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Research paper

# Random and systematic measurement uncertainties considered in the evaluation of parameters derived from the course of the tabletting process

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**Abstract**

The uncertainty of some characteristic parameters describing the course of the tabletting process, namely the area quotient according to Emschermann and Müller, the apparent net work, the slope of the Heckel-plot, and the parameters of the modified Weibull function, was calculated according to the German norm DIN 1319-4 1999. The method allows to consider random and systematic uncertainties in a consistent way as variances of normal and rectangular probability distributions, respectively, or other suitable probability distributions based on Bayesian statistics and the principle of maximum entropy. So, random and systematic uncertainties known from a calibration and validation study of the measurement of force and displacement, and the uncertainty of the true density were included meaningfully into the uncertainty of the resulting tabletting parameters using the propagation of uncertainties according to the Gauss method. The standard uncertainty for the results calculated this way seems to be suitable for a critical evaluation of the tabletting data.


*Keywords:* Uncertainty of measurement; Compression force; Punch separation; True density, Heckel parameters; Weibull parameters; Work; Area quotient

## 1. Introduction

In a previous publication, the authors discussed the problems in the assessment of parameters describing the course of the tabletting process with respect to the uncertainty of measurement [1]. They pointed out the necessity but also the difficulty to consider both, obvious random scatter in the measurement and underlying systematic influences. As the conventional statistics offer no appropriate method to combine both types of uncertainty, they simply added confidence intervals of repeated tabletting experiments and worst case estimates of the influence of measurement uncertainty obtained from a comprehensive qualification and validation study [2,3]. However the uncertainty derived this way for the parameters was large and the authors emphasized, that this method is hardly suitable to compare results from only slightly diverging force-time or force-displacement profiles generated with the same tabletting and measuring system.

Recently, Weise and Wöger [4] showed that both types of uncertainty, random and systematic ones, can be handled in a consistent way based on Bayesian statistics complemented by the principle of maximum entropy of information (PME). Bayesian statistics is able to treat random and systematic information according to the classical probability theory. Probability in the classical sense is the numerical description of the actual level of the incomplete knowledge of the occurrence of an event. Therefore, not only the information derived from the relative frequency of the occurrence of observable events in a random process, as in the case of the conventional statistics, but every information obtained rationally can be used. To guarantee the generation of an unbiased probability distribution from the information available the PME must be applied. This means that the measure for the incompleteness of the knowledge is maximized. Thus the uncertainty obtained this way reflects the incompleteness of the knowledge about the quantity caused by the limited information available. From these methods a consistent basis is formed for the calculation of the uncertainty of measurement as given in the German norm DIN 1319-4 [5] and in the ISO guide GUM 1993 [6].

The aim of this study was to apply the principles of the German norm [5] to the analysis of the data obtained from compression experiments.

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## 2. Materials and methods

The calibration of the inductive displacement transducers and the piezo-electric force transducers mounted on an eccentric tabletting machine are described in detail in previous publications [2,3]. The tabletting experiments were also taken from a preceding study [1]. In brief, five direct compression excipients, namely Tablettose® (TA), Cellactose® (CE), Vivacel 200® (VI), Karion Instant Pharma® (KI), and Starch 1500® (ST), were tabletted to three graded maximum relative densities ($D_{rel,max}$) in five replications. Some additional experiments were performed to check for reproducibility. So, samples of 0.365 g of a narrow size fraction (100–125 μm) of Pharmatose 100M® (DMV, Veghel, the Netherlands, lot 022317) were compressed to a fixed maximum geometric mean punch force of 10 kN 13 times during 1.5 years. Each time triplicate runs were carried out which are called a 'set of tablets' in the following.

The calculation of some characteristic analytical parameters for the tabletting process was mainly adopted from [1]. The area quotient B/A is related to the pressure-time curve split into two parts at the time of maximum pressure [7]. The parameters $\beta$ and $\gamma$ were derived by fitting the modified Weibull function [8] to the pressure-time data. The parameter $\gamma$ characterizes the shape of the curve together with $\beta$ which represents the time span of pressure decay. The apparent net work ($W_{net,app}$) was calculated as the total work minus the expansion work and the work of friction [9]. The slope $K$ of the Heckel plot [10] was obtained by linear regression over a sufficiently linear region. All calculations were limited to the data within contact time, namely the time span where the pressure is equal to or higher than 1 MPa. Integration was done by the Simpsons rule. Data analysis was performed with LabVIEW (Version 5.1, National Instruments, Austin, TX, USA).

The calculation of the uncertainty for the calibration functions, for the tabletting data, and for the true density of the powders was based on the German norm DIN 1319-4 1999 [5]. An in-depth description and discussion of the methods is given by Weise and Wöger [4]. In the following, only basic rules are summarized. In general, the best estimate $x_k$ of a quantity is the expectation value of the probability distribution and the variance of the distribution should serve as the measure of uncertainty $U(x_k)$. The square root of the uncertainty is called standard uncertainty $u(x_k)$.

If a quantity is measured $m_k$-times under the same experimental conditions and the measured values $v_{kh}$ are obtained, $x_k$ is calculated as the mean by Eq. (1) and the uncertainty $u^2(x_k)$ corresponds to the variance of the mean (Eq. (2)).

$$x_k = \bar{v}_k = \frac{1}{m_k}\sum_{h=1}^{m_k} v_{kh} \tag{1}$$

$$u^2(x_k) = \frac{s_k^2}{m_k} = \frac{1}{m_k(m_k-1)}\sum_{h=1}^{m_k}(v_{kh}-\bar{v}_k)^2 \tag{2}$$

If only the lower limit $a_k$ and the upper limit $b_k$ is known from a systematic influence quantity, the state of knowledge can be described by a rectangular distribution over the interval $[a,b]$. This means that no value in the interval is preferred based on the information given. The expectation value and the variance of such a rectangular distribution is given by Eqs. (3) and (4), respectively.

$$x_k = (a_k + b_k)/2 \tag{3}$$

$$u^2(x_k) = (b_k - a_k)^2/12 \tag{4}$$

If not the best estimate $x_k$ is taken for the quantity but another estimate $x_k' \neq x_k$, e.g. a result which is not corrected for an influence, the uncertainty broadens according to Eq. (5).

$$u^2(x'_k) = u^2(x_k) + (x'_k - x_k)^2 \tag{5}$$

In case that the knowledge of the quantity allows to create a probability distribution different from the basic distributions mentioned above, their expectation value and variance can be used. However, the probability distribution must be compatible with the principles of Bayesian statistics and with the PME.

The propagation of the uncertainty has to be performed according to the Gauss method. If several input quantities are involved the common components of uncertainty are expressed as covariances $u(x_k, x_l)$. For $n_x$ input quantities $x_k$, and $n_y$ resulting quantities $y_i$, the uncertainty for the results is given by the addition of the variances and covariances.

$$y_i = F_i(x_1, \ldots, x_{n_x}); (i = 1, \ldots, n_y) \tag{6}$$

$$u(y_i, y_j) = \sum_{k,l=1}^{n_x} \frac{\partial F_i}{\partial x_k}\frac{\partial F_j}{\partial x_l} u(x_k, x_l) \tag{7}$$

If the input and resulting values are arranged in column vectors, the uncertainties in a symmetric $(n_x, n_x)$-matrix $\mathbf{U_x}$, where the variances are the diagonal elements surrounded by the covariances, and the values of the partial derivatives in a $(n_y, n_x)$-matrix $\mathbf{Q}$, the propagation of the uncertainty can be written by

$$\mathbf{U_y} = \mathbf{Q}\mathbf{U_x}\mathbf{Q}^T \tag{8}$$

If the data must be subjected to an approximation the method of least squares is recommended.

$$\chi^2 = (\mathbf{z} - \mathbf{x})^T \mathbf{U_x}^{-1}(\mathbf{z} - \mathbf{x}) = \min \tag{9}$$

Here, $\mathbf{x}$ denotes the vector containing the data of the dependent variable and $\mathbf{z}$ is the vector of the resulting functional values. Note, divergent from the classical Gaussian method of least squares (Eq. (10)), the approximation is weighted by the uncertainty regarding the input values.

$$(\mathbf{z}-\mathbf{x})^T(\mathbf{z}-\mathbf{x}) = \sum_{k=1}^{n_x}(z_k - x_k) = \min \quad (10)$$

In many cases, e.g. by fitting the Heckel equation, not only the dependent but also the independent variables are noticeably uncertain. Thus, it seems to be necessary to balance both variables. In this case however, the simple linear approximation becomes a non-linear curve fitting problem. (For clarity, 'linear' refers to the dependency of the parameters of the function, not to the shape of the function.) Therefore, the classical method of Gauss was preferred throughout this study. Using this method, the vector $\mathbf{y}$ of the coefficients of the polynomial function $x = f(t)$ is given by

$$\mathbf{y} = (\mathbf{A}^T\mathbf{A})^{-1}\mathbf{A}^T\mathbf{x}; \quad (11)$$

$$\mathbf{A} = (A_{ki}); A_{ki} = (t_k)^{i-1} \quad (12)$$

The uncertainty for the coefficients $\mathbf{y}$ resulting from the uncertainties for the dependent values $\mathbf{x}$ and the independent values $\mathbf{t}$, which together build up the vector $\mathbf{v}$, was calculated by Eq. (13).

$$\mathbf{U_y} = \mathbf{Q_v}\mathbf{U_v}\mathbf{Q_v}^T \quad (13)$$

The sensitivity matrix $\mathbf{Q_v}$ was determined numerically. $\mathbf{Q_v}$ reflects the change of $\mathbf{y}$ with small changes in $\mathbf{x}$ and in $\mathbf{t}$.

Non-linear functions as the modified Weibull function were approximated by the Levenberg–Marquardt algorithm provided by LabVIEW. Although the routine offers the option to insert weights, this was only used to estimate the uncertainty for the coefficients resulting from the uncertainty of the input quantities. However, the weights are restricted to the standard uncertainty by the routine.

In addition, the uncertainty for the coefficients resulting from curve fitting was calculated in the conventional way. In the case of non-linear approximation the output of the routine was taken. In the case of linear approximation the uncertainty was calculated by means of the global standard uncertainty $u$.

$$\mathbf{U} = u^2(\mathbf{A}^T\mathbf{A})^{-1} \quad (14)$$

$$u^2 = (\mathbf{z}-\mathbf{x})^T(\mathbf{z}-\mathbf{x})/(n_x - n_y) \quad (15)$$

Although $\mathbf{U}$ includes some uncertainty which was caused by the measurement and which is thus double represented, $\mathbf{U}$ additionally provides a measure of the suitability of the model to describe the relation between the variables.

## 3. Results and discussion

Fig. 1 shows the results and their standard uncertainty for some parameters describing the course of the tabletting process. The standard uncertainty contains the standard deviation of the mean of repeated tabletting experiments and the uncertainty derived from the calibration and validation of the measuring devices. Compared with the results presented in a previous study (see Fig. 5 in Ref. [1]), the uncertainty obtained according to the German norm is small. This is reasonable, as the uncertainties of the former study are worst case estimates ($P = 1$) of systematic influences and confidence intervals ($P = 0.95$) of repeated measurements. Therefore, the probability to include the true value of the quantity is high. The uncertainties based on the DIN represent, however, a range with a considerable lower probability to include the true value of the parameter. At standard deviation the normal and the rectangular probability distribution enclose 68 and 58%, respectively, of the area of the curve. Weise and Wöger [4] pointed out that the uncertainty should not include nearly all possible estimates for the quantity as this hinders a critical comparison between results. The uncertainty should assess the quality of results neither optimistically nor pessimistically but realistically. In Ref. [1] neither the worst case nor the best case estimates calculated seemed to be an appropriate basis for the interpretation of the data. Thus, the demand for a realistic measure of uncertainty is supported by the authors.

The German norm allows to calculate confidence intervals for a single resulting quantity approximately by the standardized normal distribution, or a $n$-dimensional confidence ellipsoid for combined results approximately by the $\chi^2$ distribution. However, strictly speaking, the exact probability distribution must be known for this, which is hardly the case if several measuring quantities and influence quantities are combined. In addition, the probability in its classical sense is per se an indication of confidence [4].

In line with the Bayesian theory of measurement uncertainty, Weise and Wöger [4] recommended a factor of $\beta = \sqrt{2}$ for a critical comparison between results so that

$$|x_1 - x_2| \le \beta\sqrt{u^2(x_1) + u^2(x_2)} \quad (16)$$

They remarked that this is a strict criterion which needs no choice of a probability. Using this criterion the densification behaviour of all direct compression excipients used can be clearly distinguished from another apart from some overlappings at isolated maximum relative densities as indicated by Fig. 1 as well. Since the materials are selected to represent a variety of densification mechanisms, this observation points to the suitability of the method for a subtle evaluation of the results. In a previous study, however, the worst case estimates of uncertainty allow in many cases only for a separation of groups of materials [1] which makes a detailed data analysis impossible. On the other hand, the method can be considered to be critical as it is sensitive to the well-known problems with the Heckel function [11,12]. If the standard uncertainty of the true density (0.01–0.02 g/cm$^3$) was included into the calculations, the standard uncertainty for the Heckel slopes widens two- to threefold and the overlapping between the visco-elastic substances increases (Fig. 2).

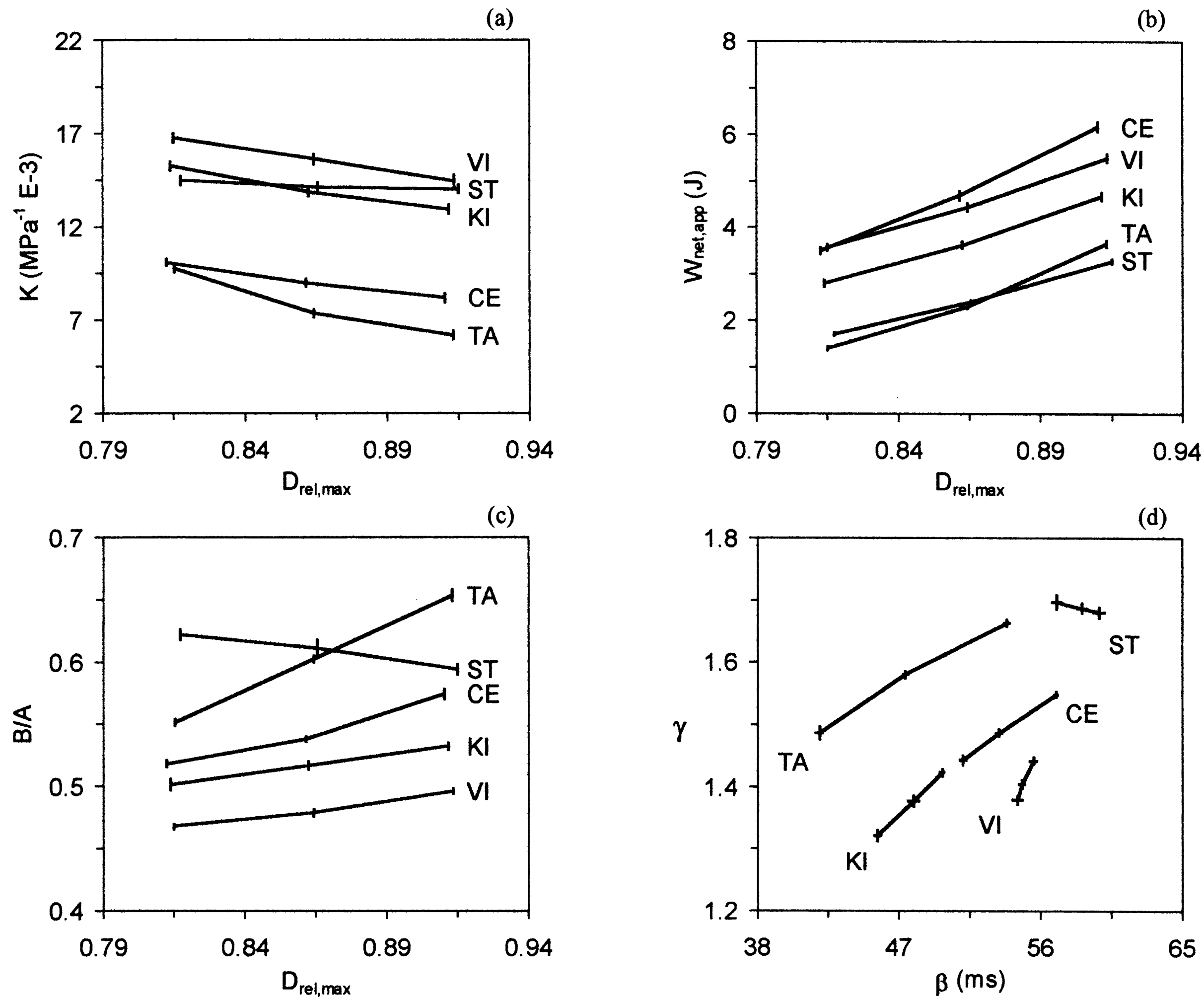


Fig. 1. Mean values and standard uncertainties in dependence on the materials and on the $D_{rel,max}$ for (a) the slope $K$ of the Heckel plot, (b) the apparent net work $W_{net,app}$, (c) the area quotient $B/A$, and (d) the Weibull parameters $\beta$ and $\gamma$ ($\beta$ increases with $D_{rel,max}$).

Furthermore, the results of the reproducibility experiments with Pharmatose, illustrated in Fig. 3, show that

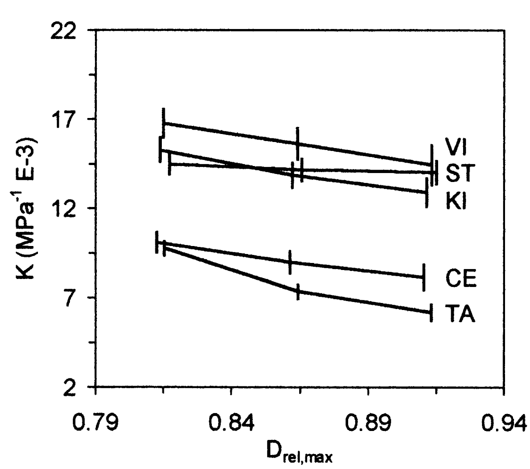


Fig. 2. Mean values and standard uncertainties for the slope $K$ of the Heckel plot including the effects of the uncertainty of the true density in dependence on the materials and on the $D_{rel,max}$.

based on this criterion all sets of tablets are not significantly different from each other with respect to the apparent net work and the slope of the Heckel plot, while a $t$-test ($P = 0.95$) based on the standard deviation of repeated measurements failed to predict the conformity for many combinations. The problem with the $t$-test is that the repeatability of successive experiments is much better than the repeatability over longer periods. However, with respect to the parameters derived from the force-time curves the significance test cannot give evidence for conformity between all sets of tablets. As for these parameters the standard deviation of repeated experiments provides the main contribution to the standard uncertainty, the $t$-test is slightly more stringent. In defence of the significance test it ought to be said that the reproducibility of the time course was no topic of the validation study and uncertainties connected with it were not considered. In addition, the mean of the tablet mass and of the upper punch force varied significantly between some sets of tablets although the ranges of the mean values were quite small (0.6 mg and 63 N, respectively).

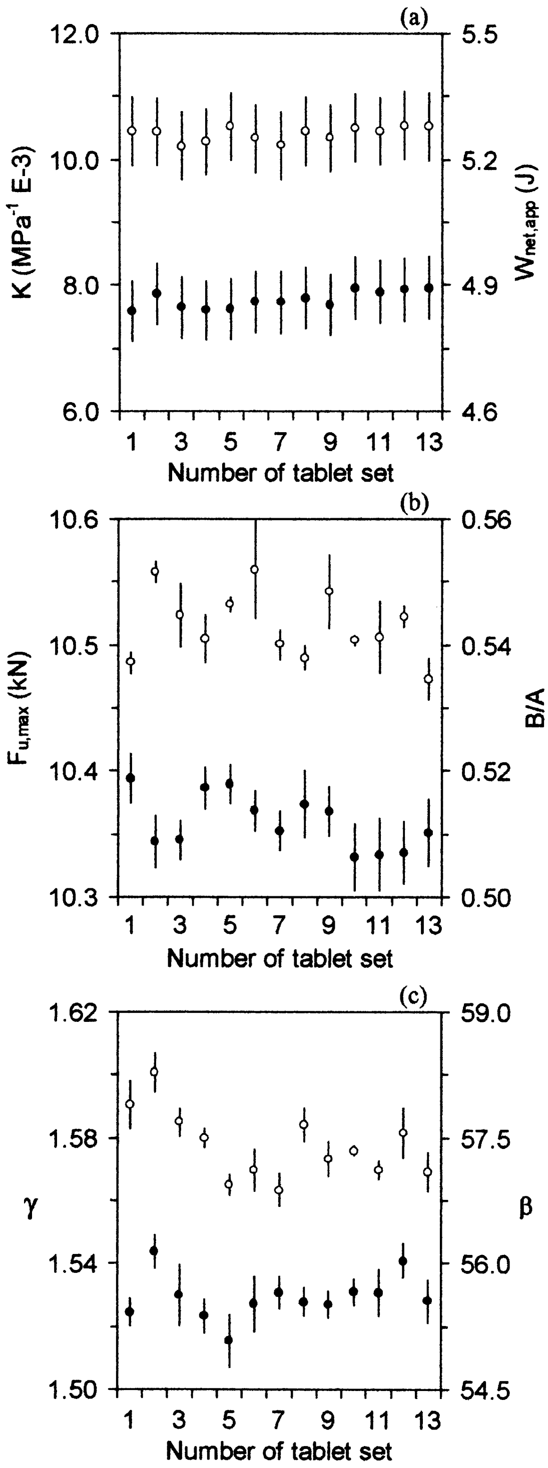


Fig. 3. Mean values and standard uncertainties for the reproducibility experiments with Pharmatose 100M for (a) the slope $K$ of the Heckel plot and the apparent net work $W_{net,app}$, (b) the maximum upper punch force $F_{u,max}$ and the area quotient $B/A$, and (c) the Weibull parameters $\gamma$ and $\beta$. The lower graphs (closed symbols) refer to the left axis of ordinates, while the upper graphs (open symbols) refer to the right axis.

However, it must be noted that the uncertainty calculated according to the German norm has its problems with the covariances. In contrast to the variances where the sign of the partial derivatives is cancelled out, the covariances can have a negative sign (Eq. (7)). Because of that, uncertainties can be incorrectly neutralized. On the other hand, the results obtained from data sampled on the same tabletting machine under only moderately varying conditions and processed partially with the same functions are strictly speaking not independent from another. But the covariance between different data sets cannot be expressed for complex parameters as used in this study and thus cannot be considered during the evaluation of the results.

Although it is difficult to assess the quality of the uncertainty calculated according to the DIN method with respect to a critical and realistic comparison between the resulting tabletting parameters, the method seems to be promising for a routine consideration of the uncertainty caused by the measuring devices and by the calibration methods.

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