Effects of True Density, Compacted Mass, Compression Speed, and Punch Deformation on the Mean Yield Pressure

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Abstract □ Compressibility properties of pharmaceutical materials are widely characterized by measuring the volume reduction of a powder column under pressure. Experimental data are commonly analyzed using the Heckel model from which powder deformation mechanisms are determined using mean yield pressure (P_y). Several studies from the literature have shown the effects of operating conditions on the determination of P_y and have pointed out the limitations of this model. The Heckel model requires true density and compacted mass values to determine P_y from force-displacement data. It is likely that experimental errors will be introduced when measuring the true density and compacted mass. This study investigates the effects of true density and compacted mass on P_y. Materials having different particle deformation mechanisms are studied. Punch displacement and applied pressure are measured for each material at two compression speeds. For each material, three different true density and compacted mass values are utilized to evaluate their effect on P_y. The calculated variation of P_y reaches 20%. This study demonstrates that the errors in measuring true density and compacted mass have a greater effect on P_y than the errors incurred from not correcting the displacement measurements due to punch elasticity.

Introduction and Background

At the present time and for the foreseeable future, most pharmaceutical forms are oral dosage forms, mainly tablets. The measurement of volume reduction of the particle bed under pressure is one of the most commonly used methods to evaluate particle deformation mechanisms. The powder and granule consolidation is often studied on cylindrical compacts, and the measurement of the compact height is an indication of particle bed volume reduction. This method, currently used for ceramic or metal powders, has been applied to pharmaceutical materials since the 1970s.

There are two methods to obtain density−pressure profiles: the "in-die" and "out-die" (or "ejected tablets") methods.[1,2] The "out-die" method calculates the compact volume by measuring its dimensions when it is ejected from the die after compression at pressure P_a. The "in-die" method measures the compacts dimensions in the die, by evaluating punch displacement(s). The "in-die" method is commonly used because it is quicker to operate and consumes less material than the "out-die" method which requires a new compact for each compression pressure of interest. The "in-die" density measurements contain an elastic component leading to falsely low mean yield pressure which is a disadvantage when using the information for tablet formulation.[3]

Several attempts have been made to fit experimental data from powder or granule bed deformation under load to a universal mathematical model. A large number of empirical models have been developed[4] (Kawakita and Lüdde, Cooper and Eaton, Heckel...) and are based on the compact relative density under pressure.

New models are being developed[5] based on physical assumptions and chemical models. The models studied in the literature to date are not a good representation of particle deformation under pressure. The most universally accepted model used to describe the volume reduction of a particle bed is the Heckel model:[6]

$$\ln\left(\frac{1}{1-\rho_r}\right) = KP_a + A \qquad (1)$$

where, ρ_r is the relative density of the compact and the constants K and A are determined by the slope and intercept of the extrapolated region.

Heckel considered the volume reduction of a plastically deforming particle bed as a first-order kinetics phenomenon, where the pores are the reactant. This is not the case for organic powders, especially pharmaceutical materials, when subjected to low pressure (B zone) (Figure 1). However, converting force-displacement data points into a relative density−pressure relationship shows that most pharmaceutical powders exhibit a linear region (C zone) between two intermediate pressures (Figure 1). The linear part (C zone) is generally accepted to be representative of particle plastic deformation. Heckel[7] suggested that the slope of the linear part of the curve is equal to the reciprocal of $3Y$, Y being the yield strength of the material, and that constant A is a function of the initial volume of the particle bed. Hersey and Rees[8] demonstrated that the mean yield pressure of a material is equal to $1/K$. It is well accepted that the slope, K, of the linear region of the Heckel model is the reciprocal of the mean yield pressure P_y and is a measure of its ability to deform plastically. Since 1961, the Heckel representation has been widely used to interpret the consolidation mechanism. It is not a surprise given the number of different techniques used to measure the compression event that discrepancies in results and disagreements between researcher's conclusions have appeared in the literature. Several parameters influence the calculation of P_y, especially operating conditions:[9] type of compression (a uniaxial press, a rotary press, an alternative press, a compaction simulator...), compression speed,[10,11]

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Table 1—Parameters of the Simulation

run no.	$P_{y(i)}$	run type
0	$P_{y(0)}$	$D_v = D_{v_0}$ $W = W_0$
1	$P_{y(1)}$	$D_v = D_{v_{min}}$ $W = W_0$
2	$P_{y(2)}$	$D_v = D_{v_{max}}$ $W = W_0$
3	$P_{y(3)}$	$D_v = D_{v_0}$ $W = W_{min}$
4	$P_{y(4)}$	$D_v = D_{v_0}$ $W = W_{max}$

contact time, type and amount of lubricant,[12,13] punch diameter,[14] maximum compression pressure, amount of powder tested and filling method (manual, automatic, constant mass or volume),[15] accuracy of the measurement of displacement for the "in-die" method, accuracy of the measurement of the compact volume after ejection for the "out-die" method, accuracy of the strain gauges or piezoelectric transducers for pressure measurements, initial particle size, type of particle being compressed (powder, granules, mixed powder or granules,[16] true density measurement[17]...).

Researchers traditionally agree that the curvature at very low pressure (B zone) is due to particle packing, rearrangement, and fragmentation in the die while some disagreement occurs when considering the curvature at very high pressure (D zone). For example, negative relative density values can be calculated toward high compression pressures when using the "in-die" method. Some researchers suggested that an increase in the true density value (i.e., polymorphic transformation[18,19]), during compression could explain the abnormal negative values. Small errors in punch displacements or true density measurements may lead to large variations in the calculation of relative density. Therefore, one should be careful when interpreting relative density data and also when comparing results which are obtained under different operating conditions.

The objective of this study is to demonstrate the effects of true density and compacted mass on the mean yield pressure (P_y). In addition, other contributing factors such as compression speed, pressure, and correction of punch displacement for elastic deformation are identified. This study was approached in three steps. In the first step, one set of force and displacement data was collected for each material at two compression speeds. In the second step, Heckel plots were generated following eq 1 using the software provided and a fixed true density and compacted mass value. P_y was then calculated from the Heckel plots. For each set of experimental data measured in the first step, five values of P_y are calculated using different true density and compacted mass values (see Table 1). The third step involved comparing the errors in the P_y values obtained by varying true density, compacted mass, and compression speed with the errors in the P_y values obtained for which no correction for elastic deformation of the punches was made.

Material and Methods

Five materials were used in this study. Three materials are classical pharmaceutical excipients: Avicel PH 102 (filler and dry binder supplied by FMC); Starch 1500 (Disintegrant supplied by Colorcon); Pharmatose DCL 21 (filler supplied by DMW). The other two materials consisted of a drug substance (DS) and its formulated drug product (DP). The DS and DP were supplied by the Pharmaceutical Sciences Department of Sanofi Recherche (patented products).

Table 2—True Density Measured with an Helium Pycnometer and Bulk Density

	starch	avicel	lactose	DS	DP
D_{v_0} (g/cm^3)	1.506	1.594	1.576	1.500	1.526
$n = 3$ (deviation)	(0.003)	(0.001)	(0.002)	(0.001)	(0.000)
D_{bulk} (g/cm^3)	0.643	0.341	0.645	0.270	0.722
$n = 3$ (deviation)	(0.001)	(0.004)	(0.008)	(0.012)	(0.003)

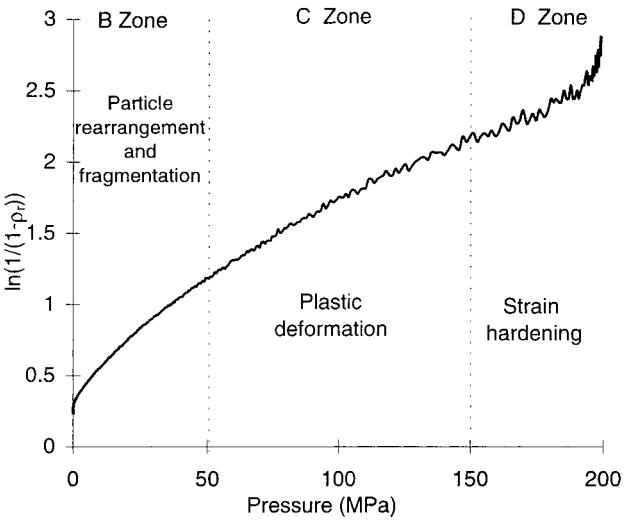


Figure 1—Determination of the linear part in the Heckel treatment.

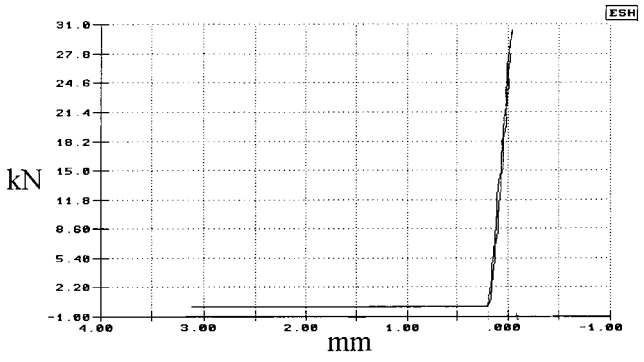
The true density was measured with a helium pycnometer (Micromeritics, Accupyc 1330), which is accurate to within 0.03% of reading values. Powders were weighed on a Mettler Toledo balance (model AG204), accurate to the nearest 0.1 mg.

The bulk density was measured in a volumenometer following European Pharmacopoeia recommendations (3rd edition, 2.9−15, "Volume apparent"). However, DS had a very low density which did not allow 100 g of powder to be placed in a 250 mL cylinder. The amount of material used for each measurement and each material was 50 g to allow a comparison between products. The measurements were done in triplicate.

Compression experiments were performed on an ESH compaction simulator at two compression speeds (16 and 166 mm·s^{-1}) using linear displacement profiles and a dwell time of zero. The amount of material required to fill a 1 cm^3 die (1 cm^2 × 1 cm) (Table 2) was calculated based on its bulk density (D_{bulk}). The die was manually lubricated with magnesium stearate. The elastic component of the punches was measured. The punch displacements were calibrated and data corrected using polynomial fitting (Figure 2, parts a and b). The punch displacements were measured by Linear Variable Displacement Transducer (LVDT), directly connected to the punches. LVDTs were a RDP Group, type D5/500/392. The accuracy of the upper punch LVDT was 99.91% while the accuracy of the lower punch LVDT was 99.98%. The load cells used to measure force were made by Veccer (U.K.), type s.1333 with a range of 0 to 50 kN. The maximum error of the upper load cell is 0.7% while the maximum error of the lower load cell is 0.2%.

The software allowed for data to be corrected or not corrected for elastic deformation of the punches. Force-displacement data were analyzed using the software provided with the ESH compaction simulator and required the true density and mass of material compacted. The software calculated the mean yield pressure (P_y) using the Heckel model (eq 1). P_y is the inverse of the slope of the C zone shown in Figure 1.

This software was used to generate Heckel plots using three different true density values and three different compacted mass values in order to estimate the effect of true density and compacted mass errors on the mean yield pressure. Experimental errors related to compression itself (i.e., filling the die, measurement of punch displacements and upper punch pressure) were not included.



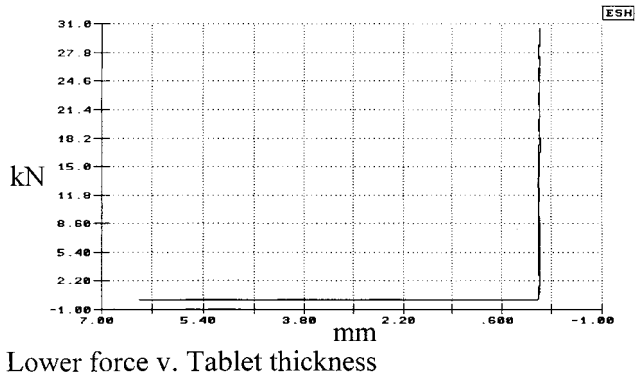


Figure 2—(a) Uncorrected data for punch displacements only. (b) Corrected data for punch displacements only.

Results and Discussion

There are three methods commonly utilized to measure the true density of a material: helium pycnometry, mercury porosimeter, and air pycnometry. True density values will differ according to the measurement method used. In this study, helium pycnometry was utilized because it is the method of choice. Helium pycnometry uses helium atoms which are smaller than both mercury and the atoms composing air. Therefore, helium atoms are able to penetrate pores and interstitial spaces more readily. One of the disadvantages of helium pycnometry is that volatile impurities or adsorbed water may cause a scatter in the measurement. We have found this variation to be up to 3%.

Even when filling material into the die is carried out manually at constant weight and not considering flow properties of materials, a significant source of error can be made on the compacted mass measurement. The amount of material weighed before compressing may differ from the real compressed value because of material losses due to poor flowability, static electricity, sticking, etc. The weight of the compact obtained after ejection may differ from the real weight of the product compacted because of sticking to punches and die walls, capping, lubrication of the die (which will smear onto the tablet and add weight), etc. For some materials such as drug substances which may be very difficult to handle, the error may be up to 10 mg (that is up to 4%, depending on the filling weight). However, for products which are more easily compressed like drug products and direct compression excipients, the weight error may be lower. The difference between the weight of the material before compression and the weight of the compact after ejection is an identification of the error made in the experimental measure. The accuracy of the balance has to be taken into account even though the experimental error made at this stage is negligible.

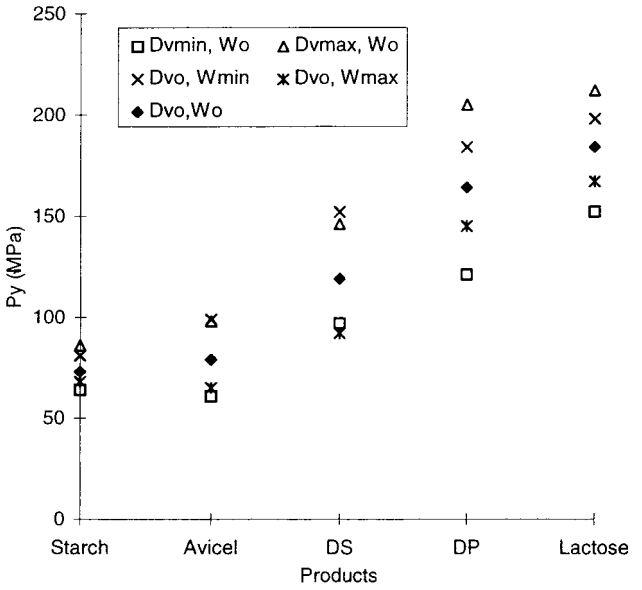


Figure 3—Error due to D_{v_i} and W_i on the mean yield pressure values (P_y, MPa) at V_c = 16.6 mm/s.

For this study, we calculated the mean yield pressure using three different values for the true density (D_{v_0}, $D_{v_{min}}$, and $D_{v_{max}}$) and three different weights for the compacted particles (W_0, W_{min}, and W_{max}) where:

$$D_{v_{min}} = 0.97D_{v_0} \quad \text{and} \quad D_{v_{max}} = 1.03D_{v_0} \qquad (1)$$

$$W_{min} = W_0 - 10\ (\text{mg}) \quad \text{and} \quad W_{max} = W_0 + 10\ (\text{mg}) \qquad (2)$$

The slope of the zone C in Figure 1 has been determined at each simulation test with a good correlation (the correlation coefficient r^2 of the linear regression is greater than 0.99) and the linear zone has been considered to be in the same pressure range [$P_1 - P_2$] for each product.

The value given by the helium pycnometer is assumed to be the best approximation of the true density (designated D_{v_0}, Table 2), and the weight of the compact after ejection (designated W_0) the closest value from the real weight of compacted particles.

Values (D_{v_i}, w_i) used for the mathematical simulations are shown in Table 1.

Figure 3 details the P_y values obtained by varying the true density by ±3% and the compacted mass by ±10 mg for the materials in this study at a compression speed of 16.6 mm·s^{-1}. Materials have been classified according to their increasing $P_{y(0)}$ value. Figure 3 demonstrates that true density exhibits a larger effect on P_y than does weight variation, except for DS. This is because DS has a low bulk density (0.270 g/cm^3). Besides, mean yield pressure decreases when the true density decreases and when the compacted weight increases. The mean yield pressure is calculated in order to determine the particle deformation mechanism(s) of a new product to help understand its compression behavior and to aid in formulation development. How do we characterize a product in such terms if the accuracy of the measurements is not adequate? Considering drug substance and drug product, the mean yield pressure varies at its maximum from 90 to 150 MPa and from 120 to 200 MPa, respectively. Therefore, according to the material deformation classification scheme presented by Roberts and Rowe's[11] (presuming the operating conditions are identical), it is difficult to classify products as plastic or brittle deforming materials.

If the true density varies from ±3% or if the mass of particles compacted varies from approximately ±10 mg, the

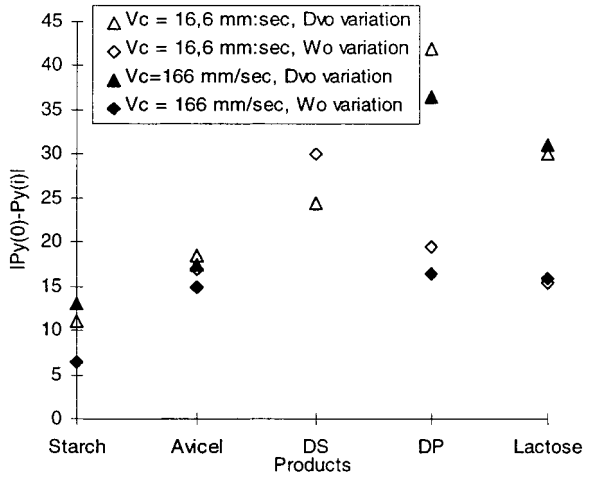


Figure 4—Influence of compression speed on the mean yield pressure variation (MPa).

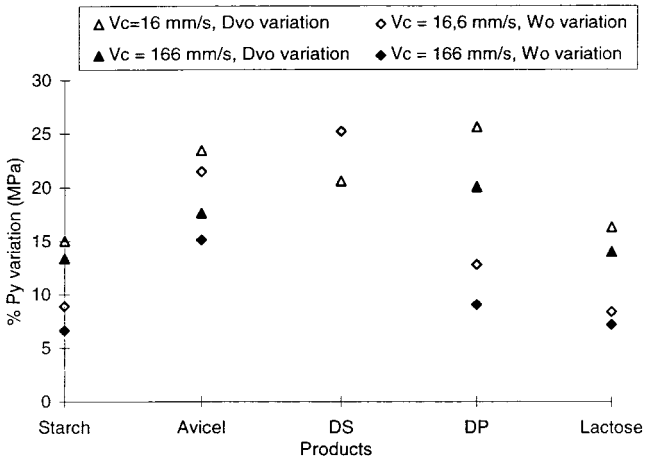


Figure 5—Influence of compression speed on the mean yield pressure relative variation (%).

mean yield pressure differs by approximately the same amount. The P_y variation can be expressed in both directions (either positive or negative) as the absolute value of the difference between $P_{y(0)}$ and $P_{y(i)}$. Figure 4 details the mean yield pressure difference $|P_{y(0)} - P_{y(i)}|$ for the materials in this study from which the effects of compression speed can be observed. Considering the small range of compression speed studied, P_y variation depends on the products and less on the compression speed: the effect of the compression speed is larger for DP than for any of the other products. However, the compression speed consequence is not studied on DS mean yield pressure variation: compacts can be produced at 16.6 mm·s^{-1} but not at 166 mm·s^{-1}. Although production of compacts is not necessary to measure the mean yield pressure, this high speed has not been studied for DS.

The mean yield pressure relative variation $\%P_y$ is defined as the percentage of the yield pressure variation relative to $P_{y(0)}$:

$$\%P_y = \frac{|P_{y(0)} - P_{y(i)}|}{P_{y(0)}} \quad (3)$$

Figure 5 details the $\%P_y$ variation for the materials in this study from which the effects of compression speed can be observed. At the lowest speed, the mean yield pressure relative variation reaches a maximum of 25% for DS and DP. When speed increases, $\%P_y$ decreases. In general, it is well-known from literature that the mean yield pressure of materials increases with increasing compression speed[10,11] (except for brittle deforming materials). Figure 4 shows compression speed does not have a considerable effect on $|P_{y(0)} - P_{y(i)}|$. On the other hand, $P_{y(0)}$ increases with compression speed. Therefore, $\%P_y$ decreases with increasing speed. The variation of the true density value and the compacted mass value has a relatively lower effect on $\%P_y$ when materials are compacted at higher speeds.

Even with the experimental errors introduced by true density and compacted mass measurements, it is possible to deduce the deformation mechanism of new pharmaceutical materials by including reference materials of well-known excipients that are measured at the same operating conditions (including an equivalent accurate measure of the true density and weight of particles compacted). Consequently, complete information about the true density measurement and accuracy of the method should be given with the Heckel model results in order for comparisons to be made.

We can estimate the error on the mean yield pressure when there is a subsequent error on the true density or compacted mass measurements by using the same upper punch force and punch displacements values for one material (also considering the linear part to be in the same pressure range $[P_1 - P_2]$).

The compact height is calculated from the punch displacement data, and depending on the true density of the material and weight of the compacted material, the relative density (ρ_i) is calculated at a pressure P_i:

$$\ln(\rho_i) = \ln\left(1 - \frac{w}{S h_i D_v}\right) \quad (4)$$

where S is the compact surface area, h_i the compact height at pressure P_i, w the compact weight, and D_v the true density of the compacted material.

Since the coefficient of regression r^2 is greater than 0.99, the slope of the linear part of the plot $-\ln(\rho_i)$ versus P (MPa) in the pressure range $[P_1 - P_2]$ can be estimated as follows:

$$K = \frac{-\ln(\rho_2) - [-\ln(\rho_1)]}{P_2 - P_1} \quad (5)$$

and the mean yield pressure can be expressed as:

$$P_y = -\frac{P_2 - P_1}{\ln(\rho_2) - \ln(\rho_1)} \quad (6)$$

From eq 6 we can calculate the error made on the mean yield pressure:

$$\Delta P_y = \frac{P_2 - P_1}{[\ln(\rho_2) - \ln(\rho_1)]^2}\left(\frac{\Delta\rho_2}{\rho_2} - \frac{\Delta\rho_1}{\rho_1}\right) \quad (7)$$

where ρ_i is dependent on the weight and true density value.

Therefore, for a weight variation Δw_0:

$$\Delta P_y = \frac{-\Delta w}{S D_v [\ln(\rho_2) - \ln(\rho_1)]^2}\left[\frac{1}{h_2\rho_2} - \frac{1}{h_1\rho_1}\right] \quad (8)$$

and for a true density variation ΔD_{v_0}:

$$\Delta P_y = \frac{w\Delta D_v}{S(D_v)^2 [\ln(\rho_2) - \ln(\rho_1)]^2}\left[\frac{1}{h_2\rho_2} - \frac{1}{h_1\rho_1}\right] \quad (9)$$

Equation 8 indicates that an underestimation of the compacted material mass ($\Delta W_0 < 0$) increases the mean

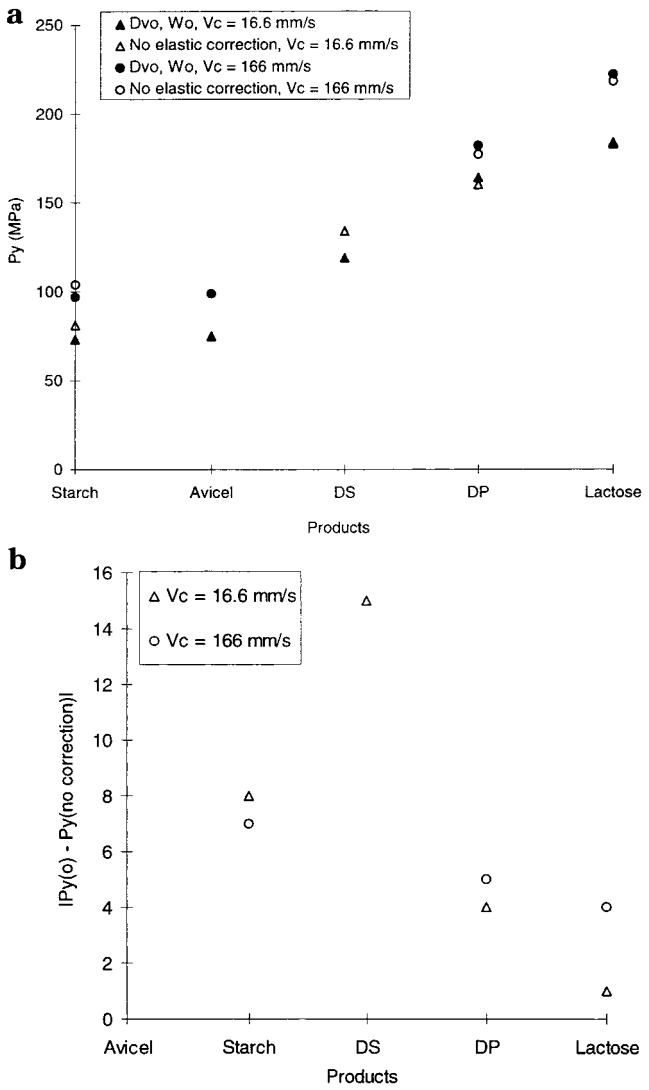


Figure 6—Impact of elastic correction on the mean yield value.

yield pressure value and overestimates the ability of the material to deform by a brittle mechanism. Similarly, eq 9 points out that an underestimation of the true density value ($\Delta D_{v_0} < 0$, which is often the case when it is not measured with a helium pycnometer) decreases P_y value and overestimates the plastic behavior. This reflects the measured variation of mean yield pressure. The two experimental values we studied could have either a complementary effect, i.e., the P_y value error is minimized, or a contradictory effect, i.e., the P_y value error is maximized. Therefore, two extreme cases may appear; if the true density value is minimized and the compacted mass maximized, or, on the other hand, if the true density value is maximized and the compacted mass minimized, the error made on the mean yield pressure would be maximized.

Figure 2, parts a and b, details force versus displacement data for uncorrected (Figure 2a) and corrected (Figure 2b) punch deformation. Most researchers point out that calibration is a significant step for obtaining correct force-displacement profiles.[17,20] The software allows analysis of force-displacement data with or without correction for elastic deformation of the punches. This is useful for comparing the effect elastic deformation of the punches has on P_y while varying the true density or compacted mass values. Figure 6a details P_y for the materials studied for corrected and uncorrected elastic punch deformation at two compression speeds. Figure 6b shows the effect of correction of elastic movement of punches and indicates it is lower than the effect of the true density variation, whatever the compression rate. No calculation of the mean yield pressure without elastic correction of punches has been obtained for microcrystalline cellulose. The greater consequence on P_y variation of the correction of the punches is obtained for DS for which the difference between the two mean yield pressures is 16 MPa. This value is the minimum difference obtained when studying the effect of the true density. The correction of elastic deformation of punches is necessary to improve the accuracy of force-displacement profiles but the consequence on the mean yield pressure is lower than the one which appears when errors occur while measuring true density or compacted mass.

The pressure range used for the Heckel analysis should be as large as possible. Since particle rearrangement and fragmentation often occurs up to 30−50 MPa, it is necessary to compress at least up to 150−200 MPa to increase the accuracy of the mean yield pressure measurement. If the strain-hardening zone[6,7] (D zone in Figure 1) exists when generating the relative porosity of the material column, the maximum amount of data can be used to describe the plastic deformation phase. Then, the mean yield pressure is calculated over a maximum pressure range.

Conclusion

This study showed that the experimental error due to punch displacement accuracy has less effect on the mean yield pressure than the error introduced when measuring the true density or the compacted mass.

Measurements of the force-displacement profiles are quite difficult to interpret according to the literature: Heckel model results are very dependent on the operating conditions. Therefore, it is suggested to analyze well-known pharmaceutical materials with well-known deformation mechanisms such as starch, microcrystalline cellulose, and/or lactose in order to interpret the deformation mechanism of new drug substances and new drug products. To compare the results of P_y between materials, it is important that the operating conditions and measurements methods be extremely accurate and well-defined.

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