ELSEVIER

European Journal of Pharmaceutics and Biopharmaceutics 48 (1999) 157–170

European Journal of Pharmaceutics and Biopharmaceutics

www.elsevier.nl/locate/ejphabio

Research paper

The tabletting machine as an analytical instrument: consequences of uncertainties in punch force and punch separation data on some parameters describing the course of the tabletting process

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Received 13 January 1999; accepted in revised form 6 April 1999

Abstract

The influence of the uncertainties involved in the measurement of punch forces and punch separation in an eccentric tabletting machine on the validity of the analytical results was evaluated using six direct compression excipients. The analytical parameters considered were the maximum upper punch pressure, the minimum punch separation, the maximum relative density, the contact time, the area quotient according to Emschermann and Müller, the Weibull and Heckel parameters, as well as the total, expansion and apparent net work. The measuring uncertainties were divided into between-run deviations (BD) and within-run deviations (WD), which are constant and variable, respectively, during a tabletting event. Both types of uncertainties were expressed as simple error limits. The effects of the measuring BD's were calculated by adding them to the force and displacement data and then computing the analytical parameters in the conventional way. The estimation of the effects of the measuring WD's needs special methods for each parameter. Their validation showed that they were in most cases able to include the true effects of some exemplary selected errors but tend to overestimate them. From the sum of the confidence interval (CI) of a mean parameter value from repeated tabletting experiments, the confidence interval with respect to curve fitting, the BD and the WD of the analytical results, the total deviation (TD) of the results was obtained, which provides a worst case measure of the uncertainties. The TD makes a differentiation between materials with similar tabletting behaviour impossible in many cases, thus providing too low a selectivity. The best case uncertainties account for the difference in the response of the data to be compared to the measuring errors. The uncertainty decreases considerably under best case conditions. However, the best case intervals predicted from the worst case limits are not generally valid. Thus, besides the TD, only the CI's remain for the assessment of the analytical results. However, in the presence of systematic errors the statistical analysis cannot assure the correctness of the conclusions drawn with the degree of certainty supposed, even if the systematic measuring errors are the same for the data to be compared.

Keywords: Validation; Measuring uncertainty; Compression force; Punch separation; Uncertainty of analytical results; Selectivity; Heckel parameters; Weibull parameters; Work; Area quotient

1. Introduction

Today tabletting machines are commonly equipped with suitable instrumentation for the measurement of punch forces. In research and development punch displacement is often measured as well. In production the instrumentation should serve for an automatic manufacturing process and a reproducible tablet quality. In research and development, however, the instrumentation is also used to investigate the process of the build-up of the tablet from the powder bed and thus to analyse the densification and deformation behaviour of pharmaceutical materials. Hence, in the latter case the tabletting machine no longer has solely the status of a production tool but also serves as an analytical instrument. Using the tabletting machine as an analytical instrument, the quality of the measurements will not only determine the quality of the tablets produced but also the quality of the analytical results represented by complex parameters describing the tabletting event. To assure this quality, a detailed qualification is necessary of the machine, of the instrumentation, and of the devices processing the output signals of the transducers. This must be followed by a validation of the methods involved, e.g. the calibration of the

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0939-6411/99/$ - see front matter
PII: S0939-6411(99)00038-7

sensors. After optimisation of the instrumentation and of the methods applied, such qualification and validation experiments will finally provide the remaining unavoidable measuring uncertainty.

Just the knowledge of these uncertainties is of course not sufficient. From the measuring uncertainties the accuracy of the analytical results has to be predicted routinely. Usually, the standard deviation or confidence intervals of repeated tabletting experiments are solely utilised for the assessment of the analytical results. When the tabletting experiments are repeated close together to restrict the cumbersome adjustment of the target maximum force or maximum relative density, these error limits cannot totally account for the overall random variability arising from tabletting. They can, however, definitely not represent inherent random and systematic uncertainties arising from calibration.

However, the consideration of the calibration errors with respect to the analytical results is fraught with problems. Application of the error propagation laws according to Gauss is not possible. Firstly, the parameters describing the response of the powder bed to volume reduction are often complex functions of the force and/ or the punch separation, apart from some simple parameters like the maximum force or the minimum punch separation. Secondly, systematic uncertainties are present, which are not accessible to statistical analysis. Thirdly, random errors caused by the calibration devices exert a systematic influence on the analysis of the tabletting data.

Alternatively, the course of systematic errors could be adapted to the force and the displacement data of the tabletting experiments. Then, their effects on the analytical parameters can be evaluated. A routine check, however, becomes time-consuming when several such errors are involved. In addition, often the precise course of an error is not known or only the limits of the tolerances can be inferred from the specifications of the measuring devices used. For example, specifications of load cells used as secondary standards for the calibration of the sensors installed include only the limits of their non-linearity and hysteresis unless a detailed calibration record is available for the reference.

The authors are unaware of any publication where the tolerances of the measuring systems are included into the evaluation of the results. The problems in predicting the consequences of the measuring uncertainty on the analytical results may explain for it. Nevertheless, the need for including the measuring uncertainty into the evaluation of the data still exists. One may argue, it is not necessary to worry about systematic errors, if only the data obtained from experiments using the same machine with almost constant machine settings and compression conditions have to be compared. However, this argument is untenable. Firstly, not all possible influence factors can be held constant within a study. At least the particular response of the powder bed compressed will be a variable. This in turn can change the course of systematic measuring errors. For example, it was shown that the dynamic hysteresis of a strain gauged load cell was strongly dependent on the course of force development, which however, varies not only with the settings of machine speed and maximum force but also with the compression properties of the powder bed [1]. Instrumentation based on the same measuring principle may show similar effects. Time-dependent effects were also observed for displacement transducer signals caused by the amplifiers used [2]. Secondly, the consequences on the analytical results resulting from even constant systematic measuring errors can change with the experimental conditions and with the material compressed depending on the shape of the force and displacement curves, as already pointed out by Lammens et al. [3].

The comparability of the analytical results may be less influenced by measuring uncertainties, when the variation in the experimental conditions is as small as possible. However, the situation deteriorates, when the results obtained on different machines of the same or different type equipped with the same or a different instrumentation have to be compared. Bateman et al. [4] performed an interlaboratory study. They compressed the same batch of material to the same maximum pressure using the same tooling and the same displacement-time profile. However, the compaction simulators used in each laboratory were of different types. The authors compared the yield pressure derived from Heckel plots and found deviations of up to 16.5% of the mean between the different laboratories. The differences found were ascribed to the methods to correct for elastic distortion of the simulator and the punches and to variations in loading characteristics of the hydraulic systems. No statement at all was made about the accuracy of the force and the displacement measurements and about the consequences of the measuring accuracy on the yield pressure. However, these experiments were performed on compaction simulators, which were developed for use as physical testing machines, while the eccentric and rotary tabletting machines normally used were optimised for production. Using such commercial tabletting machines, the measuring problems will be probably greater as a result of manufacturing tolerances of the machine or owing to deficiencies in the instrumentation. The geometric and mechanical framework of the machine will often limit the possibilities of constructing the instrumentation and installing it in the most adequate manner [5,6]. Moreover, the motions and mechanisms of commercial tabletting machines were shown to cause tilting and bending effects on the punches or punch holders [5,7,8]. Such effects may influence the force and displacement measurement.

The aim of this study was to assess the validity of the analytical results obtained from tabletting experiments in an eccentric tabletting machine using a variety of direct compression excipients. The uncertainties of the force measurement and of the determination of punch separation were received from a detailed qualification and validation study described in preceding publications [1,5].

2. Materials and methods

2.1. Tabletting experiments

2.1.1. Materials

Parmcompress® (G. Parmentier, Frankfurt, Germany, lot 91/176 2), Tablettose® (Meggle, Wasserburg, Germany, lot D287 L971 A4003), Cellactose® (Meggle, lot D195 L972 A4901), Vivacel 200® (J. Rettenmaier, Ellwangen-Holzmühle, Germany, lot 8001073), Karion Instant Pharma® (E. Merck, Darmstadt, Germany, lot M 568503), Starch 1500® (Colorcon Ltd, Orpington, Great Britain, lot 807010), magnesium stearate (Riedel-de Haen, Seelze, Germany, lot 91320), stearic acid (E. Merck, lot K03819871).

All materials were used as received. Their powder-technological properties are given in [9], except for Starch 1500 [10].

The direct compression excipients were chosen to represent a great variety of deformation mechanisms. Parmcompress® (PA) is a dicalcium phosphate dihydrate. Tablettose® (TA) is an agglomerated α-lactose monohydrate. Dicalcium phosphate dihydrate and lactose were described as predominantly brittle materials [11,12]. However, dicalcium phosphate dihydrate offers noticeably higher resistance to densification than lactose [13]. Karion Instant Pharma® (KI), a spray-dried sorbitol, belongs to the highly plastic materials [14,15]. Vivacel 200® (VI) consists of microcrystalline cellulose. Starch 1500® (ST) is a pregelatinized corn starch. Both substances exhibit plastic deformation [16], however, accompanied by considerable elastic deformation, which is more pronounced for Starch 1500® [17]. Cellactose® (CE), a co-processed product made of 75% (w/w) α-lactose monohydrate and 25% (w/w) powdered cellulose, combines the brittle and viscoelastic properties of its components, however, in an unexpected manner [18].

2.1.2. Methods

A small eccentric tabletting machine (Hanseaten Exacta E1, W. Fette, Schwarzenbek, Germany) equipped with flat, sharp-edged punches of 10 mm diameter (punch set number 1) was used. The instrumentation for the measurement of the upper and lower punch forces and of the punch displacement as well as the processing of the output signals of the respective transducers were described previously [1,5,19]. The filling depth was set to 11 mm. The amount of powder required was poured manually into the die and compressed at a machine speed of 30 strokes/min. The tablet weight of repeated experiments diverged by at most 0.7 mg, corresponding to the maximum deviation from the target weight. For the tabletting of ST, the die was lubricated with a thin film of 1.5% stearic acid in ethanol prior to the filling of the die. All other materials were internally lubricated with magnesium stearate as described by Konkel and Mielck [9]. All experiments were performed at 22–23°C and 39–42% relative humidity.

Two sets of experiments were carried out. First, constant masses of powders, 400 mg for PA and 300 mg for all other materials, were tabletted to maximum upper punch forces of 5.9 and 16.7 kN. Second, constant true volumes of powders, namely 157 mm^3, were tabletted to graded maximum relative densities of 0.81, 0.86, and 0.91. This experiment was performed without PA, because it cannot be densified to the same range of $D_{rel,max}$ suitable for the other five materials. The maximum relative densities correspond to minimum punch separations of 2.468, 2.324, and 2.197 mm. The resulting mean maximum upper punch forces are listed in Table 1. For each condition five tablets were prepared in succession.

The data for punch forces and punch displacement were sampled at 1.5 kHz. 700 sets of data were recorded and stored for each compression event. The data acquisition was controlled by ASYST software (Vers. 4.0, Keithley Instruments, Taunton, MA, USA).

2.2. Data analysis

All data analysis was performed with the ASYST software.

2.2.1. Measuring uncertainty

In a qualification and validation study described in preceding publications [1,5] the errors involved in the determination of punch forces and punch separation were estimated. The measuring uncertainties were divided into the two main categories: within-run deviations (WD) and between-run deviations (BD). While the BD's describe errors that are constant during one tabletting event and vary only between different compressions, the WD's include errors whose extent varies within one tabletting event. Thus, the change in the slope of the calibration function between quasistatic and dynamic calibration provides an example of a systematic BD. The remaining non-linearity and hysteresis of the calibration function can be classified as systematic WD's. Besides such systematic errors, random ones are present. The variabilities of the slope and the intercept of the calibration function due to repeated calibration runs are random BD's, whereas the noise of the transducer

Table 1
Mean maximum upper punch forces (kN) resulting from the tabletting experiments to constant maximum relative densities ($D_{rel,max}$), using punches of 10 mm diameter

Material	$D_{rel,max}$		
	0.81	0.86	0.91
TA	4.6	8.1	13.9
CE	6.4	9.3	13.7
VI	4.9	6.5	9.0
ST	4.1	5.5	7.4
KI	4.4	6.1	8.6

signal is a random WD. A detailed description of the items considered is given in [1,5].

The random errors were carefully separated from the systematic ones in the preceding papers. However, with regard to the estimation of the uncertainties of the analytical results it is easier and more useful to consider only two categories of errors, namely systematic BD's and WD's. However, the random contributions were not ignored but taken into consideration as systematic ones, since the importance of the random measuring errors during calibration for the evaluation of the analytical results lies in their influence on the accuracy of the calibration functions and of the estimation of the measuring errors. The random contributions were expressed in a worst case mode. This seems to be appropriate after considering that the limits of the really systematic measuring errors are taken from the maximum systematic deviations observed [1,5]. Therefore, the random BD's were calculated as the threefold standard deviation (SD) of the mean. The squareroot of the sum of their squares was added to the sum of the systematic BD's. The random WD's were no longer estimated from the resolution of the signals, but from the variability of repeated data points in the calibration series calculated as the threefold SD of the mean. The maximum SD's received and the variability of the drift of the charge amplifiers were summarised by calculating the squareroot of the sum of their squares and added to the systematic WD's. Table 2 contains the error limits obtained this way.

2.2.2. Analytical parameters

For this study the following parameters were considered, which describe discrete points in the tabletting event: the maximum upper punch pressure (p_{max}), the minimum punch separation (s_{min}), the maximum relative density ($D_{rel,max}$). In addition, the following parameters were evaluated, which describe the whole tabletting event or specific parts of it. The contact time (t_c) was defined as the time span during which the upper punch pressure exceeds 1 MPa at the ascending force phase and 1 MPa plus the mean residual pressure at the descending force phase. The residual pressure was observed during 14 ms after the upper punch separated from the tablet. The time of force decay (t_d) corresponds to the time span between the time of p_{max} (t_{max}) and the end of t_c (t_{end}).

For the calculation of the area quotient (B/A) [20], the area under the force-time curve of the upper punch within t_c was determined by integration according to the trapezoidal rule and was split into two parts at t_{max}. The area after t_{max} (B) was then divided by the area before t_{max} (A).

The course of the pressure-time profile of the upper punch was described by the modified Weibull function [9]. This function was fitted to the data within t_c by approximating the parameters γ, $t_{max,fit}$ and $p_{max,fit}$ using the Gauss-Newton algorithm provided by the ASYST software:

$$p(t) = p_{max,fit}\left(\frac{t_{end} - t}{t_{end} - t_{max,fit}}\right)^{\gamma} e^{1-\left(\frac{t_{end} - t}{t_{end} - t_{max,fit}}\right)^{\gamma}} \quad (1)$$

where $p_{max,fit}$ corresponds to the height of the fitted curve and $t_{max,fit}$ to the time of $p_{max,fit}$. The parameter γ characterises the shape of the curve together with the parameter β, which was calculated as the difference between t_{end} and $t_{max,fit}$. Divergent from [9], β was not normalised with respect to t_c.

The total area under the force-displacement curve, which represents the total work (W_{total}), and the area under the

Table 2
Summary of the error ranges involved in the measurement of low upper punch forces (corresponding to 1 MPa), of the upper and lower punch forces in the total measuring range, of punch displacement, and of punch deformation[a]

	Within-run error						Between-run error		
	Before extreme value			After extreme value					
Upper punch force at '1 MPa'	−7.2	+3.8	N	−2.1	+10.3	N	−7.9	+11.1	N
	−0.021	+0.031	%	−0.021	+0.042	%	−0.044	+0.054	%
Upper punch force	−59.0	+13.6	N	−44.8	+55.0	N	−4.0	+20.2	N
	−0.033	+0.043	%	−0.033	+0.044	%	−1.353	+0.129	%
Lower punch force	−37.6	+61.7	N	−56.5	+67.6	N	−12.6	+25.4	N
	−0.043	+0.033	%	−0.044	+0.033	%	−0.886	+0.522	%
Punch displacement	−7.4	+4.5	μm	−4.1	+4.0	μm	−7.6	+7.1	μm
	−0.000	+0.000	%	−0.000	+0.000	%	−0.044	+0.054	%
	−0.730	+0.678	%[b]	−0.506	+0.484	%[b]			
Punch deformation	−14.8	+5.1	μm	−16.8	+2.8	μm	−3.5	+3.3	μm
	−1.022	+0.712	%	−1.022	+0.712	%	−1.803	+1.697	%
	−45.989	+86.636	%[b]	−29.539	+85.122	%[b]			

[a] The systematic within-run errors are listed separately for the phases before and after the maximum force or minimum displacement. Each item contains absolutely and relatively expressed errors, which together correspond to the total error. The 'percentage change in the deviation' accounts for the total WD with respect to the calculation of the uncertainty of the work parameters. The signs of the errors in punch displacement and in punch deformation are chosen to reflect the effect on the distance between the punches.

[b] Percentage change in the deviation. This error accounts for the total WD with respect to the calculation of the uncertainty of the work parameters.

Table 3
Choice of the signs of the uncertainties involved in the measurement of low upper punch forces (corresponding to 1 MPa), of the upper and lower punch forces in the total measuring range, and of punch separation for the phases before and after the force maximum or displacement minimum in dependence on the sign of the uncertainty of the respective analytical parameter

Parameter	Sign of uncertainty of the parameter	Sign of measuring uncertainty					
		Upper punch force '1 MPa'		Punch forces (total range)		Punch separation	
		Before	After	Before	After	Before	After
p_{max}	−			−	−		
	+			+	+		
s_{min}	−			−	−	−	−
	+			+	+	+	+
$D_{rel,max}$	−			+	+	+	+
	+			−	−	−	−
t_c	−	−	−				
	+	+	+				
t_d	−		−				
	+		+				
B/A	−	+	−	+	−		
	+	−	+	−	+		
W_{total}	−			−		−	
	+			+		+	
$W_{net,app}$	−			−	+	−	+
	+			+	−	+	−
W_{exp}	−				−		−
	+				+		+

decompression phase, namely the expansion work (W_{exp}), were calculated by integration using the trapezoidal rule and expressed as absolute values. The apparent net work ($W_{net,app}$) was derived as the difference between W_{total} and W_{exp}.

The Heckel parameters K and A [21] correspond to the slope and the intercept, respectively, of a straight line fitted to a sufficiently linear region of the Heckel plot, which relates the relative density D_{rel} to the upper punch pressure p. Thus, for the linear region the following relation exits:

$$\ln\frac{1}{1-D_{rel}(p)} = K{\cdot}p + A \quad (2)$$

The algorithm for the selection of the linear region is described elsewhere [9].

2.2.3. Uncertainty of the analytical results

From the measuring uncertainties only the uncertainty of simple analytical parameters, e.g. the maximum force, can be estimated directly. The calculation of the consequences of the measuring uncertainties on analytical parameters describing the course of the tabletting event or specific parts of it is more difficult and needs special methods. The methods must be adapted to the nature of the uncertainty and of the analytical parameter.

Before calculation of the uncertainties of the analytical results, the data were analysed in the conventional way using the calibration at standard conditions. The force and displacement data obtained this way and the parameter values derived on this standard level serve as the basis for the calculation of the BDs.

As the uncertainties listed in Table 2 represent the limits of the measuring errors, their sign had to be inverted before their application in the following calculations. The uncertainties of the analytical results then give the limits within which the true value will be found.

2.2.3.1. Between-run uncertainty. The force and displacement data created on the standard level were adjusted by adding the measuring BD's. For the calculation of the BD's of t_c and t_d the measuring uncertainties derived at 1 MPa were applied. Using the adjusted data, the analytical parameters were calculated in the conventional way. Four calculation runs were performed combining the uncertainty of force measurement and the uncertainty of the determination of punch separation with equal or opposite sign. The differences between the resulting parameter values and the values obtained on the standard level provide the BD's of the analytical results.

2.2.3.2. Within-run uncertainty. The estimation of the WD provides a special problem as the information about the course of the deviations is lost due to the simplified formulation of the measuring uncertainties. Thus, as far as possible the maximum effects on the analytical results within the limits of the measuring uncertainty were calculated. This should guarantee that the limits of the uncertainty of the analytical results include the real deviations.

The adjusted data of the between-run level serve as the basis for the calculation of the WD's and the parameter values derived on this level as reference values. Thus, the WD's must be computed for all four calculation runs performed on the between-run level.

The WD's of p_{max}, s_{min} and $D_{rel,max}$ were estimated directly from the measuring WD's by transformation to the target physical unit. As no clear assignment of the maxima or minima to the phases before and after the maxima or minima is possible, the greater deviation of the two phases was chosen for these parameters.

The WD's of t_c and t_d were obtained by adding the measuring WD derived at 1 MPa to the force data. After transformation of these data to pressure the beginning and the end of contact time were determined in the conventional way. The differences between these results and the reference values provide the WD's of t_c and t_d. The signs of the uncertainties of the parameters in dependence on the signs of the measuring uncertainties can be inferred from Table 3.

For the calculation of the WD of B/A, the uncertainty of the force measurement was handled as if it was constant (with a constant relative contribution) at its upper or lower limit within the ascending and descending force phases, but with opposite sign for the two phases (Table 3). As the limits of integration will depend on the beginning and the end of t_c, the effect of a change in these limits was additionally considered.

The WD's of the parameters of the modified Weibull function were estimated by the maximum possible change in the course of the Weibull function within the error band surrounding the pressure-time curve. As can be seen in Fig. 1, the functional values derived from a variation in the respective parameter value were permitted to leave the error band to a certain extent. However, the SD of the derived functional values from the error band was not allowed to exceed the SD of the fit obtained on the between-run level for the respective data set. The functional values lying within the band of the uncertainty were included into the calculation of the SD as zero deviation. The effect that the SD of the approximation may change with a change in the shape of the force-time curve was not taken into consideration. The optimisation of the possible deviation was performed separately for the three parameters. During the optimisation of one of the parameters, the other two parameters were held constant at their reference values. Except for the parameter β, the effect of a change in t_c was not considered, as it should theoretically not influence the results. With respect to β, the previously determined deviation of t_d was added.

The WD's of W_{total} and W_{exp} were calculated by maintaining the measuring uncertainties constant (with a constant relative contribution) at their upper or lower limit within the ascending and descending force and displacement phases. The WD of $W_{net,app}$ was derived from the sum of the WD's of W_{total} and W_{exp}. The signs of the uncertainties of the parameters in dependence on the signs of the measuring uncertainties can be inferred from Table 3. With respect to punch separation only the change in the deviation from one measuring point to the next point and not the total extent of the deviation is the matter of interest for the estimation of the uncertainty of the work. Thus, the measuring uncertainties in the determination of punch separation had to be specially defined for these calculations. They are listed separately in Tables 2 and 4 as 'percentage change in the deviation'. These error limits correspond to the maximum and minimum of the first derivative of the course of the deviations divided by the corresponding change in punch displacement or punch deformation. The signs of the measuring errors are chosen to reflect the effect on punch separation.

The WD's of the Heckel parameters were estimated as the maximum possible change in the slope and the intercept of a

Table 4
Deviations between the supposed and the true behaviour with respect to non-linearity and hysteresis of the upper punch force and of punch deformation, used for the tabletting data with maximum upper punch forces of 6 and of 17 kN

			Upper punch force '1 MPa'			Upper punch force (total range)			Punch deformation		
Non-linearity	6 kN	Before and after[a]	−0.0	+8.7	N	−13.4	+11.0	N	−10.9	+0.0	μm
									−0.0	+56.0[b]	%
	17 kN	Before and after	−0.0	+34.7	N	−20.4	+35.6	N	−10.9	+0.0	μm
									−3.0	+56.0[b]	%
Hysteresis	6 kN	Before	−1.4	+0.0	N	−22.8	+0.0	N	N.a.[c]	N.a.	
									N.a.	N.a.	
		After	−0.0	+1.4	N	−0.0	+22.9	N	N.a.	N.a.	
									N.a.	N.a.	
	17 kN	Before	−0.6	+0.0	N	−40.2	+0.0	N	−1.9	+0.0	μm
									−6.2	+7.6[b]	%
		After	−0.0	+0.6	N	−0.0	+40.4	N	−0.0	+1.9	μm
									−9.2	+5.5[b]	%

[a] Before and after maximum force. The hysteresis errors are listed separately for the two phases.
[b] Percentage change in the deviation.
[c] N.a., not available.

straight line within the limits of the measuring uncertainty surrounding the linear portion of the Heckel plot, as illustrated in Fig. 2. Thus, the change in the values of the Heckel parameters can be calculated by means of the corner points of the band of uncertainty. As the data were somewhat noisy, not the original corner points but the corner points of the regression lines through the limits of the uncertainties in the linear region were selected.

2.2.3.3. Total uncertainty. Besides the two error categories mentioned above, two further types of uncertainty are present. They were represented by the confidence intervals ($P < 0.05$) of repeated tabletting events (CI) and, in the case of the Weibull and the Heckel parameters, by the confidence limits ($P < 0.05$) of the approximation with respect to the analytical parameters (CI_{fit}). The CI_{fit} takes uncertainties into account resulting from remaining random and systematic deviations of the approximated function from the data. So, the CI_{fit} reflects the limited ability of the resulting parameter values to describe the data. The CI includes random between- and within-run uncertainties. Firstly, it contains random variabilities caused by the tabletting machine, by the measuring devices, and by the analyst. Secondly, the CI reflects variabilities with respect to the powder beds compressed, e.g. variabilities in their composition or their mass. Finally, it contains variabilities resulting from the mathematical analysis of the data. For example, the precision of detecting the time of p_{max} in the noisy data is relevant for B/A.

From all the uncertainties the total deviation (TD) of the analytical results had to be assessed, viz. their accuracy. The

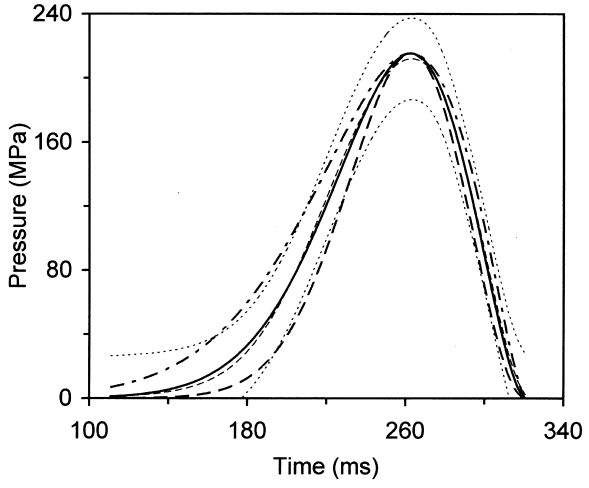

Fig. 1. Method for the estimation of the WD of the Weibull parameter γ illustrated for Tablettose® compressed to 17 kN maximum upper punch force. For clarity, a high and unrealistic measuring uncertainty of ± kN was selected. (- - -) Supposed pressure-time profile; (—) Weibull function fitted to the supposed profile; (· · ·) band of measuring uncertainty; (– · –) functional values at maximum possible change in γ towards smaller values, (– –) functional values at maximum possible change in γ towards higher values.

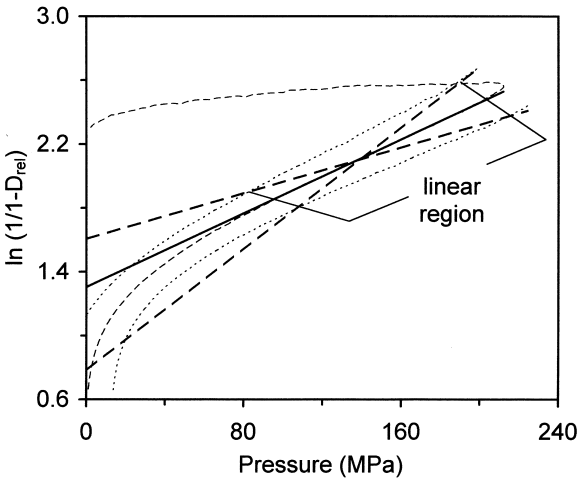

Fig. 2. Method for the estimation of the WD of the Heckel parameters illustrated for Tablettose® compressed to 17 kN maximum upper punch force. For clarity, higher measuring uncertainties than observed were selected, namely ± 1 kN and ± 25 μm. (- - -) Supposed profile; (—) Heckel function fitted to the supposed profile; (· · ·) band of measuring uncertainty; (– –) lines corresponding to the maximum possible change in the parameter values.

WD's, BD's, and CI_{fit}'s of the repeated experiments were averaged. For each experimental condition and each parameter the mean WD's were added to the mean BD's separately for each of the four calculation runs on the between-run level and separately with respect to their sign. The CI_{fit}'s, which were determined for all four calculation runs on the between-run level, were then added with the same sign as the WD's. From the eight resulting sums the maximum positive and negative deviation were selected and added to the CI to attain the TD. The CI used was obtained from the calculations on the standard level.

2.2.4. Validation of the methods for the estimation of the within-run uncertainty

As the estimation of the WD's provides the main problem, it seems to be necessary to validate the methods chosen, to get an indication how well they will match or at least include the true effects resulting from actual measuring errors. Two kinds of systematic deviations were selected, namely the non-linearity and hysteresis of the calibration of the upper punch force and of the determination of the punch deformation. The supposed and the true responses were described by suitable polynomials of at most fifth degree approximated to the experimental data of calibration. However, the goodness of the fit was not stressed. The course of the supposed behaviour with respect to the true behaviour is illustrated in Fig. 3a,b. The resulting error limits are listed in Table 4. Regarding the upper punch force, not only the standard calibration with a maximum force of about 17 kN was considered, but also the calibration data derived up to 6 kN with a second reference load cell were used, to assess the effects at low maximum forces, too.

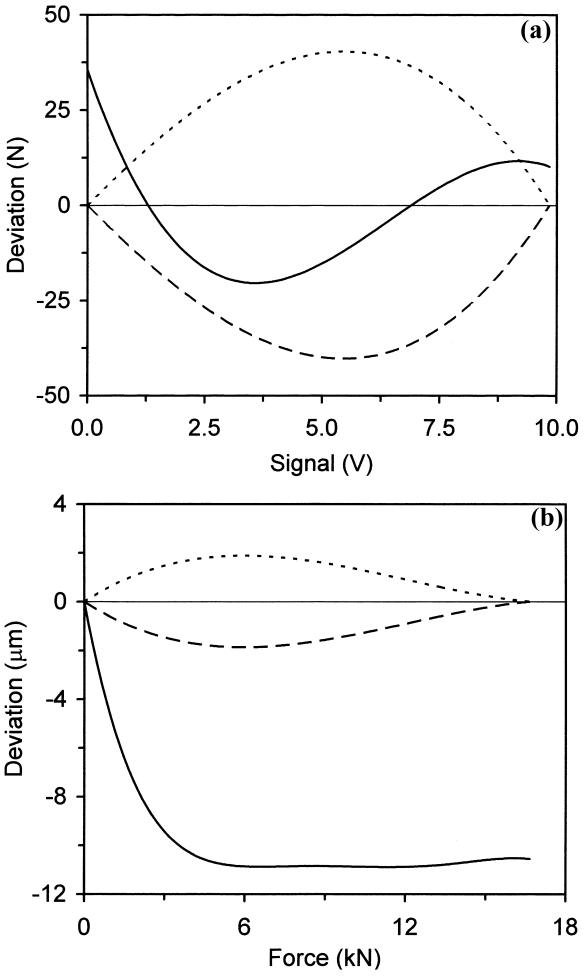

Fig. 3. Deviations between the supposed and the true behaviour with respect to non-linearity and hysteresis of (a) the upper punch force up to 17 kN and (b) the punch deformation. (—) Non-linearity; (– –) hysteresis before maximum force; (· · ·) hysteresis after maximum force.

The tabletting data obtained at preset maximum upper punch forces of 6 and 17 kN were analysed firstly with respect to the single effects. Secondly, the corresponding phenomena of force and of punch separation were combined. However, the punch deformation was not determined with a maximum force of 6 kN. Thus, the hysteresis effects of punch deformation cannot be evaluated on this maximum force level.

3. Results and discussion

3.1. Validation of the methods for the estimation of the within-run uncertainty

The true deviations are in most cases included within the estimated ones, as illustrated for the parameters B/A and K in Fig. 4a and b, respectively. Only the Heckel parameters provide some problems, as the deviations are in some cases underestimated, especially for the hysteresis involved in force and in punch deformation (Fig. 4b, fourth group, first bar). This deficiency must be ascribed to the method applied in so far as it does not consider a change of the linear region. Such an effect was indeed observed, caused by the change in the shape of the curve. However, the difference between the true and the estimated effects does not exceed the CI_{fit} in all cases.

On the other hand, the estimated deviations are in many cases highly overestimated. The calculation method for the WD's of the Weibull parameters overestimates the true effects in principle, as the change of the parameters was optimised separately, although the parameters are not independent from each other. Thus, the SD of the functional values from the limits of the error band exceeds in many cases the permitted value, when the optimised values of the

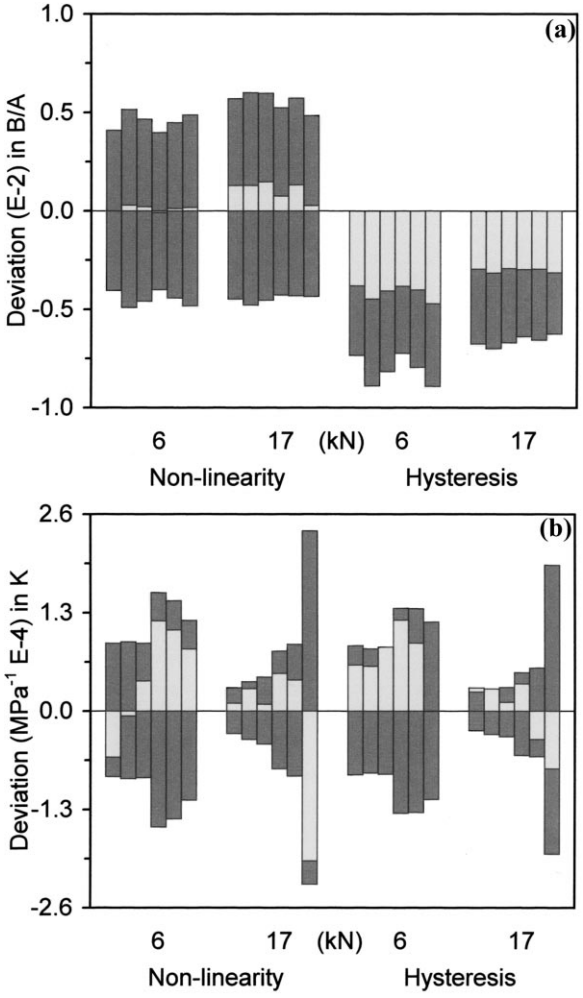

Fig. 4. Estimated and true effects of non-linearity and hysteresis involved in the determination of the upper punch force at maximum force settings of 6 and 17 kN on (a) the area quotient B/A and (b) the slope *K* of the Heckel plot. (Dark grey shaded) estimated deviations, (light grey shaded) true deviations. Each of the four groups of bars contains the results of the six materials in the sequence of PA, TA, CE, VI, KI, and ST. All results are expressed as absolute deviations from the parameter values obtained on the standard calculation level.

three parameters are combined. However, the estimated uncertainties are less than 1.9, 2.2, and 1.7% of the parameter values for γ, β, and $p_{max,fit}$, respectively, while the true deviations reach up to 0.3, 0.5, and 0.1%, respectively.

In contrast, the predicted WD's of W_{exp} reach up to nearly 100% of W_{exp} with respect to the non-linearity of punch deformation, as can be inferred from Table 5 (TA at 17 kN). This is a contribution of the method applied, which handled the measuring uncertainty as constant, at least within the descending or ascending phase of punch separation. Of course, handling the measuring WD as a constant error is somewhat inconsistent with the nature of the WD, but will provide the only way to include all possible effects. While at low maximum forces not only the estimated but also the true effects are quite high, the difference between both these deviations increases at higher maximum force. At higher forces, the maximum change in the deviation of punch deformation, which was taken as the measuring uncertainty, will no longer reflect the course of the true behaviour (Fig. 3b). As the change in punch deformation has a large share in the change in punch separation at decompression, the results are not surprising. In contrast, W_{total} and $W_{net,app}$ are less dramatically affected by this type of error (Table 5). Since the method for the estimation of the WD of B/A follows the same principle as used for the work parameters, the consequences of the measuring WD's on B/A are overestimated on principle, too. A possible solution to avoid the overestimation may be to use, for example, mean measuring deviations instead of maximum ones. However, in this case one may run the risk of underestimating the effects on the analytical results. Indeed, some preliminary model calculations confirmed this problem.

Thus, the disadvantage of the methods chosen is obvious, namely the overestimation of the effects of the measuring errors on the analytical results. This is a consequence of the underlying principle. However, they allow for an assessment of the limits within which the true values of the analytical results will be found with a high degree of certainty, without the knowledge of the course of the deviations and without the need to exactly describe the course of the deviations mathematically. This is an important advantage, as often only the limits of the tolerances can be inferred from the specifications of the calibration devices. In addition, even if the course of the response was known in detail, their mathematical description may become difficult, if there are one or more factors influencing the course of the deviations. For example, it was shown that the mechanical hysteresis of the piezo-electric force transducers follows a complex pattern with the change in maximum force [1]. This hinders the behaviour to be described by simple mathematical models. Furthermore, in some cases there will remain uncertainties about the exact course of the deviations. Of course, the curved shape of punch deformation with force derived from punch-to-punch compressions may be adequately described by a polynomial of several degrees. However, it was assumed that the punches will rather behave according to Hooke's law during tabletting. When the stress acting on the punches will become more homogeneously distributed by the mobile powder bed, the detrimental effects of the poor plane-parallelism of the punch faces may diminish [5]. Obviously, the true behaviour of the punches during tabletting is not known and may lie somewhere between the two extremes.

Table 5
True and estimated deviations (D_t and D_e, respectively) involved in the determination of W_{total} and W_{exp} for the materials Tablettose®(TA) and Karion Instant Pharma®. (KI) expressed as percentage of the mean parameter values obtained from standard calculations

Parameter	Error type	Error involved in	Deviation	Maximum force 6 kN				Maximum force 17 kN			
				TA		KI		TA		KI	
W_{total}	Non-linearity	Force	D_t	− 0.6	—	− 0.2	—	− 1.0	—	− 1.2	—
			D_e	− 1.7	2.0	− 1.2	1.5	− 2.1	1.1	− 2.2	1.2
		Punch deformation	D_t	− 0.7	—	− 0.3	—	− 0.2	—	− 0.2	—
			D_e	− 1.6	0.0	− 0.5	0.0	− 5.5	0.3	− 2.5	0.1
	Hysteresis	Force	D_t	—	0.8	—	0.8	—	0.5	—	0.5
			D_e	− 0.1	3.4	− 0.0	2.5	− 0.1	2.2	− 0.0	2.5
		Punch deformation	D_t	N.a.[a]	N.a.	N.a.	N.a.	− 0.3	—	− 0.1	—
			D_e	N.a.	N.a.	N.a.	N.a.	− 0.8	0.6	− 0.4	0.3
W_{exp}	Non-linearity	Force	D_t	—	0.1	—	0.5	− 0.2	—	− 0.0	—
			D_e	− 2.7	1.7	− 3.7	2.2	− 4.7	1.5	− 6.5	2.1
		Punch deformation	D_t	− 13.8	—	− 27.4	—	− 3.4	—	− 8.6	—
			D_e	− 32.0	0.0	− 45.8	0.0	− 96.7	5.2	− 57.3	7.6
	Hysteresis	Force	D_t	− 1.0	—	− 1.3	—	− 0.7	—	− 0.6	—
			D_e	− 3.0	1.7	− 4.4	2.9	− 3.3	1.3	− 4.7	2.2
		Punch deformation	D_t	N.a.	N.a.	N.a.	N.a.	− 5.5	—	− 7.6	—
			D_e	N.a.	N.a.	N.a.	N.a.	− 10.1	16.7	− 16.7	27.6

[a] N.a., not available.

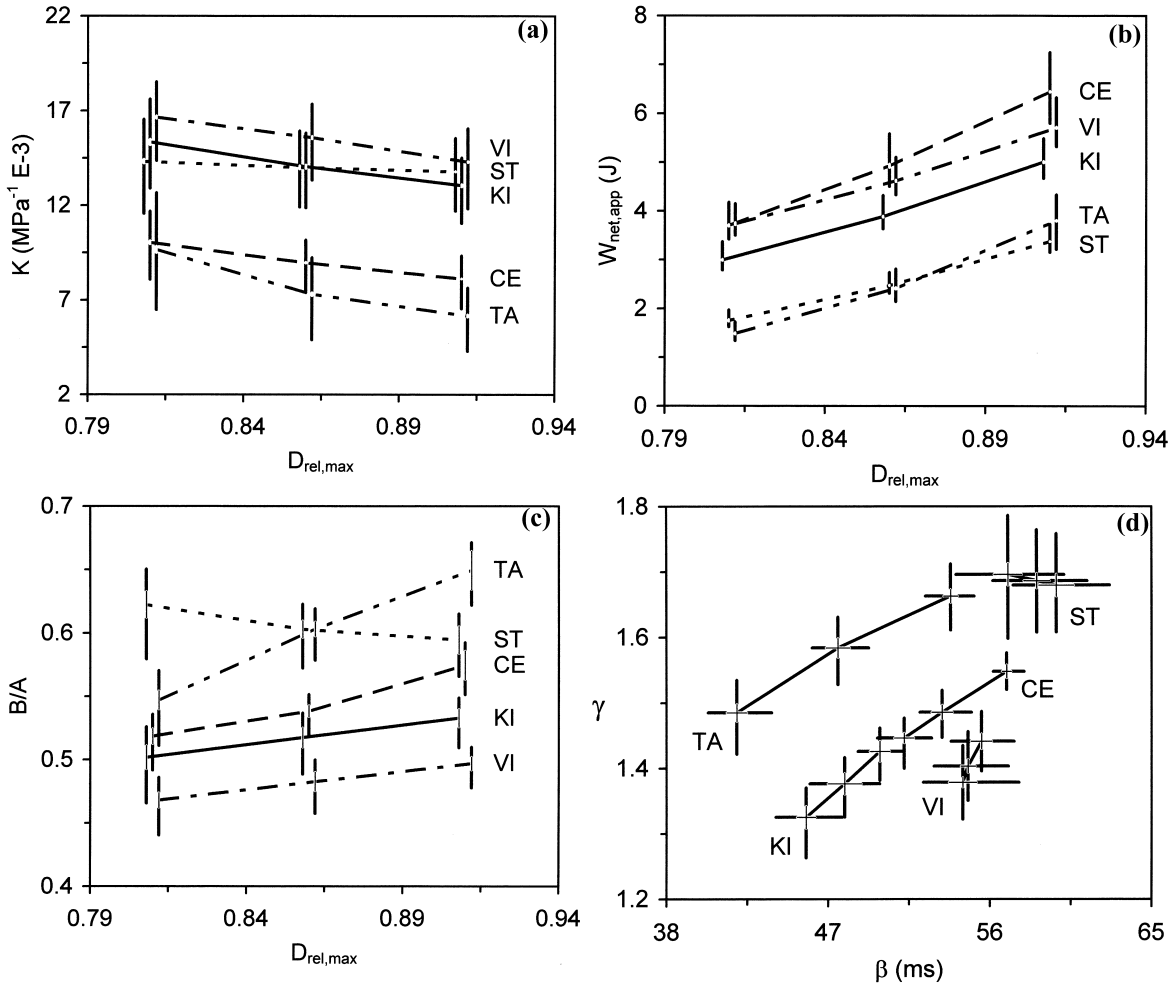

Fig. 5. Confidence intervals ($P < 0.05$) and total uncertainties of the analytical results in dependence on the materials and on the $D_{rel,max}$ for (a) the slope K of the Heckel plot, (b) the net work $W_{net,app}$, (c) the area quotient B/A, and (d) the Weibull parameters β and γ (β increases with $D_{rel,max}$). The inner error bars (free space in (a) and (b), thin lines in (c) and (d)) correspond to the confidence intervals. The outer error bars (bold lines) represent the contribution of the measuring uncertainties derived from the qualification and validation study and of the CI_{fit}. The sum of both error bars represents the total uncertainty. For clarity, the data points and the corresponding error bars are intentionally shifted horizontally slightly against each other in (a), (b), and (c).

3.2. Uncertainty of the analytical results

The confidence intervals (CI) and the total uncertainties (TD) obtained for the parameters K, $W_{net,app}$, B/A, β, and γ are presented graphically in Fig. 5. While the behaviour of all materials is clearly distinguishable from each other, when the CI's were taken as the basis for the evaluation, only the main characteristics of the substances can be identified, when the interpretation was based on the TD's. Regarding the parameter K it is possible to distinguish between easily densified materials (VI, KI, ST) and materials that exhibit a high resistance to densification (CE, TA). The materials within a group cannot be separated from each other (Fig. 5a). With respect to $W_{net,app}$ substances can be classified according to good compatibility (CE, VI, KI) or poor compatibility (TA, ST), as obvious from Fig. 5b. Again, the behaviour of the materials within a group is hardly distinguishable. With respect to B/A and the Weibull parameters β and γ, the formation of clusters is less pronounced (Fig. 5c,d). The Weibull parameters in their combined presentation offer the best selectivity, since the characteristic behaviour of the materials prevails clearly over the considerable uncertainties. Only some interferences between VI and CE must be noted. However, the latter observation leads to the expectation that small changes in the experimental conditions or in the composition of the powder bed will not be detected even by this method of analysis, when the TD was taken as the basis for the evaluation. Even if the systematic uncertainties could be considerably reduced and if the CI's and the CI_{fit}'s became the relevant uncertainties, the ability of this method to isolate slight changes in the response of the powder bed seems to be deficient. In this ideal case, $W_{net,app}$ and K may be superior to the Weibull parameters and to B/A with respect to their selectivity owing to their small random uncertainties (Fig. 5).

Table 6
Range of parameter values covered on the standard level by the selected materials tabletted to a $D_{rel,max}$ of 0.86 and relative extent of the mean absolute deviations of the parameter values with respect to the range of the parameter values[a]

Parameter	Range (unit)	CI (%)	CI_{fit} (%)	WD (%)	BD (%)	TD (%)
p_{max} (MPa)	70 − 118	0.7	0.0	1.6	1.7	4.0
t_c (ms)	166 − 218	2.3	0.0	2.2	3.4	8.0
B/A	0.48 − 0.60	5.2	0.0	11.9	0.7	17.8
β (ms)	48 − 59	5.9	1.3	8.0	2.1	17.4
γ	1.38 − 1.69	4.0	2.1	10.1	1.1	17.2
$p_{max,fit}$ (MPa)	71 − 118	0.7	0.5	3.7	1.6	6.6
W_{total} (J)	2.5 − 5.1	0.8	0.0	8.6	2.7	12.0
$W_{net,app}$ (J)	2.4 − 4.9	0.7	0.0	11.0	2.7	14.4
W_{exp} (J)	0.038 − 0.165	2.1	0.0	44.9	1.5	48.4
K (MPa^{-1})	0.0073 − 0.0156	0.9	0.4	17.2	4.6	23.1
A	0.61 − 1.20	0.6	0.4	12.9	0.7	14.6

[a] To attain the span of the uncertainty, the deviations have to be multiplied by 2.

The discussion above indicates that the extent of the uncertainties relative to the range of parameter values is the deciding factor for the assessment of the reliability of the analytical results. Although the substances selected will not cover the whole variety of tabletting behaviour, it is obvious that the parameter values are restricted to a more or less narrow range. Therefore, the mean CI's and TD's relative to the range of parameter values covered by the materials selected are summarised in Table 6 for the experiments performed at a $D_{rel,max}$ of 0.86. As the uncertainties of s_{min} and $D_{rel,max}$ cannot be expressed relative to the range of values at the fixed level given, their absolute extent should be mentioned. The mean absolute CI, WD, BD, and TD of s_{min} amount to 1, 16, 12, and 29 μm, respectively. The corresponding uncertainties of $D_{rel,max}$ are 0.001, 0.006, 0.004, and 0.011. The highest degree of selectivity of all parameters considered was observed for p_{max}, as this parameter shows the smallest relative TD's and small relative CI's in proportion to the range of the parameter values given at this $D_{rel,max}$ (Table 6). However, the quality of the selectivity changes with $D_{rel,max}$, as is the case with other parameters, too. Thus, the relative uncertainties vary by up to a few percent (absolute) in dependence on $D_{rel,max}$. Only the relative WD's of W_{exp} and K diverge at the lowest $D_{rel,max}$ by about − 20 and + 10% (absolute), respectively, from the higher levels of $D_{rel,max}$. The same holds for the relative TD's of both these parameters. The uncertainties of W_{total} behave similarly to $W_{net,app}$. W_{exp}, however, shows a much too low selectivity based on the TD's. The contribution of the uncertainty caused by the punch deformation and the inadequacy of the method to describe the consequences of this uncertainty have, of course, a share in this shortcoming.

However, the uncertainties of all analytical results were influenced by the tendency of the methods to overestimate the true effects of the measuring WD's. The extent of the overestimation depends on the type of the parameter and on the experimental conditions. This is an important aspect, as a considerable portion of the TD's must be ascribed to the WD's (Table 6). On the other hand, not all possible sources of errors in the measurement of punch forces and punch separation were considered during the qualification and validation study. In addition, the tolerances of the diameter of the die were not investigated, although they affect the relative density and thus the $D_{rel,max}$ and the Heckel parameters. Furthermore, the accuracy of the determination of the true density and of the powder weight, which have an effect on the parameters mentioned above, was excluded. An examination of the influence of the accuracy of the true density on the course of the Heckel plots is given by Krumme [8].

If the data of the different materials were obtained using different equipment or produced in different laboratories, the TD has to be used for the comparison of the data, as one must assume that the measuring errors involved vary not only in their extent but also in their nature between the experimental sets. If, however, the data were obtained using the same equipment with almost constant machine settings and experimental factors, it appears to be questionable whether the TD will be a suitable measure of the uncertainties relevant for the comparison of the data. However, the systematic contribution cannot be ignored. From Fig. 4 it is obvious that the same measuring error is reflected in different effects regarding the analytical results, since the extent of the resulting error depends on the materials. There is also evidence for the influence of the experimental conditions on the extent of the resulting error, when the effects of the non-linearity involved in punch deformation between the data obtained at different maximum forces were compared. Therefore, even constant systematic measuring errors cannot be neglected when interpreting the analytical results. Thus, the portion of the uncertainty resulting from the measuring errors that is relevant for the comparison has to be extracted. This portion corresponds to the difference between the responses of the data to be compared to these errors.

Fig. 6 compares the intervals of uncertainty derived under worst case conditions on the one hand, and best case conditions on the other for the comparison of CE with TA and VI.

While the worst case intervals provide a measure of the accuracy of the difference between the respective analytical results, the best case intervals should give a measure of their comparability under the limited variability of the experimental conditions. The worst case limits were derived from the CI's of the differences (CI_{diff}) supplemented by the differences of the remaining uncertainties combined with opposite sign. For the best case limits the differences of the remaining deviations of equal sign were added to the CI_{diff}s. As can be seen in Fig. 6, the intervals of uncertainty decrease considerably using the best case mode. However, it seems to be problematic to estimate the best case limits from the limits of maximum uncertainty of the analytical results.

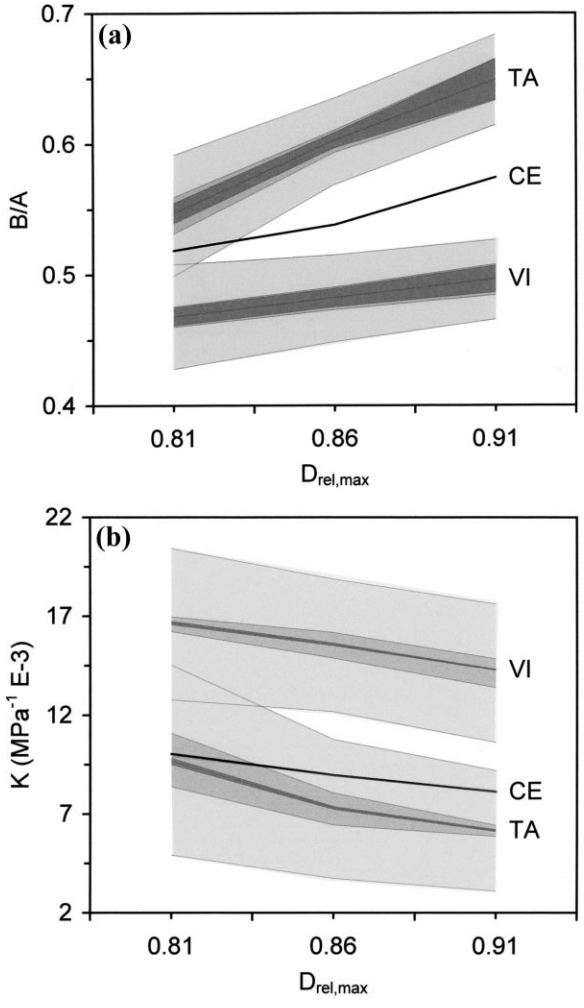

Fig. 6. Confidence intervals ($P < 0.05$), best and worst case intervals of uncertainty of the difference of the parameter values of CE and TA as well as CE and VI with respect to (a) the area quotient B/A and (b) the slope K of the Heckel plot. The intervals relevant for the comparison of CE with TA and for the comparison of CE with VI are located around the parameter values obtained for TA and VI, respectively. The course of the parameter values of CE with $D_{rel,max}$ is consequently shown without error limits. (Dark grey shaded), confidence intervals of the difference; (dark grey shaded and medium-grey shaded), best case intervals of uncertainty; and (dark grey shaded, medium grey shaded, and light grey shaded), worst case intervals of uncertainty.

Therefore, the reliability was checked using the data of the validation of the methods for predicting the WD. It was shown that the estimated differences of uncertainty can be higher than the real differences. They can, however, also be less. An underestimation of the best case limits can for example occur, when a measuring error manifests itself with opposite sign in the analytical results to be compared (Fig. 4b). A further problem is that the extent of the measuring errors will not necessarily be the same for the data to be compared. For example, the maximum width of the mechanical hysteresis involved in the force measurement changes with maximum force [1]. However, the error limits, on which the calculation of the best case limits is based, are related to the maximum measuring uncertainty observed for a broad variety of experimental conditions during the qualification and validation study. This means, the best case limits estimated this way will reflect the true relevant portions the less the more dissimilar the materials behave. Therefore, neither the worst case nor the best case limits of uncertainty will provide an appropriate basis for the interpretation of the data.

What is left are the well-tried CI's of repeated tabletting experiments. However, from the discussion above it is obvious that these confidence limits cannot be a measure of the confidence that can be set into the analytical results, as far as other uncertainties participate in the overall uncertainty. From Figs. 5 and 6 it can be inferred that the CI reflect the total uncertainty to a different degree depending on the parameters. Under best case conditions the CI_{diff} approaches on average 73, 63, and 51% of the total interval of uncertainty with respect to the parameters B/A, β, and γ, respectively. For the work parameters and the Heckel parameters the portion of the CI_{diff}'s amount to about 18–30%. Under worst case conditions the portion of the CI_{diff}'s diminishes to 16–24% for the former parameters and to 2–4% for the latter ones. Therefore, an estimation of the overall uncertainty by these CI values is not reliable. However, the validity of the CI_{diff}'s and thus the validity of the conclusions drawn changes not only with the parameters of interest but also with the experiments to be compared, as the extent of the relevant portion of the systematic uncertainty varies with the data. If the materials of interest behave quite similarly or if the variation of an experimental factor induces only minor changes in the behaviour of the material, the difference between the parameter values to be compared will be small. The difference between the responses of the data to the systematic measuring errors and thus the relevant portion of the systematic deviations of the analytical results will be small, too. In this case, the CI_{diff} reflect the overall interval of uncertainty quite well. Increasing dissimilarity in the behaviour will lead to increasing relevant portions and thus to decreasing significance of the CI_{diff}'s, but also to increasing differences between the parameter values. Thus, the inadequacy of the CI_{diff}'s may be balanced by the increasing differences between the parameter values. If the difference between the analytical results exceeds even

their worst case limit, the conclusions drawn are no longer jeopardised by the inadequacy of the CI_{diff}. However, there will remain critical cases, that is if similar parameter values result from different courses of the force or the displacement with time. This may lead to high relevant portions of the systematic uncertainty. In these cases the risk is high that the interpretation based on a statistical analysis is false. These cases are presumably no rarities, taking into consideration the deficiencies of the analytical methods. Firstly, the ability of the modified Weibull function to describe the non-statistically distributed pressure data with time is limited. Secondly, the Heckel function describes only a portion of the overall curve, the size and location of which varies with the material compressed. Thirdly, by means of integration of a curve the information about its shape is lost. Finally, normalisation ought to eliminate differences in the absolute response. Such a normalisation is inherent in the area quotient and is performed often with $W_{net,app}$ or W_{exp}.

This list of shortcomings also indicates that the selectivity of the analytical methods considered is not only restricted by the uncertainty of the analytical results, but also by their limited ability to describe the process of the build-up of the tablet from the powder bed. A method that describes the process mathematically down to the last detail may lead, on the other hand, to highly selective responses but to results that are hardly to interpret, too. However, the informational content about the process derived from the measurements of punch forces and punch displacement only and captured at some distance from the scene of the action is limited per se. Such analytical methods can give only a blurred reflection of the complex behaviour within the powder bed overshadowed by metrological problems.

4. Conclusions

Although the need was clearly demonstrated to include the uncertainties derived from the qualification and validation studies into the interpretation of the analytical results, there is no appropriate way for a routine consideration of these uncertainties. The accuracy of the results will in many cases highly overestimate the uncertainty relevant for the interpretation. The portion of the total uncertainty relevant for the evaluation of the data is, however, difficult to be quantified based on the methods chosen. Only the CI's of repeated tabletting experiments still remain as an established basis for the evaluation of the analytical results. However, statistical tests for significance based on repeated tabletting experiments cannot guarantee the correctness of the conclusions drawn with the degree of certainty supposed as long as systematic uncertainties are involved.

Therefore, uncertainties that exhibit a systematic influence on the tabletting data have to be minimised as far as possible. The methods presented in this paper may help to assess the reliability of the analytical results in the presence of the remaining unavoidable errors.

Acknowledgements

We would like to thank the companies Meggle, Parmentier, Rettenmaier, Merck, and Colorcon for the supply of the excipients.

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