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A critical evaluation of the Heckel equation

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Abstract

Great differences between published Heckel parameters, obtained from 'at pressure' data or the 'in-die' method, are outlined. The general validity of the concept of yield pressures derived from slopes of such Heckel plots is questioned. When the ability of the Heckel and the Walker equations is compared to fit density/pressure data from tabletting different pharmaceutical powders, a generally better fit is obtained with the Walker equation in the region of 5–100 MPa. The ability to discriminate between materials by data from the compression phase is improved by using the Walker model. For Emcompress®, apparent yield pressures derived from Heckel plots are dependent strongly on the maximum pressure of the compression process. © 1999 Elsevier Science B.V. All rights reserved.

Keywords: Compression; Heckel plot; Walker plot; Methodology

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1. Introduction

Several equations have been proposed in attempts to describe the compressibility of powders (Kawakita and Lüdde, 1970; Celik, 1992). Most of these formulas are based on transformations of the classical stress/strain or force/displacement relationship, where either the compaction pressure or the volume is transformed. Normalization of the volume is achieved either based on the initial bulk volume or on the true density of the powder.

As the compression process consists of several stages, it may seem unrealistic to look for one relatively simple formula with few parameters covering the entire compression process. It is, therefore, generally agreed that the mathematical models fit the data in either the initial or the final stage of the densification process. As the density during compression is varying in the tablet, it must be expected that the different stages of the process overlap each other. This makes it difficult or impossible to point out distinct regions where only one type of deformation — plastic, elastic or brittle — is dominating.

Attempts have been made to describe the entire compression profile in distinct parts by several equations (Holman, 1991) or with a polynomial with several coefficients (Chen and Malghan, 1994). These attempts are, however, of limited practical value.

The requirement for a single, informative and robust characterization of the compressibility of a powder as a material characteristic in develop-

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ment and formulation of tablets and in quality control is evident. The final goal should be to be able to predict the strength of the resulting compact from force/displacement curves and derived parameters.

Among pharmaceutical scientists, the Heckel equation has by far been the most popular in recent years, and many apparent yield pressure values ('in-die', P_y) and mean yield pressure values ('out-of-die') of active substances and tabletting excipients have been published. A review of the apparent yield pressures gives, however, a confused picture, as the values often differ significantly from one author to another. It has been reported that Avicel® PH 101 has the following apparent yield pressures: 47.6 MPa (Roberts and Rowe, 1987), 84.4 MPa (Yu et al., 1989) and 104 MPa (Paronen, 1986a). The following values on paracetamol have been published: 79 MPa (Humbert-Droz et al., 1983), 99.3 MPa (Podczeck and Wenzel, 1989) and 124 MPa (Duberg and Nyström, 1985). Considering the relatively narrow region where the apparent yield pressures are observed, these variations are too large to give a satisfactory and general valid material constant. Any methodology producing such dissimilar results should be thoroughly investigated and validated in respect to the reproducibility (intra-laboratory precision) and repeatability (interlaboratory precision).

The purposes of this study are to find possible reasons for the differences in published Heckel constants, to question the ability of the model, to reflect plastic behaviour of the compressed materials, and finally to compare the Heckel and the Walker equations and the information gained by these models.

1.1. The Heckel and Walker equations

Heckel (1961a) developed his equation by assuming similarity to a first-order chemical reaction, where the concentration is substituted with porosity and the time with pressure.

$$\mathrm{d}D/\mathrm{d}P = K*(1-D) \tag{1}$$

where P is the pressure, D the relative density of the compact and K is a constant.

Eq. (1) assumes that the rate of change in density with respect to pressure is directly proportional to the remaining porosity.

By integration, Eq. (1) gives

$$\ln(1/(1-D)) = P*K + A \tag{2}$$

where A is a constant.

The Walker equation is based on the assumption that the rate of change of pressure with respect to volume is proportional to the pressure giving the differential equation:

$$\mathrm{d}P/\mathrm{d}V = -l*P \tag{3}$$

which on integration and substituting ln with log becomes

$$\log(P) = -L*V'/V_0 + C1 \tag{4}$$

V_0 is the volume at zero porosity. The relative volume is $V'/V_0 = V = 1/D$. The coefficient L is referred to as the pressing modulus (Balshin, 1938).

Expressed in terms of the relative volume as the dependent variable, Eq. (4) is given the form proposed by Walker (1923).

$$V = -C2*\log(\mathrm{P}) + C3 \tag{5}$$

Eq. (5) gives a straight line relation of the relative volume or the inverse relative density versus the logarithm of pressure. For practical reasons, the relative volume is multiplied by 100 giving the compressibility coefficient W:

$$100*V = -W*\log(P) + C \tag{6}$$

By this notation, W expresses the change in volume in percent of the material volume when the pressure is increased by a factor 10.

W is considered a measure of the irreversible compressibility of the compact or the system of particles, while the inverse Heckel slope is claimed to describe the plastic property of the individual particles. From a pharmaceutical point of view, the former seems to be of more practical relevance.

The Heckel and the Walker equations transform the relative density completely different as seen in Fig. 1. The Heckel transformation is practically linear at low densities corresponding to the well-known lack of fit at low pressures while the

Walker transformation is most curved in this region. At high densities, the Walker equation approximates linearity while the Heckel transformation tends to infinity. This means that the Heckel plot will show an upward curvature near zero porosity.

Several authors have described the use of the Walker or Balshin equation in characterization of compression behaviour. In his dissertation, Huffine (1953) characterized a large number of substances by their pressing moduli. The Walker plot was used by Train (1956) in describing the different stages in the compression process. Huffine and Bonilla (1962) showed that the pressure modulus increased with increasing particle size by compression of sodium chloride, sucrose and quartz. The same observation was made on spray dried and crystalline lactose (Fell and Newton, 1971; York, 1978). The Walker equation was used as a test for variation in powder behaviour by Birks (1990), who showed significant differences between two batches of trisodium phosphate. Celik and Marshall (1989) found almost

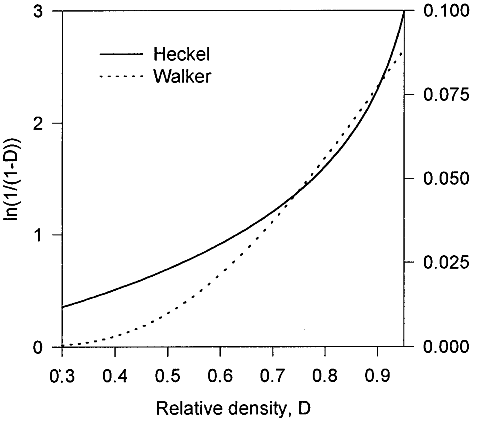

Fig. 1. The Heckel and Walker transformation of the relative density in the density region 0.30–0.95.

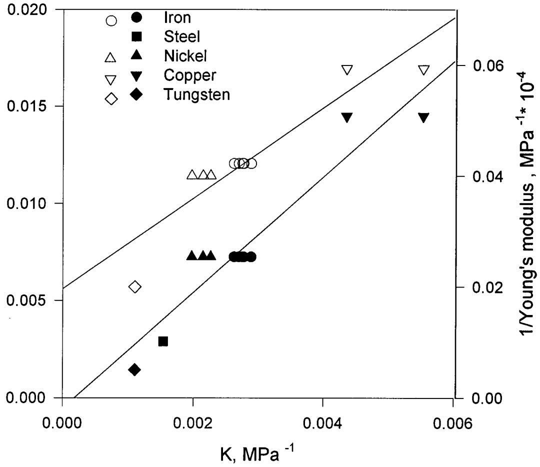

Fig. 2. Correlation between the *K* values for five metals and the inverse yield strength (closed symbols) from Heckel (1961b) (both recalculated to MPa) and the inverse Young s modulus (open symbols) adopted from Kittel (1960) omitting steel.

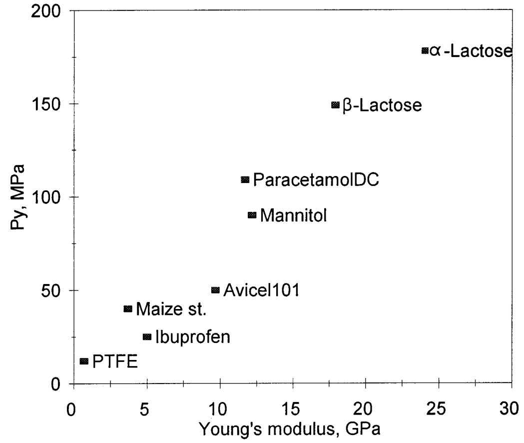

Fig. 3. Relationship between the apparent yield pressure and Young s modulus measured by beam bending data from Roberts and Rowe (1995). PTFE, polytetrafluoroethylene.

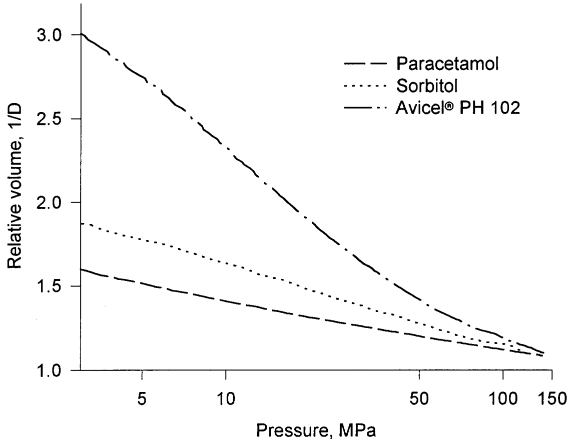

Fig. 4. Examples of Walker plots.

linear relations in the region 5–125 MPa for several pharmaceutical substances.

1.2. Drawbacks of the Heckel equation

It has been proposed to explain the variation in Heckel parameters by the different experimental techniques employed (York, 1979).

At high pressures, where the Heckel plot is linear, the punch movement is very small. This makes accurate measurement of distance and precise correction for deformation of tools and machine parts extremely important. By introducing a ± 10 μm systematic error in the measurement of the punch distance, the calculated apparent yield pressures will be 94.7 or 105.3 MPa instead of 100 MPa. (Conditions: 10 mm punch diameter, 250 mg compact, density 1.5 g/ml, slope 0.01, intercept 1.4 and pressure range 50–150 MPa.)

The apparent yield pressure is reported to be strongly dependent on the maximum pressure (Paronen, 1986b; Rees and Tsardaka, 1994; Konkel and Mielck, 1997). This observation may be one of the reasons for the observed differences and illustrates the problems with the Heckel parameters as a general material constant.

Other reasons for the divergence between the apparent yield pressures may be of mathematical or statistical nature.

It is normal practice to calculate the apparent yield pressure by taking the inverse of the estimated slope from the Heckel plot. This is, however, only correct when there is no error in the calculated slope. Actually, the inverse slope in linear regression b_{xy} is estimated as $r2/b_{yx}$ and not as $1/b_{yx}$. This is not important in most cases with correlation coefficients close to 1, but it means that a slope (b_{yx}) estimated to 0.005 with a correlation coefficient of 0.95 gives the apparent yield pressure (b_{xy}) 180 MPa, and not 200 MPa as the normal procedure would lead to.

Paronen and Ilkka (1996) recommended nonlinear techniques in calculating the slope to overcome the problem with the different weights introduced by the logarithmic transformation.

From a mathematical point of view, the Heckel equation is based on the force–displacement relationship where the volume is normalized by multiplying with the true density to give the relative volume V followed by a three-step transformation:

(1) $V \rightarrow 1/V = \mathrm{D}$	reciprocal and transformation, volume to density
(2) $D \rightarrow 1 - D$	linear rescaling, density to porosity
(3) $1 - D \rightarrow 1/(1 - D)$	Reciprocal transformation
(4) $1/(1 - D) \rightarrow \ln(1/(1 - D))$	Logarithmic transformation

These transformations lead to a tremendous effect of any errors in the measurement of the true

Table 1
Values of the apparent yield pressure and the compressibility coefficient and the corresponding standard deviations for nine materials [a]

Material	Density (g/cm^3)	P_y (MPa)	S.D. (MPa)	W	S.D.	W^*	n	MaxP-range (MPa)
Avicel® PH 102	1.557	77.6	5.8	125.0	1.30	128.5	6	80–210
Avicel® PH 101	1.566	79.0	7.3	114.6	1.28		6	80–210
Avicel® PH 301	1.550	78.4	3.1	96.8	1.29		6	80–220
Emcompress®	2.392	327.0	41.9	56.6	0.75	58.5	6	140–250
Sorbitol	1.524	95.5	13.3	50.5	0.59	48.7	6	110–190
Sodium chloride	2.134	83.3	3.9	43.5	1.11	44.2	6	110–180
Tablettose®	1.555	150.2	12.2	42.5	1.29	60.1	6	90–200
Ascorbic acid	1.694	150.1	13.1	34.1	1.29		6	100–180
Paracetamol	1.294	117.5	7.6	28.5	0.91	27.5	6	100–220

[a] W^* is data from Celik and Marshall (1989). MaxP-range is the range of maximum pressure used in the calculations of the apparent yield pressure. W and W^* is calculated in the pressure region 5–100 MPa and 5–125 MPa.

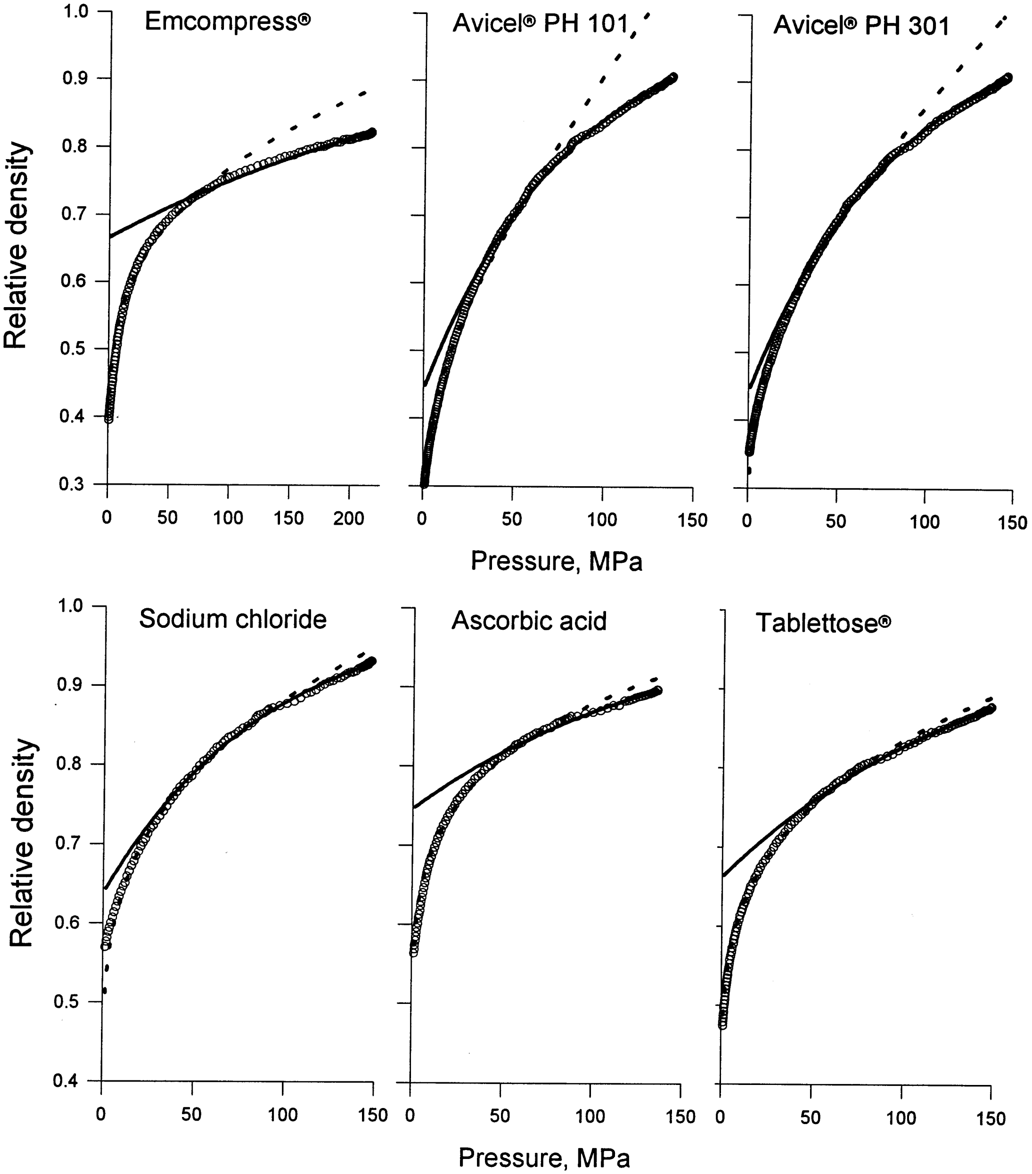

Fig. 5. Density versus compaction pressure with the untransformed fit of the Walker equation (dotted line) and the Heckel equation (solid line).

density. If for instance the true density is 1.5 g/ml, the true slope is 0.01 and the intercept 1.4, then a 1% systematic error in the density measurement (densities = 1.515 and 1.485) in the region 50–150 MPa will lead to P_y values 111 and 88 MPa, respectively. Thus, an error of 1% in density causes an error of more than 10% in the apparent yield pressure estimate.

Apart from the lack of reproducibility of the apparent yield pressure values, several other disadvantages using the Heckel equation are reported:

- The region where the Heckel plot is linear is only accounting for a small portion of the total densification (Huffine, 1953; Birks, 1990; Konkel and Mielck, 1997).

- Some investigators were unable to define any linear part of the Heckel plot (Rue and Rees, 1978; York, 1979; Celik and Marshall, 1989).
- In an interlaboratory investigation on compression simulators (Bateman et al., 1989), the apparent yield pressures differed by up to 10%. It was concluded that a degree of caution should be exercised when comparing data from different research groups. Furthermore, this investigation showed that the relative standard deviations on repeated measurements (repeatability) were in the range 1.2–8.9%.
- The pressure range where the Heckel plot is linear often exceeds what is relevant in manufacturing of tablets.
- It has been shown (Pedersen and Kristensen, 1994) that materials like acetylsalicylic acid at high pressures densify to relative densities less than one. This indicates that the assumption about constant density of the substances under compression may not be valid in particular at high pressures.

Overall it seems that the Heckel equation with the techniques applied does not fulfil the need for a reliable and reproducible material constant. Paronen and Ilkka (1996) summarized the criticism of this model: ‘So, most often the Heckel equation is strictly speaking invalid on most stages of compaction of pharmaceutical powders’. The demands to a general valid compression constant should be that it is insensitive to changes in experimental conditions (maximum pressure, punch dimensions and weight of the compact) or to different methods of calculations and measurements of the true density. The material constant should be sensitive only to changes in particle size or form, speed of compression and other formulation variables.

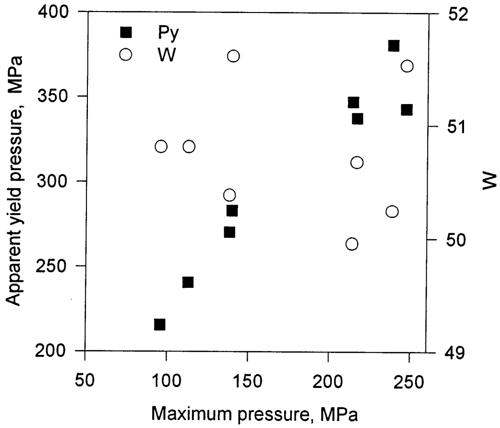

Fig. 6. Relationship between maximum pressures and the calculated apparent yield pressure P_y and compression coefficient W for Emcompress®.

1.3. The Heckel argument for plastic deformation

Heckel (1961a) argued that the linear part of the curve describes the plastic deformation of the material and considered elastic deformation to be negligible. This statement was partly based on the fact that alumina powder that densifies by crushing failed to produce any linear region.

Heckel concluded also that at low pressures the curved region of the plot is associated with individual particle movement in the absence of interparticle bonding, and that the transition from curved to linear corresponds with the minimum pressure necessary to form a coherent compact. This may be true in compression of iron, copper and steel, but many substances of interest in pharmaceutical tabletting form coherent compacts in this region.

An important part of the Heckel theorem is the observation of a correlation between the inverse yield strength and the slope of the Heckel plot for the five metals (Heckel, 1961b).

From Fig. 2 it is observed that the correlation between K and Young’s modulus inverted is at the same level as between K and the inverse yield pressure. This indicates that the K value is not necessarily as postulated a predictor of the yield pressure, but might as well be a predictor of Young’s modulus, an elastic property of the material.

Heckel calculated the relation between K and the inverse yield strength Y to $K \approx 1/(3Y)$ (95% confidence interval $1/2.28 - 1/3.67$). If this equation is generally valid then the inverse regression should lead to the equivalent result. However, using the data of Heckel, the relation $1/K = 1.03 * Y + \text{const.}$ was found (95% confidence interval of the slope 0.77–1.32).

The correlation between the inverse yield strength and the K value observed by Heckel is later treated like a functional relationship, leading to the notion of mean yield pressure (Hersey and Rees, 1970).

According to Hersey and Rees, the theoretical works of Hencky (1923), Ishlinsky (1944) show that the apparent yield pressure P_y equals $3Y$. Unfortunately neither Henckys nor Ishlinskys articles are dealing with compression of powders. They are both theoretical investigations on Brinell hardness, and the indentation of different geometrical forms in an idealized plastic body, where elastic forces are disregarded.

Hencky (1923) defined the mean pressure as the mean of the two of the three principal stresses σ_1 and σ_2, putting $\sigma_3 = \sigma_2$.

The indentation of a sphere is by Hencky calculated to give a yield point = 0.35 times the mean pressure. Comparing this result with an experimental value 0.22, Hencky concludes: 'The relationship between yield point and mean pressure can consequently not be constant but is dependent on the indentation depth and the form of the indenter'.

The mean yield pressure was not found mentioned in Ishlinsky's paper, but Ishlinsky finds by calculation that with a spherical punch, the elastic limit ($\sigma_s = \sigma_1 - \sigma_2$) is $0.383{*}H_B$, where H_B is the Brinell hardness.

It seems that the mean yield pressure does not necessarily give any information about the plasticity of a substance, but simply is the pressure region corresponding to one decade on the Heckel transformed stress/strain curve. It is interesting that there might be a linear correlation between the apparent yield pressure and the elasticity of substances as illustrated in Fig. 3.

2. Materials and methods

2.1. Materials

Emcompress® (lot W19A, E. Mendell Corp., NY), Avicel® PH 101 (lot 6616), PH 102 (lot 7641) and PH 301 (lot Q625C, FMC Corp., Philadelphia, PA), Tablettose® (lot L735 A4003, Meggle Milchindustrie, Gmbh. FRO), paracetamol (lot 9425216, Rhone-Poulenc, France), sodium chloride (lot 257251, UNIKEM, Cph. DK.), sorbitol (lot P60W Roquette Frer., France) and ascorbic acid (lot 251025, UNIKEM, Cph. DK.) were all used as purchased.

2.2. Methods

The true densities were determined with 3 purges and 7 runs on a helium gas pycnometer, (AccuPyc 1330, Micrometrics). The materials were compacted using the compaction simulator described previously (Pedersen and Kristensen, 1994). The accuracy of the distance between the two punches were 2.42 μm and the accuracy of the force measurements were 16.2 N. The elastic deformation of the punches and equipment was 18.8 μm/KN and the displacement data were corrected with this value.

Six to eight samples of ~ 500 mg (495–505 mg) were compacted using 15.0 mm diameter flat faced punches. When necessary, the die and punches were lubricated with a 5% suspension of magnesium stearate in acetone. The compression profile was a simulation of an excentric press with a total process time of 2.2 s, corresponding to a contact time from 400 to 540 ms depending on the material. Data were collected every 2.15 ms. One hour after compaction, the actual weight of the tablets was determined. ASCII-data from the sampling computer were transferred to a spread sheet program (Quattro Pro, ver. 6.0), where further calculations and linear regression were performed on the upper punch pressure and the distance between punches.

The W coefficients were calculated by linear regression with the relative volume as dependent and the logarithmic transformed pressure as independent variable. The pressure range for all substances was selected from 5 to 100 MPa or to the maximum pressure. All estimated slopes in the Walker plots were within 1% relative standard deviation (calculated as the standard deviation of the slope divided with the slope estimate) and for the Heckel slopes within 1.5%.

The apparent yield pressure values ('in-die') were calculated from 40 MPa to the maximum pressure, except sodium chloride starting at 30 MPa, and Emcompress® starting at 50 MPa. The pressure ranges were selected by analysis of residuals and evaluation of the standard deviation of the slope.

3. Results and discussion

The Walker plots in Fig. 4 show that sorbitol and paracetamol fit the model quite well whereas Avicel® PH 102 deviates in the upper pressure region. This corresponds to the observations made by Celik and Marshall (1989) and implies that the pressure range where the calculation is performed may be optimized.

Comparing the Heckel parameter P_y and the W value from the Walker plot in Table 1 it is apparent that the former is estimated with a poorer discrimination among the materials. The three qualities of Avicel® have the same apparent yield pressures while there is a significant difference between the W values. The larger standard deviations of P_y are partly caused by the dependency of the compaction pressure. The excellent tabletting properties of the Avicel® qualities correspond with high W values whereas ascorbic acid and paracetamol known to have poor compaction properties have low W values. This indicates a correlation between the W values and the tabletting properties at least at a qualitative level.

In Table 1 there is excellent agreement between the values observed by Celik and Marshall (1989) and our data except the values for Tablettose® where Celik and Marshall used fast flo lactose. However, compared with the inverted pressing modulus for lactose published by York (1978) who found values between 43 and 49 depending on the particle size there is no significant difference.

As expected the Walker equation in Fig. 5 fits the data well in the lower pressure region while the lack of fit of the Heckel equation in this region is significant. It is a question whether the information obtained from the Heckel plot for Emcompress® Tablettose® and ascorbic acid is much better than a simple linear relation between density and pressure, corresponding to an elastic deformation. The Walker equation does not fit at high pressures where the density is increasing at a slower rate than predicted by the model.

The apparent yield pressure dependency of the maximum compaction pressure is visualized in Fig. 6, where the P_y values vary between 200 and 400 MPa almost linearly by increasing the maximum pressure from 100 to 250 MPa. The strong influence of the maximum pressure is observed for all the tested materials except for sodium chloride. A careful examination of the residuals shows that this phenomenon is caused by a small deviation from linearity although the correlation coefficient was better than 0.993 in all cases. Determination of W is restricted to the pressure range 5–100 MPa and is therefore independent of the maximum pressure. When W is calculated in the pressure region 5–75 MPa only small deviations from the actual data are observed. The largest deviation is observed for Emcompress® (5.1%).

4. Conclusions

It is demonstrated by calculations that the Heckel plot and the derived parameters are extremely sensitive to small errors in the experimental conditions and variations in the true density value.

The yield pressure dependency of the maximum compaction pressure may be one of several factors that accounts for the variation between published apparent yield pressure values.

We have not found any proof in the literature that the linear part of the Heckel plot describes plastic deformation or that the apparent yield pressure should be the pressure where the plastic deformation of the material starts.

Compared with the Walker equation the Heckel model is less reproducible and has less discriminative power as a general compression constant.

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