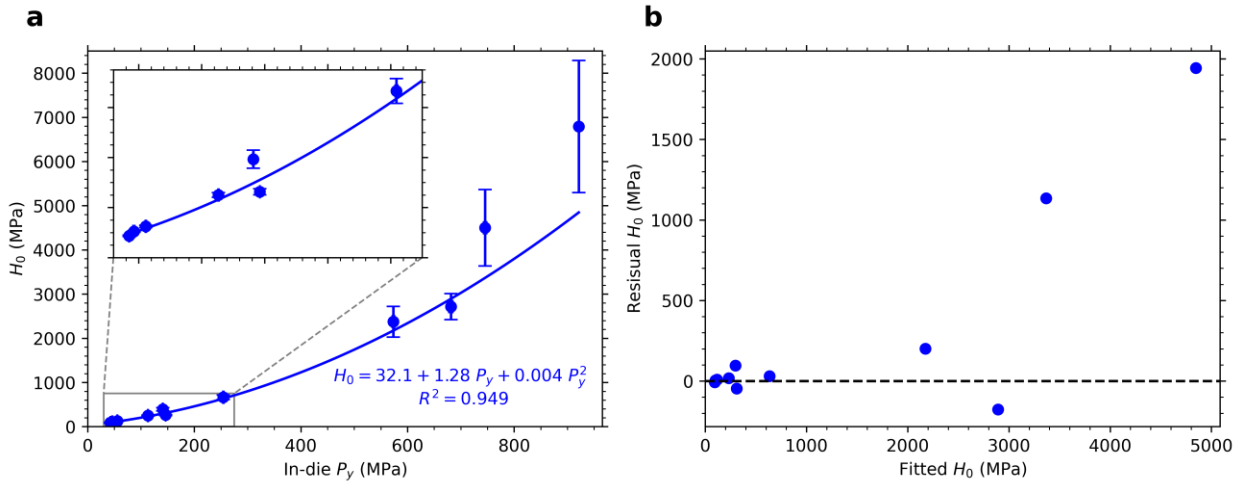


Figure 2. (**a**) In-die P_y versus macroindentation hardness, H_0, and (**b**) the residuals versus fitted plot.

The relationship between in-die P_y and H_0 data can be reasonably described with a quadratic equation, $H_0 = 31.8 + 1.28P_y + 0.004P_y^2$, $R^2 = 0.897$ (Figure 2**a**). 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 (Figure 2**b**). This could be due to a combination of fewer data points available for hard materials and larger errors of the estimated H_0 values, as suggested by the relatively large error bars (Figure 2**a**).

It should be pointed out that the polynomial fitting suggests a small finite H_0 value of 32.1 at a hypothetical in-die P_y of zero. This impossibility may result from 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 is observed (Figure 3). The relatively lower R^2 value (0.954) 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 value. Hence, the overall correlation is deem strong.

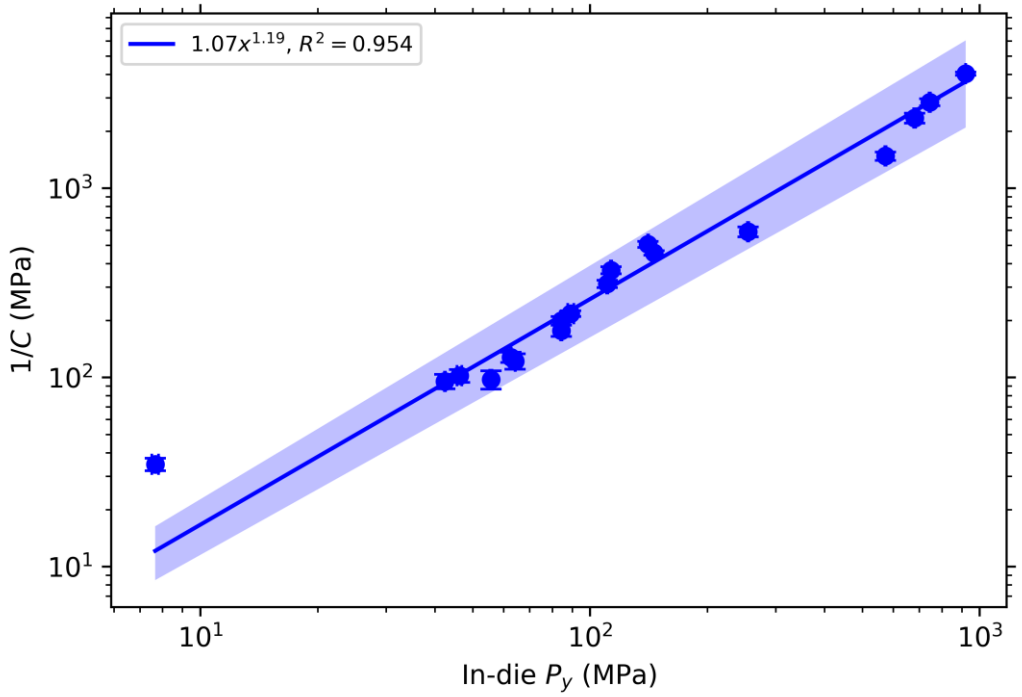


Figure 3. The relationship between $1/C$ and in-die P_y. The line is the best-fit power-law function. The shaded region is ±1 standard error on the fitting parameters.

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; Patel et al., 2010, 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, 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%) (Figure S4). Following the procedure for 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 (Figure S5). We attribute the earlier observations of pressure dependence of in-die P_y (Patel et al., 2010, 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 (Figure S6). 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 at high pressures (Figure S7). The non-linearity at high pressures, due to elastic deformation of particles (Sun and Grant, 2001), can be easily achieved for soft materials but does not show until the pressure is very high. 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 (Figure S8), as was previously suggested (Denny, 2002). 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-to-diameter ratio to accurately determine P_y (Denny, 2002). The criterion for an optimal compact size may be material-dependent. However, if a criterion can be established, it 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 thickness for tablets made with the tooling with an 11.28 mm diameter ranged 3 – 4 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 (Figure S9). However, P_y increased at the 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 (Figure S10). 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 more effective transmission of stress from the punches to the tablet interior (Table S2). 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 was similar to the externally lubricated tablets, which is aligned with their similar in-die P_y (Table S2).

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 additionally supported by the fact that 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 that using the literature values that were correctly determined.

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.

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Declaration of interests

☒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.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: