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Determination of the solid ("true") density of pharmaceutical powders and the impact on tablet compression characterization

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1. Introduction

To characterize and develop a tableting process the compressibility (porosity vs compression stress), tabletability (tensile strength vs compression stress) and compactibility (tensile strength vs porosity) are commonly investigated as described e.g. in USP<1062> [1]. In addition to these so called out of die characteristics the in-die process can be analyzed using an instrumented tablet press with high resolution force – distance measuring systems. With this approach specific energy values, elastic recovery and in-die compressibility data are obtained [11]. Very common is the analysis of the porosity decrease with increasing compression stress in terms of the well-known Heckel plot assuming a constant solid density. Analyzing the in-die compressibility of materials with low bulk modulus, apparent porosity values below zero were frequently observed at elevated compression stress but are rarely described and discussed in the literature. These observations can be handled in pragmatic ways as neglecting high compression stress data, "adjusting" the volume of the compact or assuming errors of the "true" density values used.

The elastic compressibility of the solids is a prerequisite for the elasticity of the tablets, which in turn is also a major hurdle for the formulation development as capping and lamination are induced by elastic recovery after compression. Thus, the wide spread assumption of a constant solid density may have some limitations regarding the tablet compression process. To explore variations of the solid density of materials, XRPD analysis and mercury porosimetry were applied to investigate the thermal expansion coefficient and the elastic bulk modulus of Paracetamol API powder and other organic materials related to pharmaceutical powders used for tableting.

Furthermore, tableting experiments with Paracetamol API powder were performed and out of die and in-die characteristics were obtained using the aforementioned solid density values. Considering the elastic compressibility of the solid, the in-die compressibility data of Paracetamol API powder were described with a simple function with two exponential terms. The data fit yielded reasonable non-negative porosity values over the whole compression stress range up to 400 MPa. The experimental precision and accuracy of gas-pycnometry, XRPD and mercury-porosimetry for the determination of the solid density and the elastic bulk modulus are discussed in detail.

2. Out of die tablet compression characterization

Tableting experiments were performed using Medelpharm StylCam compaction simulator equipped with an external high-resolution force – distance measuring system DAQ4 provided by Technical Services Consult R. Lammens / M. Hucke (2013). With this equipment, the tableting behavior during the in-die compression phase was analyzed in addition to the out of die characteristics. Tablets of neat Paracetamol API powder were compressed and the obtained out of die data are summarized in table 1.

Property	**Unit**	AVR	STD	AVR	STD	AVR	STD	AVR	STD	AVR	STD
Stress max.	[MPa]	51	3	108	4	201	10	302	2	390	5
Tablet Porosity	[%]	15,5	0,4	12,2	0,3	11,7	0,4	9,6	0,5	13,8	0,6
Tensile Strength	[MPa]	0,17	0,02	0,37	0,02	0,33*	0,03	0,16*	0,03	0,13**	0,03**

* fissures detected; ** n = 3 only due to flaws.

Table 1. Out of die characteristics of round, flat tablets of Paracetamol API powder with a particle size of x_{50} = 206 µm. Maximal compression stress levels of 50 MPa, 100 MPa, 200 MPa, 300 MPa and 400 MPa were applied and at each level n = 6 tablets were evaluated. The table lists average and corresponding standard deviation values.

A pivotal value for tableting characteristics is the achieved porosity ε of the tablets given by

$$\varepsilon = \frac{V_{pores}}{(V_{solid} + V_{pores})} \qquad (1)$$

With the specific volume of the pores V_{pores} and the specific volume of the solid V_{solid}. The latter being the inverse of the solid density ρ_{solid}.

$$\rho_{solid} = \frac{1}{V_{solid}} \qquad (2)$$

The density or specific volume of the solid can be measured by gas-pycnometry or crytstallography as described in [2].

3. Pycnometric and crystal density of organic solids

The solid density of the Paracetamol API and four other organic crystalline powders were determined by He gas pycnometry (Quantachrome Ultrapyc 1200e) at 25°C and by XRPD (Bruker D8 Advance) crystal structure determination at room temperature.

Material	Pyc-Density [g/cm^3]	$\delta\rho_{\_0.95}$ [g/cm^3]	Cryst-Density [g/cm^3]	$\delta\rho_{\_0.95}$ [g/cm^3]	$\Delta\rho$ [g/cm^3]	$\Delta\rho_{\_rel}$ [%]	"True" Density [g/cm^3]
Paracetamol_200µm	1,2863	0,0001	1,2936	0,0031	0,007	0,6	1,290
Adamantane*	1,0621	0,0001	1,0752	0,0048	0,013	1,2	1,069
Benzoic Acid	1,3151	0,0023	1,3161	0,0022	0,001	0,1	1,316
Benzophenone	1,1996	0,0001	1,2096	0,0058	0,010	0,8	1,205
Pyrene	1,2666	0,0006	1,2703	0,0004	0,004	0,3	1,268
	Average	0,0006	na	0,0032	0,007	0,6	na

Table 2. Pycnometric and XRPD solid density values of Paracetamol API, Adamantane, Benzoic acid, Bezophenone and Pyrene powders. For XRPD analysis, 3 samples of each compound were prepared and measured at room temperature. For pycnometric measurements, the samples were degassed in vacuum (< 0.1 hPa, RT) for at least 0.5d, except Adamantane. From each powder material 3 to 6 samples were prepared, each measured n = 10 times.

Table 2 lists the average values and the corresponding 95% confidence interval $\delta\rho_{\_0.95}$ for each compound obtained with both methods. The pycnometric density of Paracetamol was ρ_solid = 1.286 g/cm^3 with a very good repeatability of $\delta\rho_{\_0.95}$ = 0.0001 g/cm^3. The overall repeatability of the He-pycnometry data obtained for the five organic compounds was 0.0006 g/cm^3, indicating the high precision of the method.

The crystal structure of organic materials is typically determined at liquid nitrogen temperature. Here the crystal unit cell volume was re-calculated using the room temperature XRPD data and the known crystal structure. The obtained Paracetamol solid density was ρ_solid = 1.294 g/cm^3. The repeatability of this approach was also very good with an overall 95% confidence interval of 0.003 g/cm^3.

The obtained solid density values of both methods were in close agreement, however the XRPD results were slightly higher in all cases. On average the XRPD data were 0.007 g/cm^3 higher than the pycnometric values, which is above the repeatability band of both methods. The crystal density is often called the "true" density of the materials [2]. Crystal structure analysis is restricted to ordered, symmetric, crystalline domains whereas with He-pycnometry the specific volume of the bulk material is measured, including all crystal defects or amorphous regions. This may contribute to the observed small difference between the two methods. Nevertheless, the close agreement of the data indicating a high accuracy for both methods. For most purposes the values of either method may be used. For further data evaluation, the average of both methods is regarded as "true" density and the relative deviation between the data sets of $\Delta\rho_{\_rel}$ = 0.6% is considered as accuracy level. Thus, for Paracetamol we obtained ρ_solid = 1.290 ± 0.004 g/cm^3. It should be noted that such a close agreement between the methods cannot always be obtained, especially if the crystal structure contains void volume or volatile molecules.

As mentioned above the crystal structure can be determined at different temperatures. In figure 1 the specific volume measured by XRPD at room temperature are plotted together with literature values, dependent on the temperature of the measurements.

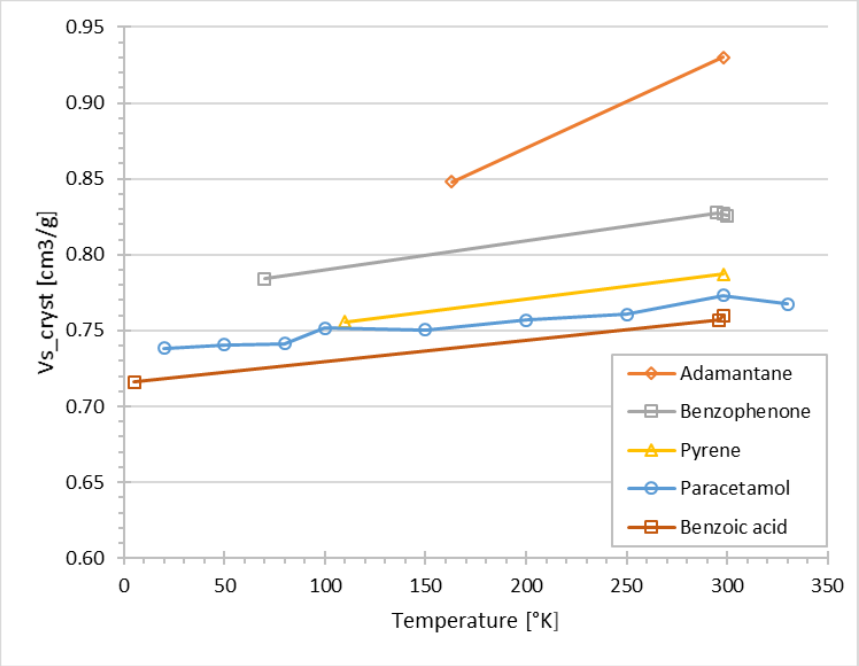

Figure 1. Thermal expansion of specific solid volume of Paracetamol API, Adamantane, Benzoic acid, Bezophenone and Pyrene measured by X-ray and neutron scattering methods [3, 4, 5, 6, 7, 8].

Assuming a linear relation between temperature T and specific volume, the thermal expansion coefficient α was calculated according to

$$V_{solid}(T - T_0) = V_0 (1 + 3\alpha \Delta T) \qquad (3)$$

with V_0 denoting the specific volume at T_0. For Paracetamol the lowest value $\alpha = 4.6\ 10^{-5}\ K^{-1}$ was obtained, slightly higher values for Benzoic acid, Pyrene and Benzophenone $6.4\ 10^{-5}\ K^{-1} < \alpha < 7.5\ 10^{-5}\ K^{-1}$ and a 3-fold higher value $\alpha = 22\ 10^{-5}\ K^{-1}$for Adamantane. Excluding the latter, a typical value for API powders of $\alpha = 5\ 10^{-5}\ K^{-1}$ could be used to assess temperature effects. For comparison the thermal expansion coefficient of steel and concrete is about 5-times lower.

Assuming a relative specific volume uncertainty of 0.6% is acceptable, the corresponding temperature working range would be $\Delta T = 40°K$ based on the thermal expansion coefficient $\alpha = 5\ 10^{-5}\ K^{-1}$. Typical pharmaceutical tableting conditions are well within this temperature range. If higher temperature variations occur, the corresponding change of the specific volume could be considered as shown above.

4. The bulk modulus of organic solids

Crystal structure determination was also widely used to investigate the impact of pressure on the specific volume of solids. For Paracetamol data up to 5 GPa were reported in [9]. From these data a decrease of the specific volume of about 3% can be estimated if the pressure increases from ambient conditions to 400 MPa. Like the thermal expansion effect such small changes can be described by a linear pressure relation using the elastic bulk modulus K of the materials.

$$V_{solid}\,(p - p_0) = V_0\,(1 - \Delta p / K) \qquad (4)$$

with V_0 denoting the specific volume at p_0.

Here Hg-porosimetry (Quantachrome Poremaster 60 GT) was applied to evaluate the bulk modulus of different organic materials.

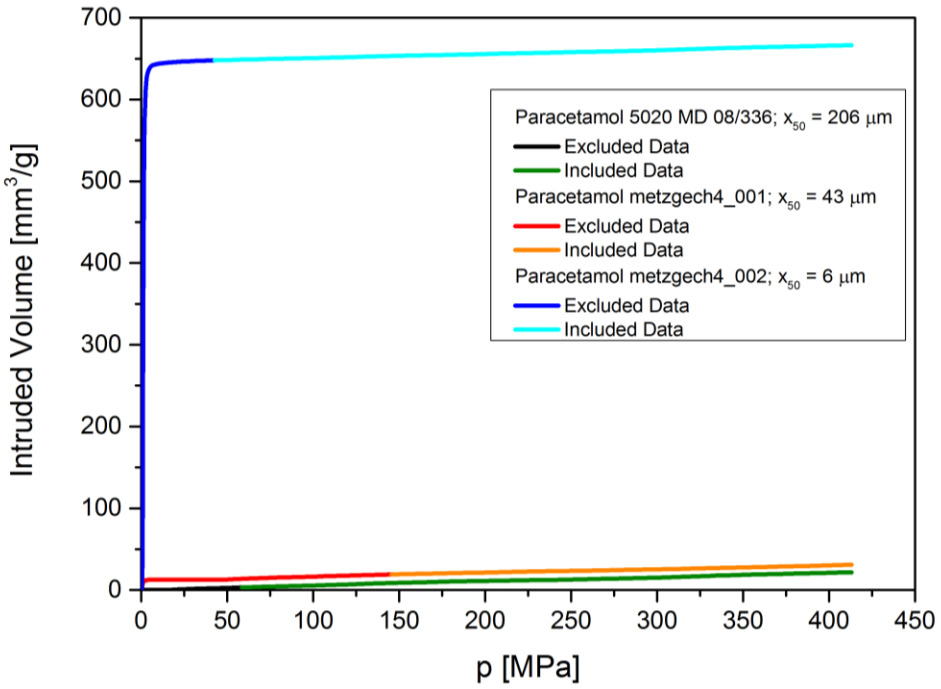

Figure 2. Hg-porosimetry intrusion data of three different milling grades of Paracetamol API powders with particle size x_{50} values, from top to bottom, of 6 µm, 43 µm and 206 µm. The intruded volumes at 20 MPa indicate the inter particle pore volumes of the three milling grades. The linear range used for data evaluation is indicated by slightly different colors within each line. The data shown are from representative single experiments for each milling grade.

In figure 2 intrusion data of three different milling grades of Paracetamol API powder are plotted. For each milling grade 4 - 5 samples (replicates) were prepared and measured several times (repetitions) until reversible intrusion – extrusion cycles were established. The linear intrusion pressure range was typically from 100 MPa to 400 MPa. Within this pressure range absolute Hg volume changes of 3 mm^3 to 12 mm^3 were detected. The linear intrusion pressure range was evaluated according to eq.(4). The individual bulk modulus values of the three milling grades are summarized in figure 3 in terms of box plots, average values and corresponding 95% confidence intervals.

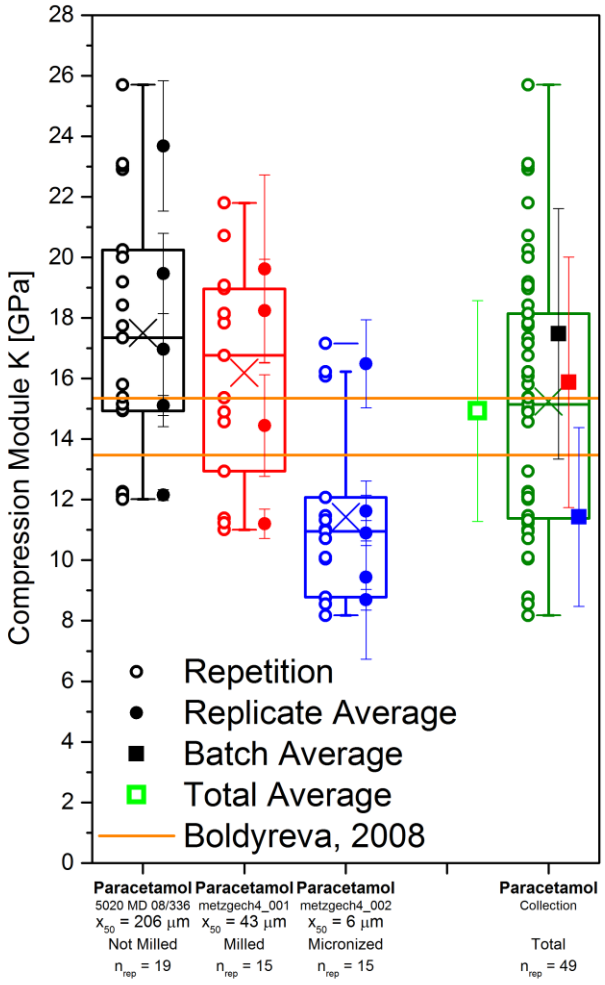

Figure 3. Box plots and average values with 95% convidence interval of bulk modulus values K of Paracetamol API powders obtained with Hg-porosimetry. Milling grades with x_{50} = 206 µm (black), x_{50} = 43 µm (red) and x_{50} = 6 µm (blue) were analyzed. The green data represent the data collection over all milling grades. In total n = 49 measurements were evaluated. For comparison the estimated bulk modulus range from [9] is indicated with orange horizontal lines.

The applied method worked well but bulk modulus values in a broad range from 8 GP to 26 GPa were obtained. Due to this limited repeatability a high number of individual measurements were performed in order to achieve a suitable confidence interval. For Paracetamol API powders a bulk modulus of $K_{average}$ = 15 GPa was obtained with an estimated error range of ± 5 GPa.

Further organic materials were investigated with porosimetry and the obtained K values are summarized in figure 4.

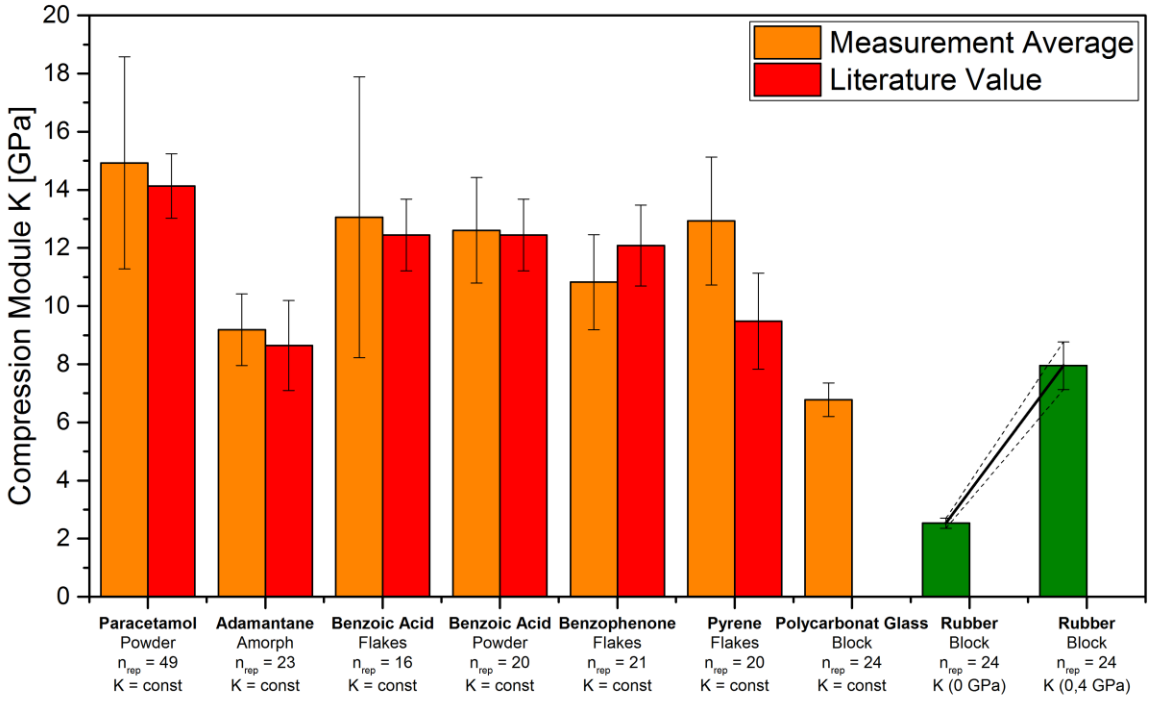

Figure 4. Bulk moduli measured by Hg-porosimetry and comparison with literature values [9] [10] of different organic materials. For the porosimetry data average values with 95% confidence interval are given. For the rubber block the volume – pressure relation was nonlinear. The linear approach yielded K = 2 GPa at low pressure and K = 8 GPa at high pressure. Such materials are better described by the Birch Murnaghan equation [10].

The obtained values and comparison with literature show that the method can be applied for a broad range of different materials with an estimated upper detection limit of K < 40 GPa.

5. In-die tablet compression characterization

For the in-die tablet compression characterization the force distance data measured during the compression-, de-compression- and ejection phase can be evaluated in many ways. Very common is the evaluation of compaction energy, quick elastic recovery and compressibility [11] as described below. Integrating the compression phase and de-compression phase yields the total

compression energy E_{tot} and the elastic recovery energy E_{elast}. The specific compaction energy of the tablet is then calculated according to

$$E_{Tab} = (E_{tot} - E_{elast}) / (m_{Tab}\, V_{solid}) \qquad (5)$$

with m_{Tab} denoting the mass of the final tablet. Furthermore, the quick elastic recovery ER´ of the tablet volume during the de-compression phase can be evaluated using

$$V_{Tab}(\sigma=0) = (1 + ER') V_{min} \qquad (6)$$

where V_{min} and $V_{Tab}(\sigma=0)$ denote the minimal volume during compression and the volume after de-compression at zero compression stress, respectively.

Property	**Unit**	AVR	STD	AVR	STD	AVR	STD	AVR	STD	AVR	STD
Stress max.	[MPa]	51	3	108	4	201	10	302	2	390	5
Tab. Energy	[J/cm³]	4,2	0,2	8,2	0,3	13,5	0,6	18,2	0,4	21,0	0,4
Elast. Recovery	[%]	3,9	0,2	5,5	0,2	7,8	0,5	11,0	0,6	12,0	0,6

Table 3. In-die tablet compression characteristics of round, flat tablets of Paracetamol API powder with a particle size of x_{50} = 206 µm. Maximal compression stress levels of 50 MPa, 100 MPa, 200 MPa, 300 MPa and 400 MPa were applied and at each level n = 6 tablets were evaluated. The table lists average and corresponding standard deviation values.

In table 3 these values are given for tablets made with the Paracetamol, x_{50} = 206 µm API powder. Both characteristics increased continuously with increasing maximal compression stress.

The in-die compressibility is commonly evaluated using the so called Heckel plot [12]. For this the apparent porosity is plotted versus in-die compression stress and the data set is fitted by a single exponential decay function. The apparent in-die porosity is calculated according to

$$\varepsilon_{app}(\sigma) = 1 - \frac{m_{Tab}}{volume_{Die}(\sigma)} V_0 \qquad (7)$$

$volume_{Die}$ denoting the stress dependent die volume during compression and V_0 the specific volume of the solid at ambient conditions. As describe above the solid density of Paracetamol was determined as ρ_{solid} = 1.290 ± 0.004 g/cm³ which corresponds to V_0 = 775 mm³ ± 0.3%. Analogous to eq. (4) the elastic compression of the solid can be calculated by

$$V_{solid}(\sigma) = V_0 (1 - \sigma / C_{elastic}) \qquad (8)$$

$C_{elastic}$ denoting the elastic compressibility of the solid, similar to the bulk modulus K at isotropic compression. Combining eq. (7) and eq. (8) the in-die porosity is given by

$$\varepsilon(\sigma) = 1 - \frac{m_{Tab}}{volume_{Die}(\sigma)} V_{solid}(\sigma) \qquad (9)$$

In figure 5 different porosity data are plotted for a single compression of Paracetamol, x_{50} = 206 µm API powder up to 400 MPa compression stress.

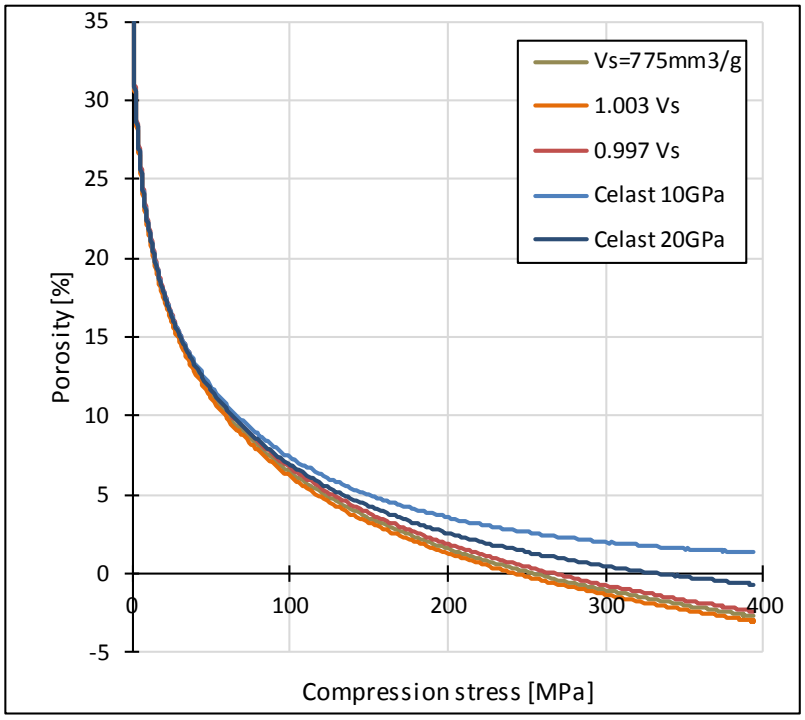

Figure 5. In-die porosity data of Paracetamol, x_{50} = 206 µm API powder during a single compression up to 395 MPa maximal compression stress. In grey the apparent porosity $\varepsilon_{app}(\sigma)$ with V_0 = 775 mm³/g. Bright and dark red curves are $\varepsilon_{app}(\sigma)$ data with V_0 = 775 mm³ ± 0.3%. Bright and dark blue curves are the $\varepsilon(\sigma)$ data according to eq. (9) with $C_{elastic}$ values of 10 GPa and 20 GPa, respectively.

The apparent porosity line $\varepsilon_{app}(\sigma)$ with V_0 = 775 mm³/g decreased with increasing compression stress. At σ > 250 MPa negative values were calculated. The impact of the relative accuracy range ΔV_{solid} = 0.6% is illustrated by the red lines. The deviations increased with increasing compression stress. At σ = 400 MPa the distance between the lines, representing the absolute deviation, was $\Delta\varepsilon_{app}$ = 0.6%, which illustrates the need for an accurate determination of the solid density. The blue lines show the in-die porosity data $\varepsilon(\sigma)$ according to eq. (9). As the elastic compressibility $C_{elastic}$ was unknown the data were calculated using the limit bulk modulus values K = 15 ± 5 GPa. The pronounced impact of $C_{elastic}$ values is illustrated in figure 5. At compression stress σ = 400 MPa the absolute deviation of the porosity data was $\Delta\varepsilon$ = 2.0% and

with $C_{elastic}$ = 10 GPa positive porosity values were calculated over the whole compression stress range.

Following the Heckel plot approach the $\varepsilon_{app}(\sigma)$ data with V_0 = 775 mm^3/g were fitted (Excel, Solver) to a single exponential decay function in the range 20 MPa < σ < 250 MPa, i.e. in the positive $\varepsilon_{app}(\sigma)$ range.

$$\varepsilon_{calc}(\sigma) = \varepsilon_{initial} e^{-\frac{\sigma}{\sigma_y}} \qquad (10)$$

yielding an initial porosity $\varepsilon_{initial}$ = 22% and a yield stress of σ_y = 79 MPa. These data are presented in figure 6 including the residuals which varied within ±0.8%.

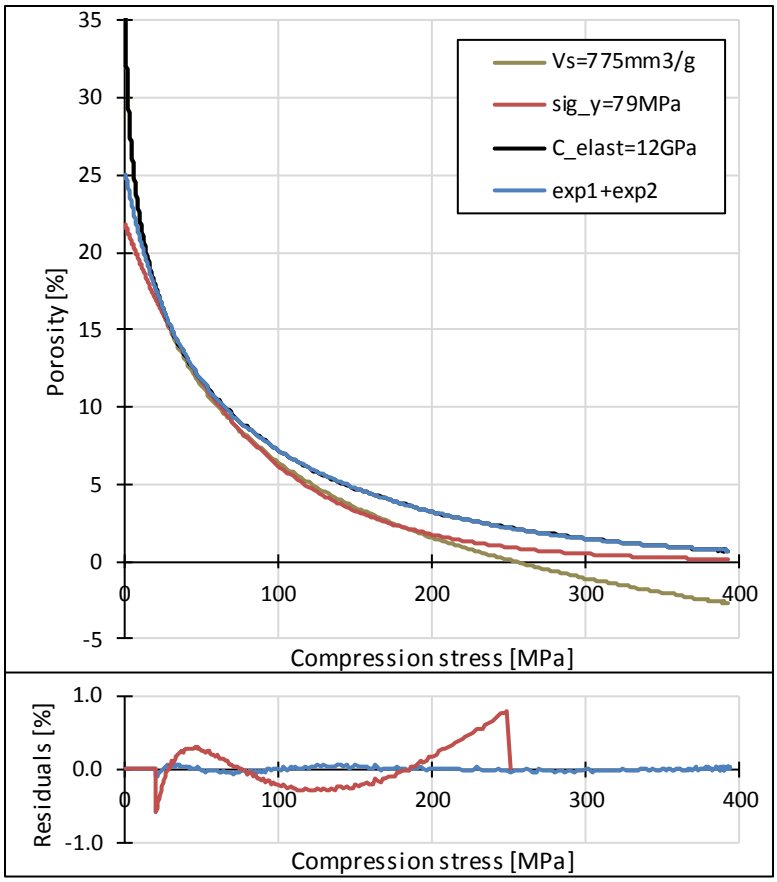

Figure 6. In-die porosity data of Paracetamol, x_{50} = 206 µm API powder during a single compression up to 395 MPa. In grey the apparent porosity $\varepsilon_{app}(\sigma)$ with V_0 = 775 mm^3/g. In red the fitted data according to eq. (10) and the corresponding residuals within the data fit range 20 MPa - 250 MPa. The black line is the porosity $\varepsilon(\sigma)$ according to eq. (9) with $C_{elastic}$ = 12 GPa. The calculated data according to eq. (11) are shown in blue. Below in blue the corresponding residuals in the data fit range 20 MPa - 395 MPa.

On the other hand, the data can also be fitted with two exponentials and $C_{elastic}$ as additional free fit parameter as described in [13]. The applied fitting equation was

$$\varepsilon_{calc}(\sigma) = \varepsilon_{low} e^{-\frac{\sigma}{\sigma_y^{low}}} + \varepsilon_{high} e^{-\frac{\sigma}{\sigma_y^{high}}} \qquad (11)$$

with two porosity (ε_{low}, ε_{high}) and two corresponding yield stress parameters (σ_{y_low}, σ_{y_high}). The data of this 5-parameter fit are also plotted in figure 6 together with the obtained residuals. As expected, smaller residuals within ±0.1% were achieved. Furthermore, the fit range was expanded to 20 MPa < σ < 400 MPa and the porosity was above zero level in the whole compression stress range. The results of n = 6 individual compression runs are summarized in table 4 below.

Sample No	$C_{elastic}$ [GPa]	$\varepsilon_{\_low}$ [%]	σ_{y_low} [MPa]	$\varepsilon_{\_high}$ [%]	σ_{y_high} [MPa]	$\varepsilon_{\_initial}$ [%]	$\sigma_{\_min}$ [MPa]	$\sigma_{\_max}$ [MPa]	**MErr** [%]
1	12.0	10.2	26.0	15.2	131	25.4	20	395	0.03
2	12.0	10.1	27.1	15.1	132	25.2	22	395	0.03
3	11.8	10.2	25.8	15.2	129	25.4	20	395	0.03
4	11.9	10.1	26.4	15.0	130	25.1	22	395	0.02
5	11.8	10.0	25.7	15.2	127	25.2	22	386	0.02
6	12.0	10.2	26.3	14.9	129	25.1	22	386	0.03
Average n=6	**11.9**	**10.1**	**26.2**	**15.1**	**130**	**25.2**	**21**	**392**	**0.03**
STD	0.1	0.1	0.5	0.1	1	0.2	--	--	--
STDrel [%]	1	1	2	1	1	1	--	--	--

Table 4. Repeatability of in-die compressibility characteristic of Paracetamol API powder with a particle size of x_{50} = 206 µm. 5 - parameter data fit was performed according eq. (9), (11). Individual results, average and relative standard deviation values of n = 6 compression runs are summarized. Furthermore, the initial porosity $\varepsilon_{\_initial} = \varepsilon_{\_low} + \varepsilon_{\_high}$, the fitting stress range $\sigma_{\_min}$ to $\sigma_{\_max}$ and the mean error MErr of the data fit are shown in the right side of the table.

The five fit parameters of n = 6 compression runs were determined with a relative standard deviation STDrel ≤ 2% indicating a good repeatability of the approach. In comparison to the mono exponential data fit, the obtained initial porosity was slightly higher $\varepsilon_{initial}$ = 25% and the two yield stress values were lower σ_{y_low} = 26 MPa and higher σ_{y_high} = 130 MPa than the value obtained with the conventional Heckel plot. The obtained elastic compressibility was $C_{elastic}$ = 12 GPa, which is within the range of the bulk modulus measured with porosimetry K =15 ± 5 GPa.

6. Conclusion

For tablet process characterization an accurate value of the specific volume of the solid is needed for the evaluation of the porosity data of out of die and in-die characteristics. A relative accuracy

of < 1% can be achieved with gas pycnometry and/or crystallography. Most desirable would be if both methods can be applied and a close agreement of the values is achieved. Significant deviations might be a hint to volatile molecules or void volume within the unit cell of the crystal. The specific volume of the solid depends on temperature and pressure. For pharmaceutical powder process technology this can be described by a linear approach with thermal expansion coefficient α and bulk modulus K. Typical values obtained for organic materials are $\alpha \approx 5\ 10^{-5}$ K^{-1} and $K \approx 10$ GPa. For specific materials of interest α and K can be measured with crystallography. However, for these measurements dedicated instrumentation is needed. Here bulk modulus measurements were performed using Hg porosimetry which is widely used in pharmaceutical technology. This approach worked well for materials with K < 40 GPa although the precision of the method should be further improved. The elastic compressibility of the solid plays a significant role above a compression stress of 100 MPa. For in-die compressibility characterization this can be described by an elastic compressibility term $C_{elastic}$ which however is not equal to the bulk modulus, since from the point of view of a particle embedded in a tableting die, the environment is neither isotropic nor homogeneous.

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