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Research paper

Development of computerised procedures for the characterisation of the tableting properties with eccentric machines: extended Heckel analysis ☆

Markus Krumme[a], Lothar Schwabe[b], Karl-Heinz Frömming[b,*]

[a]LTS Lohmann Therapie-Systeme, Andernach, Germany
[b]Institute of Pharmacy, Department of Pharmaceutical Technology, Free University Berlin, Berlin, Germany

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Abstract

Heckel plots are a suitable and valuable method for analysis of powder compaction with very small amounts of powder. The determination is based upon a non-linear transformation of compression data and thus the signal errors that might be introduced into the analysis might be enlarged and become critical. The method of determination of true density affects the results dramatically as does the accuracy of the powder height determination. The porosity should be corrected for compression of the solid fraction. The accuracy of the powder height detection is the most demanding parameter. The statements are proven by simulations based on real data and analytic calculation. According to these highly corrected Heckel plots, the shape of the plots during the compression phase gives the information about fragmentation and plasticity and additionally about the time dependency of the compression behaviour within one compression on an eccentric press.

Keywords: Tablets; Compression; Instrumentation; Powder density; Heckel analysis; Yield pressure; Qualification

1. Introduction

The basis for studies on tableting properties of drugs and excipients is the use of instrumented tablet machines [1]. The most important parameters used for the characterisation of powders are displacement and force signals. In previous articles [2–4] we described a new computer-based system suitable for acquisition and automated data analysis, and an investigation of some non-transformed and model-independent parameters for characterisation of the properties of substances under compression.

The tablet machine is the main tool for the production of tablets of interest. In order to achieve the characterisation of the powders' properties the task of the tablet machine is somewhat changed: it is modified to become more or less an analytical instrument. Numerous approaches have been taken to describe the powders' properties under compression [5], including several compression equations [6]. The compression analysis based on the application of an equation suggested by Heckel is widely used in the literature [7–11]. Despite its common use, large differences in the shape of the curves can be observed if curves published by different authors are compared [12]. The values of the most important parameters seem not to be transferable between different experimental set-ups [7], although in theory the Heckel plots should use and provide absolute parameters (e.g. pressure, porosity, yield pressure). These observations gave rise to the assumption that the Heckel plots should be used carefully and should not be used for the determination for absolute values. The tablet machine in the sense of an analytical instrument has been investigated in terms of a qualification (e.g. [4,13,14]). Recently a qualification approach to the application of the Heckel plots has been published [13].

In this article, some improvement of the method of determination of Heckel Plots as a tool for characterisation of powder properties will be described, and a critical evaluation of necessary parameters and their influence on the overall accuracy of the model-dependent transformation is given based upon a mathematical approach.

2. Theoretical aspects

The ability of a substance to withstand its own deformation when the apparent volume is reduced can be described by usage of force–displacement curves. These curves and

☆ Dedicated to Professor Dr B.C. Lippold on the occasion of his 60th birthday.

* Corresponding author. Institute of Pharmacy, Department of Pharmaceutical Technology, Free University Berlin, Kelchstrasse 31, D-12169 Berlin, Germany. Tel.: +49-30-7700-0442; fax: +49-30-7700-0475.

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curves derived from those raw data are usually taken as the 'compaction fingerprint' of a powder. The raw data are, however, mainly defined by the construction of the tablet machine. To prove this, let us make following theoretical experiment: If the powder bed between the punches is replaced by an ideal incompressible material and the punches are adjusted to produce a force signal of a certain maximum (ideal flat-faced punches) during a cycle, the result is a purely elastic compression of machine parts. which is in theory exactly linear. Replacement of the incompressible disk by a powder bed does more or less leave the displacement profiles unchanged but affects the force signal due to plastic and viscous components in the powder bed. The properties of the powder is the underlying information, that is hidden mainly in the force signals. The optimum method for the characterisation of the compaction process would be a robust method, being sensitive for assessing the powder properties and being as independent from the experimental environment as possible.

Upon integrating the force–displacement curves energy terms can be obtained and taken as model independent signals [4]. Although they are valuable in describing the compression process, all energy terms are calculated directly from raw displacement data. Normalization to the diameter or the porosity is not possible, because

$$\int P_a \cdot ds \tag{1}$$

with P_a the compressive stress, s the displacement, does not have the dimension of an energy. So the data are not independent of the experimental conditions. The energy itself can be normalised to the powder weight thus resulting in better independence of experimental conditions [4].

The Heckel model provides a method for transforming a parametric view of the force and displacement signals to a linear relationship for purely plastic materials. Assessing the linearity of a given data set is an easy task, so the Heckel model is a convenient method for interpretation.

For the derivation of his equation Heckel considered that the reduction of the voidage should obey a first-order kinetics type of reaction with applied pressure [15]. With this approach Heckel derived via integration an equation, which describes the changes in relative density as a function of the applied compressive stress of a system performing these first-order kinetics. Eq. (2) shows a linear relationship between $\ln(1/1 - D_{rel})$ and the compressive stress

$$\ln\left(\frac{1}{1-D_{rel}}\right) = kP_a + A \tag{2}$$

with D_{rel} the relative density, P_a the compressive stress, and k, A constants.

Supposing the model is valid, then the plot consisting of the transformed signal $\ln(1/1 - D_{rel})$ vs. the applied compressive stress should be a linear function. The equation, however, proposes neither that the compression event can be described as a linear function, nor that the model of first-order kinetics can be applied. But, as Heckel proposed in his second paper [16], there should be a relationship between the constant k and the yield strength of the material Y

$$k = cY \tag{3}$$

with c a constant factor.

The constant factor was determined to be 3 in the cases of those metal powders investigated in that paper. It is not known what this factor is like in other cases and for other materials. Later Hersey and Rees [17] related the constant k to the mean yield pressure P_y as

$$k = \frac{1}{P_y} \tag{4}$$

3. Materials and methods

A more detailed description of the experimental environment has been published elsewhere [2,3].

3.1. Tablet machine

The compressions were carried out using a Korsch EK0 (Berlin, Germany) eccentric press. The main switch was replaced by a computer-controlled contactor.

3.2. Force measurement

The force measurement was carried out using strain-gauge-based force transducers. The strain gauges were connected to form a four-arm Wheatstone bridge. The signal conditioning was done by 5-kHz carrier frequency bridges (HBM MG 3171, HBM, Darmstadt, Germany). The voltage output was fed into an VMEbus ADC with a resolution of 12 bits; the main computer was an Atari Mega ST. The software was written in-house and is published elsewhere [2].

The maximum error of the whole force measurement chain was 0.4% (60 N) under static conditions and 2% (300 N) under dynamic conditions.

3.3. Displacement measurement

The displacements of the upper and lower punches were followed with two linear inductive displacement transducers (W10T for the upper, W20T for the lower punch, HBM). The transducer for the upper punch was mounted at the frame and was driven by a lever connected to the upper part of the punch holder. The LIDT of the lower punch was attached in the central compression axis to the frame, and the calliper was driven by the lower surface of the lower punch holder. Both were conditioned by 5-kHz carrier frequency amplifiers (HBM MG 3171). For high-precision experiments the powder height was followed directly with a new compact instrumentation [3]. This is based on two LIDTs (HBM W5N) which are amplified through HBM K 51 and digitized separately. DAQ was done with a VMEbus-

based system (AD12/1, Rhotron, Homburg/Saar, Germany) with our own software. All of the displacement signals were calibrated against slip gauges. The raw data were corrected with the calibration functions for non-linearities, offset errors and machine deformation. The maximum error of the direct height instrumentation was below 5 μm in the most important parts of the calibration plane and below 10 μm under all conditions. The maximum error of the standard instrumentation was 20 μm.

3.4. Powder compression

The compression experiments were carried out using Avicel PH 101 (FMC Co., Philadelphia, PA), α-lactose monohydrate (Merck, Darmstadt, Germany), Starch 1500 (Colorcon, Orpington, UK), sorbitol (crystal grade, Merck), wheat starch (Caelo, Hilden, Germany) and dicalcium phosphate-dihydrate (Emcompress, Mendell, Patterson, NY). The powders were compressed with flat-faced punches at constant machine adjustment to tablets with an average height of 1.5 mm and a diameter of 9 mm. The variation of minimum porosities were adjusted by weight variation. Each experiment was repeated five times. The powders were weighed on an analytical balance (Mettler AT 200, Mettler, Greifensee, Switzerland), poured into the prelubricated die and compressed. After each compression the die was polished with a stick with a cotton-wool tip, and dry-coated with magnesium stearate using a second stick. After compression the tablets were weighed again on an analytical balance (Mettler AT 200) connected via serial link (RS 232C) to the computer.

Compression data were collected during the total cycle. The endpoint of data evaluation was set to the beginning of the phase, where the upper punch rested on the tablet surface during decompression, when the piston travelled through the gap in the ball and socket joint between the connecting rod and the piston. During that time the upper punch has no coupling to the eccenter and thus the upper force remains constant due to friction in the liner and the weight of the piston. For more details see Ref. [2].

3.5. Determination of true density by compression

For the assessment of the true density a certain amount of powder was weighed precisely (Thermobalance M3, Mettler), poured into an unlubricated die similar to that of Ford and Wilkinson [21], and compressed under vacuum at 0.73 GPa using an instrumented hydraulic press (Specac 25.011, Specac, Orpington, UK) as described below. The inner diameter of the die was determined with a high-precision micrometer screw with ±5 μm accuracy to be 12.995 mm. In order to minimise the effect of radial elastic deformation of the die, the ratio of tablet height to diameter was set to 0.16. For determination of the height a special instrumentation of the punch was built, based upon two mechanical callipers (DIN 878). The linearity of both devices was determined with slip gauges (DIN 861), the distortion of the set-up due to deformation was determined, and the values were corrected for both the non-linearities and deformation with the same method as applied to the tablet press itself as published previously [3].

The accuracy of the height detection was within ±3 μm limits after application of all correction methods.

First the material was compressed to maximum load under vacuum. The dwell-time was set to 15 s. The readings of the height were taken at 100%, 80%, 60%, 40% and 20% of the maximum load during decompression. The experiments were repeated five times each.

3.6. Air-comparison pycnometry

About 70% of the volume of the measuring chamber of a Beckman model 930 (Beckman Instruments, Fullerton, CA) was filled with powder, weighed, and the volume of the solids was assessed using air at room conditions as gas phase.

4. Results and discussion

4.1. Determination of true density and modulus of compression

The true density is a necessary parameter for the calculation of relative density or the degree of densification. The necessary precision of the true density is affected by the degree of densification; as for the calculation of Heckel plots, the difference between actual densification as a function of time and complete densification at zero porosity are evaluated. The higher the degree of densification investigated, the higher the accuracy required for both parameters.

In Figs. 1 and 2 the effect on Heckel plots by errors in the determination of true densities is demonstrated. In Fig. 1 a Heckel plot has been calculated based upon a certain data set describing the force- and displacement-time series of a compression of Avicel to 3% minimum porosity. Based upon the same data set an additional two Heckel plots have been calculated, but the true density was taken as (i) the determined value, (ii) the determined value plus 0.03 g/ml

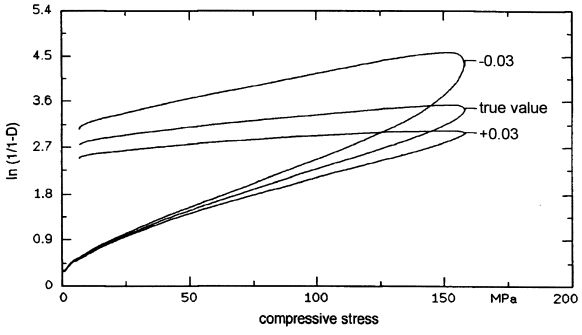

Fig. 1. Influence of errors in true density measurements upon Heckel plots, simulated using signals of a compression of Avicel to 3% porosity with correct true density D, $D - 0.03$ and $D + 0.03$ g/ml.

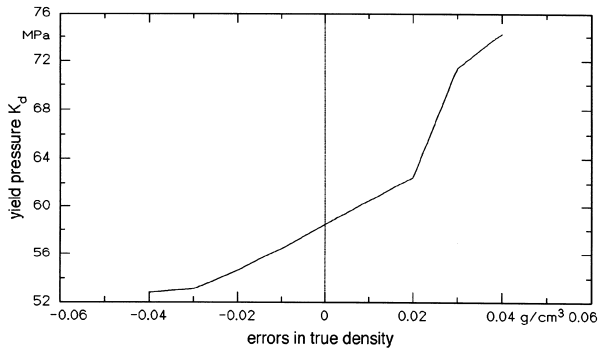

Fig. 2. Influence of errors in true density measurements upon the Heckel parameter K_d. Avicel, 3% porosity.

and (iii) the determined value minus 0.03 g/ml, respectively. The reason for the choice of this certain value is mentioned later. It is evident that even this relatively small error in determination of the true density has large effects on the accuracy of the apparent Heckel plot. The differences include the slope during densification, the slope during elastic recovery and the shape of the curve. Evaluation of the linearity of the curve seems to be difficult, if based upon an accuracy of the true density determination of about 0.03 g/ml or worse.

Fig. 2 shows the simulation of the effects of different errors of the true density values as basis for the calculation of the yield pressure parameter K_d. As a result of non-linear transformation of small differences of time-based raw data, a remarkable reduction of accuracy has to be registered. For that reason a high-precision determination of the true density is necessary.

True density in the sense required here has to be defined differently than usual. Usually we should define the 'true density' as the density of a crystallographic unit cell as assessed by X-rays. This is the most exact approach. However, in non-ideal crystallites this definition leads to a wrong approach, as the density of real crystals is different, mostly lower than the X-ray density due to and dependent on the kind and concentration of lattice imperfections. This effect can be used to assess the crystallinity in the sense of Huettenrauch and Keiner [19,20]. An improved definition would take these lattice imperfections into account. This definition, however, is difficult to formulate as the discrimination of 'lattice imperfection' from 'internal pore' is not sharp. Even the outer surface of the particle as such can be regarded as a big lattice imperfection. In the tableting field mostly the apparent particle density as assessed by helium pycnometry is defined as the true density. This approach does not take into account internal pores, which cannot be assessed via pycnometers and effects due to physisorption of air. Especially, N_2 and O_2 can be absorbed due to formation of induced dipoles. Correct determination of helium density has to desorb the air from the particles with a high vacuum prior to the inflow of helium. The problem of internal pores cannot be solved. Size reduction of particles probably makes some internal pores accessible by helium, but increases the concentration of lattice imperfections, which leads to decreased density as mentioned above. Pressure-induced crystallinity changes cannot be considered with helium pycnometry. As a result it is evident that the definitions mentioned so far are not optimal.

The Heckel approach is based on the idea of describing the reduction of voidage in the powder bed. Under high loads internal pores might collapse and become part of the voidage reduction process. During the tableting process working under helium atmosphere is not practical, so we have to deal with particles which have possibly absorbed air. It is unclear whether application of high loads will desorb air. As tableting is done under atmospheric conditions, we propose that the same conditions should be taken for the estimation of the true density. A definition of the true density in the sense of Heckel should be the density of a compact of zero voidage at atmospheric pressure. This compact has no pores, real surfaces (including absorbed material) and the same crystallinity as the compacts under evaluation.

A method for measuring the true density that meets the specifications of this definition cannot easily be found. We have chosen two approaches: air-comparison pycnometry or compression experiments at very high load levels under vacuum by investigation of the apparent density of the compacts in the decompression phase. Air-comparison pycnometry takes into account the possible surface loading (adsorption of air, water, etc.); it does not see internal pores and pressure-induced changes in crystallinity. Under high load levels the apparent density as determined by instrumented presses will asymptotically move towards the true density. The high-pressure compaction method sees the reduction of internal pores, the possible surface loadings and the changes of crystal structures, as mentioned by Cole et al. [18] and Huettenrauch and Keiner [19,20], that might be released by extensive plastic flow of some particles. The extent of reduction of internal pore volume remains unclear and the possible pressure-induced changes of crystallinity may be overestimated, as the pressure is much higher.

In Figs. 3 and 4 the calculated apparent densities are plotted as functions of the applied pressure for samples

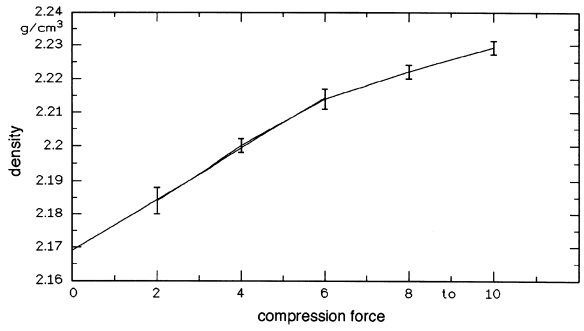

Fig. 3. Determination of true density via compression at very high load levels in a hydraulic press, sodium chloride.

made of sodium chloride and potassium bromide, respectively. The theoretical values are reported to be 2.75 and 2.16 g/cm^3 [22]. The resultant curves are roughly linear; a slight decrease of slope has to be registered upon the application of very high loads. As the readings were taken during the decompression after a significant time of bond formation, the profiles show the elastic recovery of the compacts. The recovery is obviously slightly non-linear, which can be observed in engineering often due to contact problems with growing contact areas. Formation of micro-cracks upon releasing the pressure might be an explanation for this phenomenon. As the degree of non-linearity is not high, we approximated the lower part of the curve with a linear regression in the linear part (lower three levels) in order to extrapolate to zero load.

From the curves obtained it can be seen that the extrapolated values for sodium chloride and potassium bromide are about 2.17 and 2.75 g/cm^3, respectively. The theoretical values are met with high precision. It may be derived from the experiments that under the described conditions a porosity close to zero was achieved and that the higher densities registered under compression with high loads are due to compression of the solid itself. Thus the modulus of compression K can be determined from the slopes. The Young's modulus is then obtainable according to

$$E = K \cdot 3(1 - 2n) \quad (5)$$

if the Poisson's ratio $1/n$ is known [34]. For most solids this ratio is reported to be near 0.3 [23].

4.2. Comparison with air-comparison pycnometry

The following experiments were performed in order to compare the results of the compression method with those obtained by air-comparison pycnometry. The measurements were taken using a Beckman model 930 air-comparison pycnometer with the materials microcrystalline cellulose Avicel, lactose, Starch 1500 and wheat starch (Fig. 5). The 95% confidence intervals of the readings were about 0.004 g/cm^3. All data showed that the air-comparison pycnometry always results in lower densities than compared to the compression method. The largest difference is found with Starch 1500 and is assumed to be due to a high amount

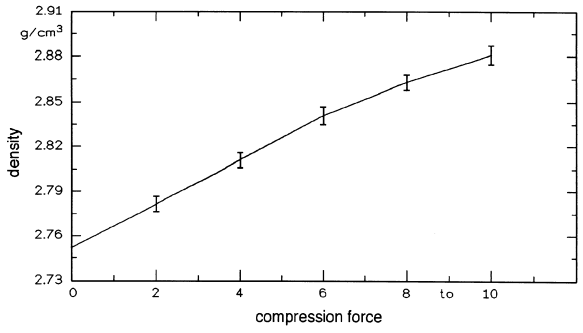

Fig. 4. As Fig. 3, potassium bromide.

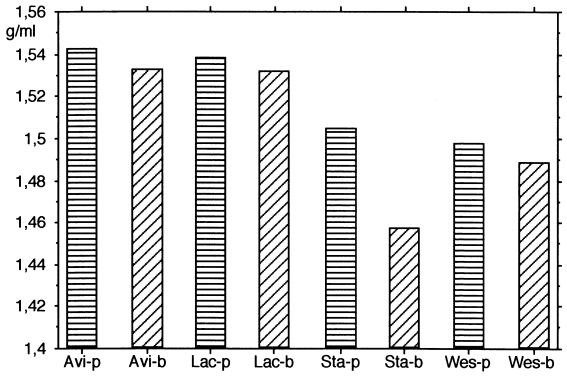

Fig. 5. Comparison of true density values as determined by compression and Beckman air-comparison pycnometer (Avi-p, Avicel compressed with the hydraulic press; Avi-b, determination by Beckman pycnometry).

of internal pores. Considering all substances investigated, the mean difference is about 0.03 g/cm^3 (see above). If during compression experiments the densification is near 100%, the change of the true density of the particles due to compression of solids has to be considered. Otherwise the apparent density, which is calculated from displacement data under compression, might become even larger than the 'true' density. This results in negative porosities and thus in non-defined parts of the Heckel plots. In order to determine accurate Heckel plots under high load conditions the true density has to consider the modulus of compression of solids. These moduli were detected with the compression method for true density determination. Fig. 6 shows two Heckel plots based on the same set of data, one of them corrected for the compression of solids. The difference between corrected and uncorrected curves is moderate in the case of Avicel. Nevertheless all data were corrected for this effect.

4.3. Effects of determination of powder height during compression

The determination of the relevant densification presumes the knowledge of the powder height and the inner diameter

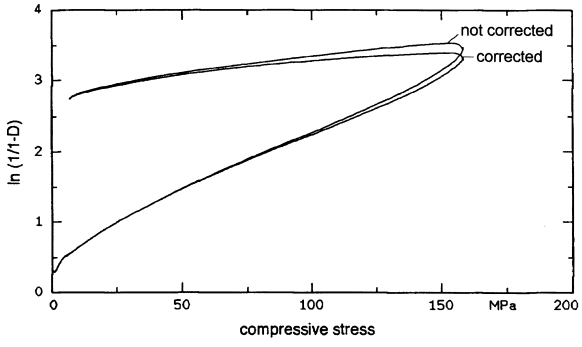

Fig. 6. Influence of errors in the porosity calculated from tablet dimensions and true density caused by the compression of solids upon Heckel plots. Avicel, 3% porosity.

of the die. The inner diameter of the die was determined to be 9.01 mm with ±5 μm accuracy using a dial indicator for inside diameters (Mauser, Oberndorf, Germany). The deviation from the exact cylindrical shape was less than 5 μm (not detectable). The powder height was registered using the instrumentation method published previously [3].

As described above, the stability of the Heckel plots against inaccurate readings of raw data is poor. To calculate the sensitivity of the Heckel plots against inaccurate displacement readings a simulation was calculated based upon the same data set as above. In addition to the calculation of the 'true' Heckel plot two others were calculated upon adding a constant error of powder height of +20 μm and −20 μm, respectively. The results are shown in Fig. 7. A positive error in powder height results in negative deviation in the Heckel plot, the linearity is apparently better than compared to the true one. The negative error results in positive deviations of the Heckel plot and in decreased linearity. In reality a highly corrected, but conventional instrumentation shows signal distortions due to tilting of the punch holder of positive errors up to 20 μm during the compression phase, rather exact values near the compression maximum but negative errors up to −20 μm during the decompression phase [3]. If a Heckel plot would be calculated based upon these data, the resulting plot would be affected to the maximum errors possible within the specification.

4.4. Analytical solution of the error propagation

The Heckel equation in general can be analysed in terms of sensitivity against inaccurate signal sources. For that reason the Gaussian approach for propagation of errors during signal transformations was used to evaluate the accuracy of the results. The Heckel equation can be expressed as a function of the true density, the inner radius of the die, the mass of the tablet and the powder height reading

$$\ln\left(\frac{D_{\text{true}}}{D_{\text{true}} - D_{\text{apparent}}}\right) = k{\cdot}P + A \tag{6}$$

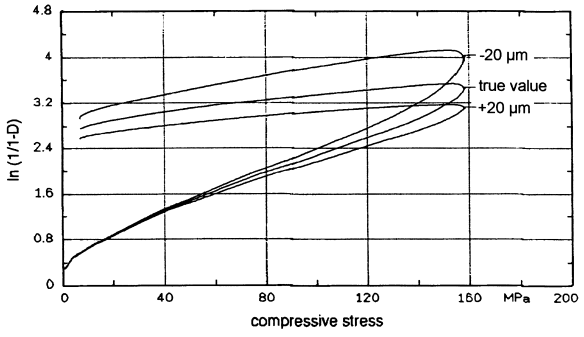

Fig. 7. Influence of errors in the porosity calculated from tablet dimensions and true density caused by errors in powder height detection upon Heckel plots. Avicel, 3% porosity.

$$\Leftrightarrow \ln\left(\frac{D_{\text{true}}}{D_{\text{true}} - \dfrac{m}{\pi{\cdot}r^2{\cdot}h}}\right) = k{\cdot}P + A \tag{7}$$

with m the tablet mass, r the inner die radius, and h the powder height.

From these parameters the mass can be regarded as not critical, as the weighing process is usually taken on analytical balances with 0.1% accuracy. The other variables remain as values, which might be inaccurate with a finite error. The propagation of errors is then given by the total differential of the Heckel equation, which can be analytically solved

$$\Delta\text{func}(D,r,h,m) = \left|\frac{\partial\text{func}}{\partial D}\right|{\cdot}|s_D| + \left|\frac{\partial\text{func}}{\partial r}\right|{\cdot}|s_r| + \left|\frac{\partial\text{func}}{\partial h}\right|{\cdot}|s_h| + \left|\frac{\partial\text{func}}{\partial m}\right|{\cdot}|s_m| \tag{8}$$

with s_D being the variation in D, s_r being the variation in r, and so on.

Let func be the Heckel parameter which is the left-hand side of Eq. (7); the partial derivatives are given by

$$\frac{\partial\text{func}}{\partial D} = \frac{\partial\left(\ln\dfrac{D}{D - \dfrac{m}{\pi{\cdot}r^2{\cdot}h}}\right)}{\partial D} = \frac{m}{(m - D{\cdot}A{\cdot}h){\cdot}h} \tag{9a}$$

$$\frac{\partial\text{func}}{\partial r} = \frac{\partial\left(\ln\dfrac{D}{D - \dfrac{m}{\pi{\cdot}r^2{\cdot}h}}\right)}{\partial r} = \frac{2{\cdot}m}{(m - D{\cdot}A{\cdot}h){\cdot}r} \tag{9b}$$

$$\frac{\partial\text{func}}{\partial h} = \frac{\partial\left(\ln\dfrac{D}{D - \dfrac{m}{\pi{\cdot}r^2{\cdot}h}}\right)}{\partial h} = \frac{m}{(m - D{\cdot}A{\cdot}h){\cdot}h} \tag{9c}$$

$$\frac{\partial\text{func}}{\partial m} = \frac{\partial\left(\ln\dfrac{D}{D - \dfrac{m}{\pi{\cdot}r^2{\cdot}h}}\right)}{\partial m} = \frac{1}{(m - D{\cdot}A{\cdot}h)} \tag{9d}$$

with A = cross-sectional area of the tablet.

The total error of the Heckel parameter is then

$$\text{er}(\text{d}D,\text{d}r,\text{d}h,\text{d}m) = \left|\frac{m}{m - D{\cdot}A{\cdot}h}\right|{\cdot}\left(\left|\frac{\text{d}D}{h}\right| + \left|\frac{2{\cdot}\text{d}r}{r}\right| + \left|\frac{\text{d}h}{h}\right| + \left|\frac{\text{d}m}{m}\right|\right) \tag{10}$$

Let D be $m/(A{\cdot}h')$, with h' = height at 0 porosity, then

$$m - D{\cdot}A{\cdot}h = m{\cdot}\left(1 - \frac{h}{h'}\right) \tag{11}$$

and thus

$$\frac{m}{m - D{\cdot}A{\cdot}h} = \frac{1}{1 - \frac{h}{h'}} \tag{12}$$

h/h' is a linear densification ratio and may be called f. f is always $\geqq 1$. Then follows

$$\mathrm{er}\left(\frac{\mathrm{d}D}{D}, \frac{\mathrm{d}r}{r}, \frac{\mathrm{d}h}{h}, \frac{\mathrm{d}m}{m}\right) = \left|\frac{1}{1-f}\right| \cdot \left(\left|\frac{\mathrm{d}D}{D}\right| + \left|\frac{2{\cdot}\mathrm{d}R}{r}\right| + \left|\frac{\mathrm{d}h}{h}\right| + \left|\frac{\mathrm{d}m}{m}\right|\right) \tag{13}$$

The relative error can be expressed as

$$\mathrm{rel\_er} = \frac{\mathrm{er}\left(\frac{\mathrm{d}D}{D}, \frac{\mathrm{d}r}{r}, \frac{\mathrm{d}h}{h}, \frac{\mathrm{d}m}{m}\right)}{\ln\left(\frac{D}{D - \frac{m}{A{\cdot}h}}\right)} = \frac{\mathrm{er}\left(\frac{\mathrm{d}D}{D}, \frac{\mathrm{d}r}{r}, \frac{\mathrm{d}h}{h}, \frac{\mathrm{d}m}{m}\right)}{\ln\left(\frac{1}{1 - \frac{1}{f}}\right)}$$

$$= \frac{\frac{\mathrm{d}D}{D} + \frac{2{\cdot}\mathrm{d}r}{r} + \frac{\mathrm{d}h}{h} + \frac{\mathrm{d}m}{m}}{|1-f| \cdot \ln\left(\frac{1}{1 - \frac{1}{f}}\right)} \tag{14}$$

and with $f - 1 = \mathrm{void}$, void being the voidage, expressed as per cent of the true volume, it follows that

$$\mathrm{rel\_er} = \frac{\frac{\mathrm{d}D}{D} + \frac{2{\cdot}\mathrm{d}r}{r} + \frac{\mathrm{d}h}{h} + \frac{\mathrm{d}m}{m}}{\mathrm{void}{\cdot}\ln\left(\frac{\mathrm{void} + 1}{\mathrm{void}}\right)} \tag{15}$$

Using Eq. (15) the relative errors of the Heckel parameter can be calculated with regard to deviations in the true density D, the radius r, the mass m and the powder height h. The values of D, r and m are constant when compressing one tablet. The height h, however is time-dependent and thus the error $\mathrm{d}h$ is not constant during the compression. To calculate the error, suppose the error of the displacement $\mathrm{d}h$ can be described as caused by an uncertainty in the slope x and in an offset y. x shall be defined as per cent of the range and y as per cent of the value thus giving the relative error in h

$$\frac{\mathrm{d}h}{h} = \frac{x}{100} \cdot \frac{\mathrm{Range}}{h} + \frac{y}{100} \tag{16}$$

Eqs. (15) and (16) and the definition of the voidage as $\mathrm{void} = f - 1 = h/h' - 1$ allow the calculation of the relative error of the Heckel parameter as function of voidage and h' according to

$$\mathrm{rel\_er}(\mathrm{void}, h') = \frac{1}{\mathrm{void}{\cdot}\ln\frac{\mathrm{void} + 1}{\mathrm{void}}} \cdot \left(\frac{x}{100} \cdot \frac{\mathrm{Range}}{(\mathrm{void} + 1){\cdot}h'} + \frac{y}{100}\right) \tag{17}$$

The relative error as being relevant for the compression event can be visualised as surface plots (Figs. 8–10). In Fig. 8 the errors of the Heckel parameter are shown using different final powder heights and different voidages, as the voidages change during compression. Fig. 8 (lower surface) is calculated for a displacement transducer of 0.5% error of the slope and 0.3% offset error, Fig. 8 (upper surface) for 1% error of the slope and 0.9% offset error, respectively. The errors chosen for calculation are the specifications of commercially available linear inductive displacement transducers (type WET, HBM). It is obvious that the Heckel parameter is extremely sensitive to errors in powder height at lower porosities and as the surface does not show linear portions, the error does increase non-linearly upon decreasing voidage thus resulting in a loss of linearity of the Heckel plots at high load levels. The same kind of graphs can be calculated for the inner diameter of the die and the true density, which is shown in Figs. 9 and 10. The calculation of the relative error as function of $\mathrm{d}m/m$ shows a reduced order of magnitude as does $\mathrm{rel\_er}(\mathrm{d}D/D)$ (see Eq. (15)).

As a conclusion it can be stated that for the calculation of Heckel plots, high demands for accurate methods of determination of true densities and very high demands for accurate powder height should be made. The powder height instrumentation has to be independent from tilting effects and has to be specified to a precision of 10 μm or better under all conditions. The determination of true density should be more accurate than 0.01 g/cm^3, and the modulus of compression of solids should be considered.

As can be seen in Figs. 7 and 8, the sensitivity of the Heckel parameter to inaccurate powder height is not constant but increases non-linear with the densification. Most of the measuring devices, e.g. amplifiers, add a certain

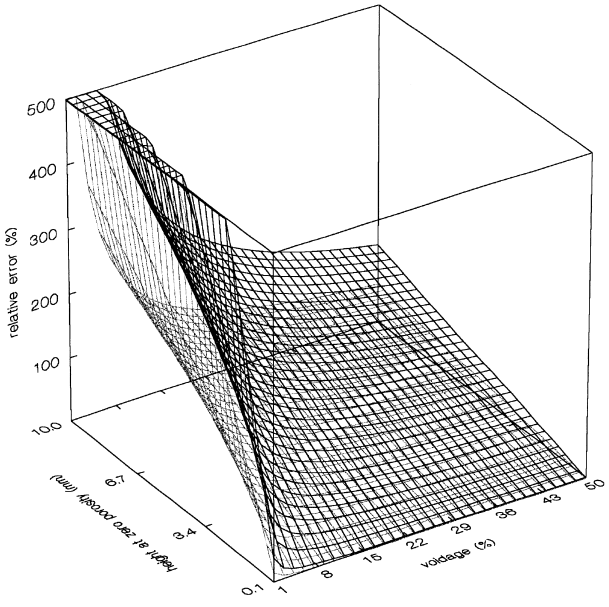

Fig. 8. Calculation of errors in Heckel plots by Gaussian error propagation: Influence of errors in powder height detection. See text for details.

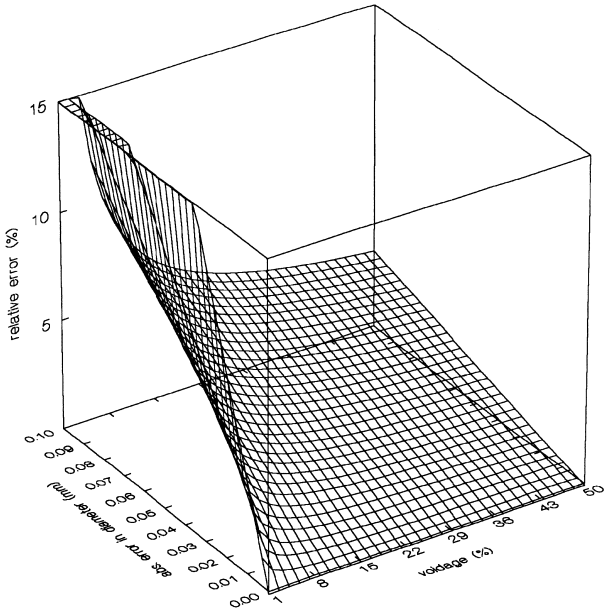

Fig. 9. Calculation of errors in Heckel plots by Gaussian error propagation: Influence of errors in determination of the inner diameter of the die.

kind of noise to the signals. Even if the noise of the powder height signal has a constant amplitude, which would be the less critical case, the Heckel plots would show an increasing noise level with increasing densification. The detection of linearity of a Heckel plot becomes more difficult under these circumstances. A solution to these problems might be a smoothing algorithm by use of polynomials, which are fitted to the data. Mueller and Emschermann [24] demonstrated the goodness of fit of force and displacement vs. time data as assessed by eye and used the coefficients of the polynomials

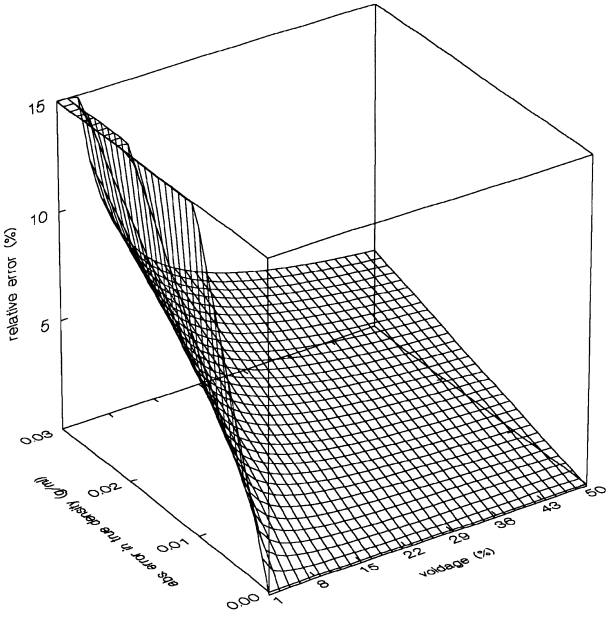

Fig. 10. Calculation of errors in Heckel plots by Gaussian error propagation: Influence of errors in determination of the true density.

as a space-saving method of storage of compression data. The goodness of fit of Heckel plots is a critical parameter and depends on several details. (a) What kind of fit algorithm is used? (b) Values of which compression phase are used? (c) What kind of values? (d) As function of which values are to be fitted and (e) by which-order polynomials?

Regarding (a), the most robust method is the least-squares method which is analytically solved and results straight forward in the polynomials with the lowest sum of squares.

For (b), the phase of compression used for fitting is of importance: the smaller the time window, the smaller the curvature of data within that time window and thus the smaller the sum of squares. That would mean dividing the compression event into several small time windows, and running the fit routines there would give the best possible fitting results. A problem that arises from this strategy is the introduction of seams. A possible solution for this problem is the use of a Bezier algorithm, which guarantees the identity of both the slopes at each seam but results in addition of turning points, as is described with the higher order polynomials. As a convenient method the compression event was divided into two parts: the first one begins at the first force level detectable and lasts up to the force maximum as detected according to Krumme [4]. The second phase lasted from the force maximum up to the beginning of the play in the ball and socket joint.

With regard to (c), although it is impossible from the theoretical point of view, the goodness of fit does depend on the choice of digits or floating point numbers, scaled to provide correct mechanical values. This effect might be due to problems of rounding of numbers inside the algorithms. We used the floating point numbers scaled in millimetres in order to achieve independence of the experimental and computational set-up.

For (d), transformation of the signals by introduction of a constant offset x' in x according to the equation $f_1(x) = f(x + x')$ has been shown to result in smaller sums of squares for certain values x'. The resulting polynomials have to be retransformed after fitting.

Finally as regards (e), the higher the degree of polynomials, the lower the sum of squares, as the polynomials get more degrees of freedom with each added order. But due to increased degrees of freedom certain additional characteristics such as inflection points and local turning points might be introduced, that might affect the performance of later on applied analysis algorithms. Third-order polynomials were found to be sufficient in flexibility to fit the data and to show roughly the same curvature as the original data. As the data are internally stored as integers with 12-bit resolution (1 in 4096 or 0.024%; higher resolution would overestimate the accuracy of the raw data), it is more important to ensure that not a single fitted value shows more than 1 bit deviation than the sum of squares to be very low. Under certain conditions it was observed that the goodness of fit as indicated by the sum of squares is very good, but some values show considerable differences to the raw data. In order to result in the

low sum of squares most of the other values are then very close to the raw data, but upon the representation as integers with a certain resolution, differences smaller than half the resolution cannot be resolved. For that reason the results of the non-linear distortions correction have to be controlled manually.

Fitting of polynomials is a linear regression method. This means that all data points are weighed equally. A non-linear transformation of signals must not be calculated with the fitted data, because due to non-linear distortions the shape of the curves might change significantly. For that reason, if a non-linear data transformation is to be applied, the data have to be transformed first, the fit has then to be calculated and the fit will smooth the transformed data. The retransformation is then not allowed for the same reason as mentioned above. The side effect of this procedure is the non-linear weighing of the noisy data near the compression maximum, which will result in a better representation of the curvature of the fitted function than the fitted raw data would do. Fig. 11 shows a Heckel plot of Avicel, as it is calculated directly from the raw data and after polynomial smoothing as described above, respectively. The goodness of fit, as assessed by eye, seems to be sufficient.

4.5. Dependency on the degree of densification

In order to evaluate the dependency on the degree of densification, compression experiments were undertaken with constant machine settings and various amounts of powders. Several examples of compressions of Avicel to minimum porosities of about 3% and 7% are shown in Fig. 12. The actual differences in force maxima are due to unavoidable variations in tablet mass. During the compression phases the Heckel plots show only very small differences. The character of the curvature is constant. The small differences are due to different punch velocities at the same compression force levels, even if the machine settings were constant. This effect is due to the elimination of the time axis by a two-dimensional point of view. This can be proven by the cube in Fig. 13. In the cube the Heckel parameter is shown as a function of the punch velocity and of the upper compressive stress. The facets show the projections of the

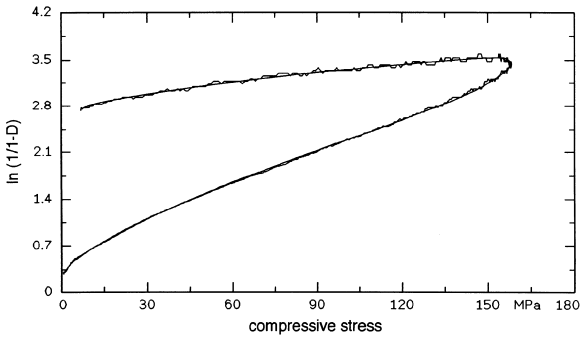

Fig. 11. Distortion of Heckel plots by polynomial smoothing. Avicel, 3% porosity.

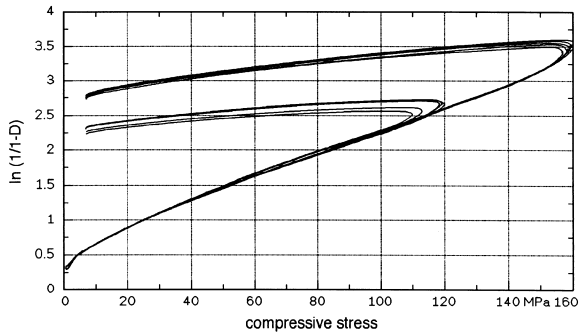

Fig. 12. Heckel plots of Avicel when compressed to 3% and 7% porosity.

three-dimensional curve onto themselves. It is obvious that the punch velocity changes during the compression phase; during the decompression phase the constancy is better. The velocity increases roughly linearly with time and the acceleration is approximately constant. During the decompression phase as a result of fast elastic recovery of the tablet, the velocity curve is disturbed and shows an approximately constant value. If the amount of powders increases, the stress curve will change and the velocity curve will be roughly the same, unless the machine is not driven under overload conditions. This means if the compressive properties are time-dependent, they will affect the stress signal more the larger the relative changes in velocity are. Upon decreasing the absolute value of the punch velocity the relative changes will increase, and the effects on the compression event will increase too. For that reason during the beginning of the compression curve the time-dependent properties do not affect the stress curves very much, but near the compression maximum, as the punch velocity

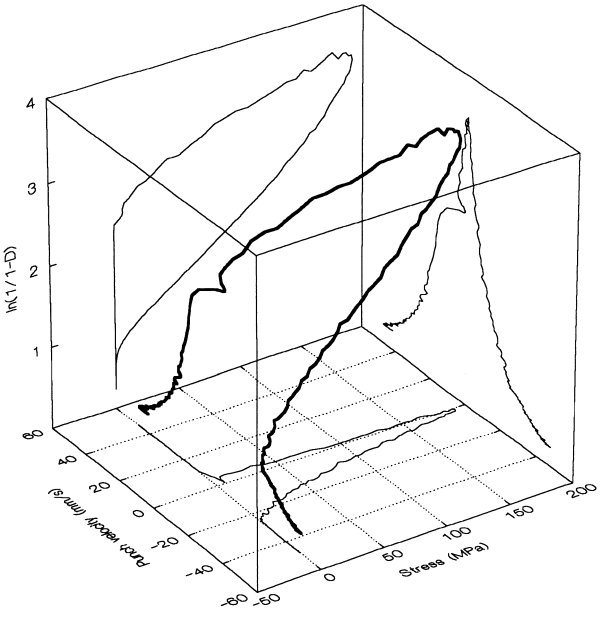

Fig. 13. Compression cube compressive stress–punch velocity–Heckel parameter, Avicel, 3% porosity, no polynomial smoothing.

shows large relative changes, the effects increase. In terms of Heckel plots this could mean that the non-linearity at low force levels, as can be seen below, can be related to an absolute material property. The non-linearity of the upper parts of the Heckel plots, however, are at least affected by time-dependent effects. If no deviation from linearity during high load compression can be registered, the substance does not show time-dependency within the covered velocity range.

Nevertheless, the differences are very small and the compression phase seems not to be very dependent on the maximum degree of densification. It can be concluded from the experiment that the compression to higher degrees of densification includes the information obtainable from those to lower degrees of densification. The slope of the decompression phase, however, indicates according to Paronen [25] the fast elastic recovery, and it may be used for parameterisation. The numerical value of those slopes of the decompression phase have been calculated by the same algorithm, as described for the compression phase, but the numerical stability was found to be extremely poor. This is due to the fact that the elastic recovery as indicated by the raw data was mostly found to be within ten times the resolution [4] and thus the parameterisation of the slope after non-linear transformation would result in poor stability of the value.

4.6. Examples of Heckel plots

Finally it will be shown what the highly corrected Heckel plots look like for some very common and well-known substances as a kind of reference. We have chosen three common classes of main deformation mechanisms although reduction of complex product properties to three classes is somewhat critical. We do not want to make new findings related to the substances but to 'calibrate' the new tool against well-known effects and demonstrate how these effects can be seen using these very precise Heckel plots.

4.6.1. Plastic deforming materials

Alkali halogenides mostly show plastic deformation behaviour (e.g. sodium chloride [26,27]). In Fig. 14 the Heckel plots of compressions of two sieve fractions of sodium chloride, 63–71 μm and 315–500 μm, respectively, are shown. During compression an extensive linearity is obvious, indicating a plastic deformation mechanism [25,27]. The yield pressure decreases with increasing particle size, which may be related to a hindered plastic gliding at slip planes, as a result of the increasing number of contact points of smaller particles. The elastic recovery is not very extensive.

Avicel [28–30] and sorbitol [31] are also mainly plastic-deforming materials. The Heckel plots (Fig. 15) of both substances show good linearity during compression. Upon compression of sorbitol a slight non-linear section below 20 MPa has to be considered, indicating some fragmentation

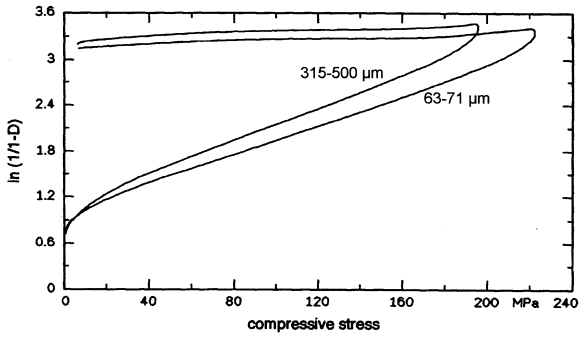

Fig. 14. Heckel plots of sodium chloride, two different sieve fractions, 3% porosity.

within that phase. Sorbitol shows very low elastic recovery and extensive force relaxation, which implicates a time dependency, as discussed above. The curvature due to relaxation is only a slight one; the effects of erroneous determination of Heckel plots can easily supersede the effect of the substance, as in the high densification phase.

4.6.2. Viscoelastic materials

Paronen and Juslin [32] showed by means of scanning electron microscopy the deformation mechanisms of starches to be perfectly within the particles. The particles do change their shapes but each of them remains as the same individual particle.

These materials seem to be ideal models for deformation free of any fragmentation. The Heckel plots of both starch derivatives (Fig. 16) show almost perfect linearity in their lower pressure sections but a certain amount of relaxation which is indicated by increasing steepness near the maximum force. Again the curvature in the high densification phase is low, but can be detected if the effects due to misleading data generation can be excluded by design of the experiments.

4.6.3. Fragmenting materials

Different Heckel plots can be found with lactose and Emcompress (Fig. 17). Below 80 MPa both materials show significant deviations from linearity. In that phase the yield pressure increases and the primary particle size is reduced.

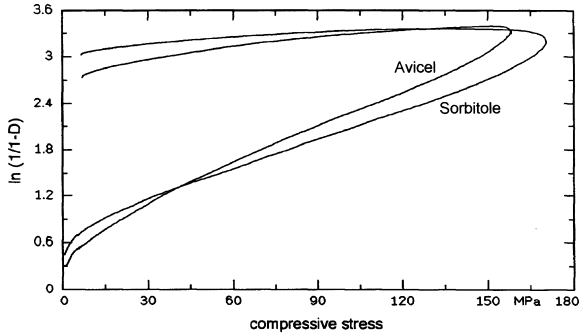

Fig. 15. Heckel plots of Avicel and sorbitol, 3% porosity.

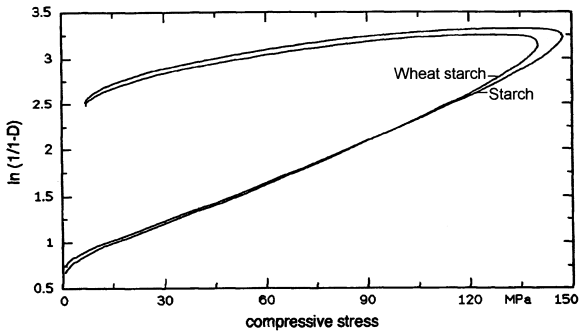

Fig. 16. Heckel plots of wheat starch and Starch 1500, 3% porosity.

Further reduction of the particle size requires an increasing amount of energy which in turn results in an increasing yield pressure. Upon reaching a critical particle size the energy required to further reduce the particle size increases dramatically [33]. The densification mechanism changes upon passing that point and a plastic behaviour supersedes. This can be seen in the perfect linearity beyond 80 MPa.

The slope of the elastic recovery is very low, thus indicating a low elastic recovery. The phases of maximum compression are very linear, indicating very low viscoelastic behaviour. This finding is the proof for the statement that linear Heckel plots do exist up to the highest compressive stresses. Therefore a plastic behaviour of these usually called 'brittle' substances beyond a certain densification can be assessed using these Heckel plots.

The linearity of the Heckel plots in the high load area indicates a very low strain-rate sensitivity as the relative change of punch velocity during that time is high, as discussed above. This confirms the results of Roberts and Rowe [8], who found no dependency of the compressive properties of calcium phosphate on the punch velocity when compacted with a compression simulator. The strain-rate sensitivity can be seen within a single stroke of an eccentric press.

4.7. Conclusions

Summing up, several statements can be made for the application of the highly corrected Heckel plots:

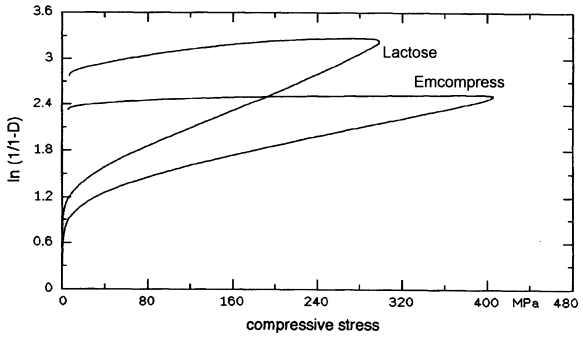

Fig. 17. Heckel plots of lactose (3% porosity) and calcium-phosphate (7% porosity).

- linearity can be associated with plasticity as the main densification mechanism;
- an increase of yield pressure as indicated by a decreasing steepness can be associated to fragmentation, which has been observed only in the lower compression phase;
- a decreasing yield pressure in the upper compression phase shows relaxation effects and gives a hint towards strain-rate sensitivity;
- the elasticity can be assessed semiquantitatively; however, there are more robust parameters available, e.g. the fast elastic recovery.

These highly corrected Heckel plots allow the characterisation of the main compression characteristics of new entities using only a couple of compressions, which is a valuable tool in early phases of development. They require, however, careful consideration concerning the tablet machine instrumentation, especially of the displacement and of the density used to calculate the relative densification as required by Heckel. The specifications are the more critical, the higher the densification of the powder is.

As a rule of thumb following specifications should be met:

- accuracy of height of powder bed under all circumstances better than 10 μm (±5 μm);
- determination of the diameter of the die should be better than ±5 μm;
- true density should be measured using a very high-pressure experiment and be better than 0.01 g/ml;
- correction for compression of solids is recommended, but is less critical.

Acknowledgements

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