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

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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, 1925) 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...
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 \( \sim 1 \mu m \) 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; Pearltitol® 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), cellexobiz (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).

2.3. True density and tablet porosity

The true density (\( \rho_y \)) of pure LM, Mann, DCPD, DCPA, IBN, and CEL was determined using helium pycnometry (Quantachrome Instruments, Ultrapycometer 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 \( \rho_y \) of pure MCC and HPC was determined by fitting pressure (\( P \)) – \( \rho \) 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).

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

(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 \( \rho_y \) 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 (\( \rho_1 \) and \( \rho_2 \)) and their corresponding weight fractions (\( x_1 \) and \( x_2 \)) according to Eq. 2.

\[ \frac{1}{\rho_{1,2}} = \frac{x_1}{\rho_1} + \frac{x_2}{\rho_2} \]

(2)

Tablet porosity (\( \varepsilon \)) was calculated according to Eq. 3.

\[ \varepsilon = 1 - \frac{\rho}{\rho_i} \]

(3)

2.4. In-die \( P_y \) analysis

In-die \( \varepsilon \) data was calculated from tablet thickness measured with the compaction simulator (accuracy of 1 \( \mu m \)) 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 \( \varepsilon \) versus pressure), according to Eq. 4 (Heckel, 1961a, 1961b).

\[ -\ln(\varepsilon) = \frac{1}{P_y} P + A \]

(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 $P – y$ data to the KL equation (Eq. 5) (Fig. S3).

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

where $\varepsilon_c$ 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 $P – y$ 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 ($R^2 = 0.975$), 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 ~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 compact experiments 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 ($y = 0.89 x^{1.28}$) 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
3.4. Robustness of the observed correlations

Following the procedure for the Heckel analysis adopted in this work, exhibiting very small relative standard deviations (\( \pm 1 \) standard error on the fitting parameters), the 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; Gabade 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 \( P_y \). 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.
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 compaction 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 only on 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.

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Appendix A. Supplementary data

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