European Journal of Pharmaceutics and Biopharmaceutics 47 (1999) 231–245

European Journal of Pharmaceutics and Biopharmaceutics

Research paper

The tabletting machine as an analytical instrument: qualification of the tabletting machine and the instrumentation with respect to the determination of punch separation and validation of the calibration procedures

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Received 14 July 1998; accepted 9 October 1998

Abstract

The quality of the determination of punch separation in an eccentric tabletting machine equipped with two inductive displacement transducers was carefully investigated, since this tabletting machine is used as an 'analytical instrument' for the evaluation of the compression behaviour of pharmaceutical materials. For a quasistatic calibration procedure using gauge blocks, the repeatability under standard conditions and the robustness against variations in machine settings, installation conditions, equipment and methods were examined. The readings during calibration can be easily influenced by machine parameters as a result of deficiencies in the construction of the machine and in the mode of instrumentation. The poor plane-parallelism of the punch faces has a further negative effect on the accuracy of punch separation. In addition, the response at loading to lower and higher forces as during calibration was investigated. While at loading up to 100 N, the response of the system to the gauge blocks is systematically influenced by punch separation, for slow manually applied punch-to-punch loading up to 16.5 kN at a broad range of penetration depths, no significant effects were observed in the region of interest for tabletting. To get an indication of the transferability of the calibration and the determination of punch deformation to normal operating conditions, the lateral tilting of the punches during dynamic idle runs, punch-to-punch loading, and compression of microcrystalline cellulose was analyzed. A transfer of the response derived from punch-to-punch compression to tabletting conditions seems to be possible, although this must be questioned on grounds of theoretical considerations. From all the experiments performed, a total error of about ±30 μm must be assessed for the determination of punch separation.

Keywords: Punch displacement; Punch separation; Punch deformation; Eccentric tabletting machine; Inductive displacement transducers; Calibration; Qualification; Validation

1. Introduction

In contrast to the measurement of the compression force during tabletting, a common procedure even in production, the measurement of punch displacement is only used in research and development. In production, knowledge of the punch displacement is not a prerequisite to guarantee homogeneous quality of the tablets produced – this can be realized by force measurement as well. In research and development, however, knowledge of the course of the punch separation during the tabletting event is nearly indispensable, as it provides essential information about the densification behaviour of the powder bed. This densification is not driven by means of a force, but by the movement of the punches relative to each other, and the profile of punch displacement with time is not only related to the construction of the machine [1,2] and the setting of machine parameters [3], but also to the specific resistance of the consolidating powder bed [4], which makes it necessary to actually measure the punch displacement in situ.

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0939-6411/99/$ - see front matter
PII: S0939-6411(98)00093-9

If the tablet machine is adopted to evaluate the compression properties of a particular powder bed, the machine is no longer a production tool only, for which it was constructed by the manufacturer, but also an analytical instrument. To serve for this purpose, the machine must often be equipped by the analyst with a suitable instrumentation. For such an analytical instrument, the demands on the quality of the measurements are inherently high. However, the possibilities of an expedient installation of the sensors are limited by the given geometrical and mechanical construction of the machine, and with it the achievable quality. The quality of the instrumentation depends not only on the sensor used and its electronic circumference [5,6], but also on the application of the transducers [7,8] and on the machine [2]. So, often one must make a compromise. The more important becomes the knowledge of the precision and accuracy involved in the measurement of the displacement in situ. Lammens et al. [6] performed a detailed evaluation of their displacement measuring system in an eccentric tabletting machine. They were able to limit the error involved in the determination of powder bed height to twice the resolution of the A/D-converter, corresponding to ± 21 μm. Nowadays, it becomes nearly impossible to reduce the measuring uncertainty to the limitations given by the acquisition board, because the electronic processing was considerably improved, but the construction of the tabletting machines remained essentially the same, and with it the measuring problems associated with the mechanisms of the machine.

The quality of the displacement measurement will not only influence the significance of the parameters derived from the analysis of the tabletting data, but also the repeatability and the reproducibility of the tabletting event and the final tablets, if the tabletting experiments are performed at preset maximum relative densities as usual in our group instead of maximum force levels. However, independent of the method chosen, each parameter which is not a direct function of the displacement (e.g. the work of compaction) but is related to the volume of the powder bed (e.g. the maximum relative density or the parameters of the Heckel function [9]) is not only affected by the precision and accuracy of the displacement measurements but also by the quality of the transferability of the displacement measured at some distance from the punches to the punch tip separation. Then, the calibration in situ as the connecting link between both these variables is the focus of attention. However, often the calibration is performed with gauge blocks positioned between the punches and loaded with quite low forces to avoid a damage of the gauge blocks. This method cannot totally account for the punch separation at higher forces, since the punches and other fittings between the supports of the displacement transducers are shortened by elastic deformation during loading. Furthermore, the response of the machine can change due to distortion and tilting of machine parts [10]. Such effects may participate in the differences reported between experimentally derived punch deformation and theoretically calculated ones [11, 12].

With all that in mind, the quality of the displacement measured at two inductive displacement transducers mounted in an eccentric tabletting machine, which was used as an analytical instrument, as well as the quality of the determination of punch separation at low forces and at higher loadings, were carefully investigated.

2. Methods

2.1. Equipment and installation

An eccentric tabletting machine (Hanseaten Exacta E1, W. Fette, Schwarzenbek, Germany) was instrumented with two inductive displacement transducers (type W10, class 0.2, Hottinger Baldwin Messtechnik, Darmstadt, Germany) according to Krause [1]. The inductive displacement transducers (IDTs) were mounted on aluminium supports, which were applied to the punch holders as illustrated in Fig. 1. With the selected arrangement the displacement of the upper punch relative to the lower punch was determined. The displacement was measured on the left and right of the punches, to account for the tilting expected due to the characteristic mode of motion of the eccentric shaft, which rotates in the lateral direction. The output signals of the IDTs were processed by 5 kHz carrier frequency amplifiers (KWS 3082 A, Hottinger Baldwin Messtechnik), digitized by an interface with 14 bit A/D-converter (System 500, Keithley instruments, Cleveland, OH, USA) and fed to a computer (DECpc 333, Digital).

By means of a cylindrical gauge block (according to DIN

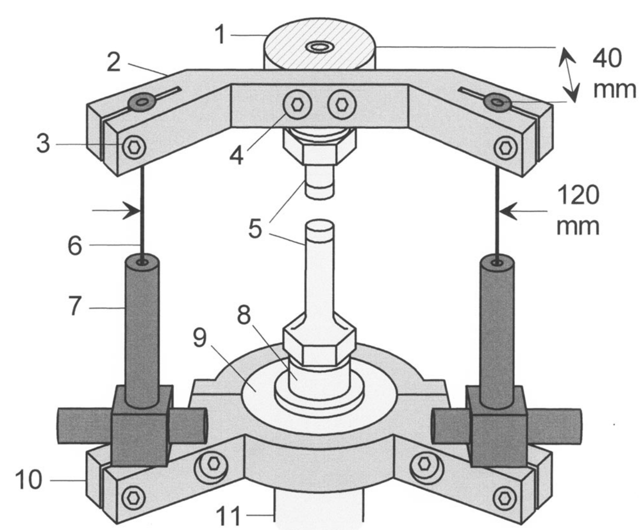

Fig. 1. Front view of the instrumented part of the tabletting machine. The die table is omitted. (1) Upper punch holder, (2) upper IDT support, (3) clamp screw, (4) fixing screw, (5) upper and lower punch, (6) guide rod of the core, (7) coil of the IDT, (8) piezo-electric load washer, (9) ejection nut, (10) lower IDT support, (11) lower punch holder.

861, degree of accuracy 1, Kolb & Baumann, Aschaffenburg, Germany) of 9 mm diameter and a height of 2 mm, the position of the cores relative to the coils was adjusted to an output signal of zero voltage. After the signals of the two IDTs were electronically averaged, the selected measuring range of ±10 mm displacement was correctly spread at the amplifier with a second gauge block of 5 mm height to attain minimum deviation from linearity within the range of 2–5 mm punch separation.

In the following text, the term 'measuring displacement' will be used for the position of the core of the IDT relative to its position at zero voltage, expressed in micrometers.

The upper and lower punch forces were measured with piezo-electric load washers, mounted between specially designed lower and upper punches and punch holders under a pre-stress of 10 kN, according to Krause [1]. The quality of the measurement of the punch forces is described in detail by Belda and Mielck [13]. Two sets of flat, sharp-edged punches of 10 mm diameter were used.

2.2. Repeatability and robustness of the calibration procedure

2.2.1. General calibration procedure

A quasistatic calibration procedure was chosen as follows: after the upper punch penetration depth was fixed to its target value, the gauge block was placed centrically onto the surface of the lower punch. The upper punch was lowered carefully on the 2 mm gauge block, until a specific upper punch force was reached, which was held constant for a few seconds, before the measuring displacement was read from the computer display. Then, the installation angle of the gauge block was rotated four times in increments of 90°. After each rotation the measuring displacement was recorded. Without changing the penetration depth of the upper punch, the procedure was repeated using a 5 mm gauge block. Thus, the routine calibration procedure is a two-point calibration only.

2.2.2. Factors influencing the results

The main subject of validating the calibration procedure was the investigation of the influence of machine settings, installation conditions, fittings and methods on the calibration results. The following factors were checked during the different stages of the validation.

- 'penetration depth': maximum penetration depth of the upper punch into the die relative to the penetration depth at contact with the 2 mm gauge block.
- 'maximum force': maximum upper punch force at contact with the gauge block.
- 'direction penetration depth': direction of the adjustment of the upper punch penetration depth, namely in direction of increasing or decreasing penetration depth.
- 'filling depth': position of the lower punch tip relative to the top of the die at a fixed maximum penetration depth of the upper punch.
- 'direction filling depth': direction of the adjustment of the filling depth, namely in direction of decreasing or increasing filling depth.
- 'twisting moment die': twisting moment of the screw which fixes the die one-sided radially.
- 'position gauge block': installation angle of the gauge block relative to the standard positions on the one hand, and relative to the lower punch on the other hand, as well as its centricity relative to the centre of the lower punch. The maximum possible shift of 0.5 mm was realized by the latter experiments.
- 'die': application of another die or renouncement of the die.
- 'punch set': utilization of the first or second punch set.
- 'gauge block': utilization of the cylindrical or of commercial rectangular gauge blocks (according to DIN 861, degree of accuracy 0, Hahn&Kolb, Hamburg, Germany). The latter experiments must be performed without the use of a die and can therefore only be compared to the respective experiments with the cylindrical gauge blocks without the die.
- 'combination gauge blocks': As only five gauge blocks were available (2, 3, 4, 5, 6 mm), these gauge blocks must be combined for the calibration of greater punch separations.
- 'averaging': averaging of the signal of the IDTs electronically or mathematically.
- 'laboratory': response obtained in situ or calibration at the laboratory of the supplier (HBM).

Only one parameter was varied at a time, while all other parameters were held constant at their standard levels. The measuring series were carried out in random order. Triplicate runs were performed.

2.2.3. Preliminary investigations

When performing a validation, the main factors influencing the calibration results must be detected first. Then, the variability of the results must be reduced by appropriate modifications with respect to the installation, the fittings, or the procedures. Factors with systematic and detrimental influence which cannot be remedied, e.g. the influence of unavoidable variations in machine settings, must then be included into the calibration procedure to attain a representative response of the system, or must be taken into consideration as error tolerances.

Therefore, in this first phase several factors which may influence the results of the calibration were investigated at coarse variation levels. These experiments were performed during the installation of the first punch set. The standard calibration procedure using the 2 mm gauge block was applied. Some experiments were corroborated with the 5 mm gauge block. The factors tested, as well as their standard and variation levels are summarized in Table 1.

2.2.4. Repeatability and robustness at constant installation of the IDTs

The main topic of this second phase was firstly to examine the repeatability of the selected calibration procedure at standard conditions, which reflects the analyst's own normal variability and the random variability of the system. Secondly, the robustness of the calibration was investigated, which provides a measure of systematic effects owing to either small or greater but necessary variations in the method parameters. The routine calibration procedure using the 2 and 5 mm gauge blocks was extended to punch separations of up to 10 mm in increments of 1 mm, to additionally allow for an assessment of the influence on the shape of the calibration curves. The factors tested, as well as their standard and variation levels are summarized in Table 2. The repeatability was checked in triplicate. The second punch set was used.

Table 1

Influence factors, standard and variation levels, and deviation from the results derived at standard conditions for the first phase of the validation

Factor	Level		d_0^a (μm)
Penetration depth (μm)	−100	SL[c]	
	−600		+2.4
	−1100		+2.6
Maximum force (N)	15		+2.5
	50		+1.8
	100	SL	
Direction penetration depth	Increasing	SL	
	Decreasing		−15.2[b]
Twisting moment die (Nm)	1		+0.6
	2	SL	
	3		+0.5
Position gauge block	+0°	SL	
	+45°		+0.8
	0° only		−0.5
	90° only		−0.2
	180° only		+0.2
	270° only		+0.3
	360° only		+0.3
	Centrically	SL	
	Front shift		−0.2
	Backward shift		+0.5
	Left shift		+0.2
	Right shift		−0.9
Die	#1	SL	
	#2		−2.3
	Without		−10.4[b]
Gauge block	Cylindrical	SL	
	Rectangular		−0.2

[a]Deviation of the zero readings at 2 mm punch separation.
[b]Significant effects.
[c]SL, standard level.

2.2.5. Repeatability and robustness at varying installation of the IDTs

Whereas the experiments described above were performed at fixed installation of the IDTs, now the transducers and their supports were removed and reinstalled, and the amplifiers were balanced anew. As before, the response of the IDTs at calibration was investigated at punch separations ranging from 2 to 10 mm in increments of 1 mm. The repeatability of the calibration was checked under standard conditions in triplicate, at installation of the second punch set. In addition, the robustness with respect to the application of other punches, the first punch set, was analyzed. The response was compared with the calibration at the suppliers laboratory. The results are included in Table 2.

2.2.6. Repeatability during tabletting experiments

The repeatability of the calibration was also examined during subsequent tabletting experiments, using the first punch set. Before and after the daily work, duplicate measuring series at 2 and at 5 mm punch distance were performed according to the standard procedure.

2.3. Accuracy of the calibration procedure with respect to punch separation

Besides the information about the quality of the measuring displacement derived from the preceding studies, which will also allow to assess the quality of the determination of the punch separation, some additional experiments must be performed. One aspect not yet covered is the homogeneity of the punch separation across the punch tip surface and, therefore, the transferability of the derived punch separation to the overall distance between the punch tips, since the smallest distance between the punch tip surfaces determines the readings during calibration.

At first, the contact behaviour was examined qualitatively by means of 'vaseline imprints': a thin film of vaseline was applied to the surface of the upper punch tip. Then the upper punch was lowered on the lower punch, by moving the fly wheel by hand until a specific force was reached. After removal of the upper punch from the surface of the lower one, an image remained on the lower punch, reflecting the contact of the punch surfaces during loading. The maximum upper punch force was set to about 16.5 kN. The loading levels were in conformity with the quasistatic punch-to-punch compressions described below, supplemented by two levels in the range of low forces. The experiments were performed with and without the application of a die using both punch sets.

To get a quantitative estimate of the error, the variation of the tablet height over the tablet area was determined. With both punch sets, tablets were prepared from Karion Instant Pharma® (Merck, Darmstadt, Germany, lot M568503), a plastically deforming material [14]. It was slightly milled in a mortar to achieve a more homogenous die fill. The sieve fraction below 315 μm was used. The die was lubricated externally with 1.5% stearic acid in ethanol and the powder was filled manually into the die. Ten tablets were compressed to maximum relative densities of 0.85 and 0.95, respectively, at a machine speed of 30 strokes/min. The minimum punch separation was set to 2 and 3 mm at each density level. The tablet height was measured with a digital micrometer (Digimatic ID-110M, Mitutoyo, Tokyo, Japan), equipped with a spherical probing head on a tablet radius of about 3.5 mm, in increments of 90° for the first punch pair used, and in increments of 45° for the second one. Obviously, no complete height profile was obtained by this procedure, but the profile derived is sufficient to reflect the main problem as deduced from the qualitative experiments.

Table 2

Influence factors, standard and variation levels, and deviations from the results derived at standard conditions for the second phase of the validation

Factor	Level		d_0^a (μm)	d_s^b (%)	+md[c] (μm)	−md[d] (μm)
Penetration depth (μm)	−120		+0.2	−0.01	+0.1	+0.8
	−100	SL[f]				
	−90		+0.6	0.00	−0.1	0.0
	+400		n.c.[g]	n.c.	−0.2	−0.4
	+900		n.c.	n.c.	−0.3	−0.1
Maximum force (N)	90		−0.1	0.00	−0.4	+0.3
	100	SL				
	110		−0.3	+0.01	0.0	−0.5
Filling depth (mm)	11.00	SL				
	10.95		−0.6	+0.02	−0.2	−0.6
	9.75		+6.0[e]	+0.03	−0.1	−0.9
	9.50		−0.2	+0.03	+0.3	−0.5
	9.25		−3.2[e]	+0.02	0.0	−0.5
	8.00		+1.4	+0.04[e]	+0.1	+0.8
Direction filling depth	Decreasing	SL				
	Increasing		−0.6	+0.02	0.0	−0.5
Twisting moment die (Nm)	1		−1.0	+0.02	−0.1	−0.2
	2	SL				
	3		−0.4	+0.01	+0.2	−0.1
Position gauge block	−45°		+0.1	+0.01	0.0	+0.4
	+0°	SL				
	+45°		0.0	−0.01	+0.4	+0.1
	Centrically	SL				
	Front shift		0.0	0.00	0.0	0.0
	Backward shift		+0.2	0.00	−0.4	+1.1
	Left shift		+0.3	−0.01	0.0	+0.5
	Right shift		+0.1	+0.01	−0.3	−0.2
Die	#1	SL				
	#2		+0.1	−0.04	+0.1	+1.5
Punch set	#1		n.c.	n.c.	+0.9	−1.5
	#2	SL				
Combination gauge blocks	2, 3, 4, 5, 6, 2 + 5, 2 + 6, 3 + 6, 4 + 6	SL				
	2, 3, 4, 2 + 3, 2 + 4, 3 + 4, 3 + 5, 4 + 5, 4 + 6		0.0	0.00	−0.3	+0.3
Averaging	Electronically	SL				
	Mathematically		n.c.	n.c.	0.0	−0.3
Laboratory	In situ	SL				
	HBM		n.c.	n.c.	+1.4[e]	+0.1
Repeatability at constant installation	#1		+0.1	+0.02	−0.2	+0.1
	#2		+0.3	−0.01	+0.1	0.0
	#3		−0.4	−0.01	+0.1	−0.2
Repeatability at varying installation	#1		n.c.	n.c.	+0.2	−0.3
	#2		n.c.	n.c.	−0.1	+0.3
	#3		n.c.	n.c.	−0.1	0.0

[a]Deviation of the zero readings at 2 mm punch separation.
[b]Deviation of the slope between 2 and 5 mm punch separation.
[c]Deviation of the mean deviation at 3 and 4 mm punch separation.
[d]Deviation of the mean deviation at 6 to 10 mm punch separation.
[e]Significant effects.
[f]SL, standard level.
[g]n.c., not to be calculated due to experimental restriction.

To assess the contribution of the punches themselves to the observations, the punches were removed from the machine. Their surface profiles relative to their base were determined on a radius of 3.5 mm in increments of 45°, on a radius of 2 mm in increments of 90°, and in the centre. The contribution of the piezo-electric load washers and the sliding disks was investigated, also.

2.4. Verification of the calibration method with respect to normal operating conditions

Clearly, it is scarcely possible to assess, how the particular reference, positioned between the punches and exerting a specific resistance to the movement of the punches, will influence the behaviour of the machine and thus indirectly the readings during calibration. As a result the response of the machine may change, when the machine operates in its normal mode. As no reference is available which can be used during normal operation, an attempt was made to analyze this problem at least qualitatively with the present measuring configuration. The change in the response of the machine was examined by means of the lateral tilting. In this arrangement, the mean displacement serves as a reference and the deviation of the displacement, measured separately at the left and right transducer, from the mean displacement can be assessed.

The response to idle runs, to the compression of microcrystalline cellulose (Avicel PH101®, FMC, Philadelphia, USA, by Lehmann&Voss, Hamburg, Germany, lot 6603) to 5 and 15 kN at a minimum punch separation of 2 mm, and to punch-to-punch loading to the same maximum upper punch forces was investigated at a machine speed of 30 strokes/min. All experiments were performed at the standard filling depth of 11 mm, the punch-to-punch compressions additionally at 9 mm. A quasistatic calibration of the single IDTs in the range of 2 to 10 mm punch separation in increments of 1 mm, was carried out to correct the response of the single IDTs for their own non-linearity. Each aspect was checked in triplicate. The second punch set was used only.

2.5. Punch displacement as a function of loading

2.5.1. Low forces

For the calibration of the IDTs a load of 100 N was selected. The choice was based on two aspects: Firstly, the load must be high enough to provide sufficient contact between the metal surfaces in order to ensure sufficient repeatability of the procedure. Secondly, the load should be so low that virtually no deformation occurs. The error brought about by the comparatively high load of 100 N was experimentally determined by means of slow, manually applied loading up to 100 N. The displacement and the force were continuously recorded. The difference between the measuring displacement at the first increase in force and at 100 N will provide an estimate of the error induced by the selected method. The whole measuring range from 2 to 10 mm in increments of 1 mm was checked using the respective gauge blocks. Three data sets for each increment were recorded. The second punch set was used only.

2.5.2. High forces

Since the calibration of the IDTs described above account only for the distance between the punch tips at quite a low force, the deformation of fittings which widens the punch separation with increasing load must be determined. The deformation of the punches and fittings between the displacement transducer supports was investigated in situ, by means of punch-to-punch loading in quasistatic and dynamic mode. The quasistatic procedure, which was applied only with the first punch set, was in compliance with the method used for the calibration of the punch forces, and is described in detail elsewhere [13]. The dynamic loading to a maximum upper punch force of 16.5 kN was performed at 30 strokes/min. The standard filling depth of 11 mm was used. The experiments were conduced in triplicate, with and without the application of a die. Additionally, the repeatability at varying installation of the IDTs and their supports was checked with the second punch set at 30 strokes/min in triplicate.

The question remains whether the behaviour of the punches at a single location within the die can reflect the response during tabletting, where the force develops over several millimetres instead of not even 100 μm. With respect to the tilting behaviour, this question was already examined in Section 2.4. However, a quantitative statement about the effects of the upper punch penetration depth on the mean measuring displacement is still necessary. In principle, two methods of varying the position of the upper punch within the die during force application are possible. Firstly, metal disks of specific heights can be inserted into the die. This method was used by Krumme [7]. Secondly, the filling depth can be varied. The former procedure has the advantage that the lower punch can remain in the same position as during tabletting. However, additional elements must be added to the system, which may influence the system in an unpredictable manner, if they do not comply with the quality of a gauge block. However, high loading of gauge blocks with metal surfaces which are not of the same quality may damage the gauge blocks and make them useless as a reference. Therefore, the latter method was applied.

Three factors were investigated: the maximum penetration depth of the upper punch, the difference between the actual penetration depth at contact with the lower punch and the setting of the maximum penetration depth, and the level of the maximum upper punch force, namely 8 and 16.5 kN. The influence of the maximum penetration depth was checked at several settings of the filling depth, which are listed in Table 3. The experiments were performed dynamically at 30 strokes/min and by slowly moving the fly wheel by hand. The latter experiments will serve as 'reference series' for the following investigations. The effect of the

Table 3

Settings of the filling depth for the levels of the actual and the maximum penetration depth of the upper punch (fd_a and fd_m, respectively) and the corresponding revolutions of the filling depth adjustment nut for the investigation of the influence of (A) the maximum penetration depth and (B) the difference between the actual and the maximum penetration depth on the measuring displacement during punch-to-punch loading

Revolutions of the nut	fd_a (mm)	A ($fd_m = fd_a$)	B (fd_m = 9 mm)	B (fd_m = 8 mm)
0	11.00	•		
$1^2/_6$	9.00	•	•	
$1^3/_6$	8.75	•	•	
$1^4/_6$	8.50	•	•	
$1^5/_6$	8.25	•	•	
$2^0/_6$	8.00	•	•	•
$2^1/_6$	7.75	•	•	•
$2^2/_6$	7.50	•	•	•
$2^3/_6$	7.25	•		•
$2^4/_6$	7.00	•		•
$2^5/_6$	6.75	•		•
$3^0/_6$	6.50	•	•	•
$3^2/_6$	6.00	•	•	
$3^4/_6$	5.50	•	•	•
$4^0/_6$	5.00	•		•
$4^2/_6$	4.50	•	•	•
$5^0/_6$	3.50	•		•

difference between the actual and the maximum penetration depth was analyzed at two levels of the maximum penetration depth of the upper punch. The two levels were chosen, according to the viewpoint of the upper punch, to simulate tabletting events with a minimum punch separation of 2 and 3 mm. The settings of the filling depth for actual penetration depth are included in Table 3. These experiments can only be conducted by moving the fly wheel manually, as the upper punch cannot pass the lower turning point. Finally, the region of interest, namely the relevant range of force in dependence on punch penetration, was checked by compression of two materials at 30 strokes/min to 8 and 16.5 kN maximum force, and minimum punch separations of 2 and 3 mm each: α-lactose monohydrate (Tablettose®, Meggle Milchindustrie GmbH, Wasserburg, Germany, lot D287 L971 A4003) and microcrystalline cellulose (Vivacel 200®, J. Rettenmaier, Ellwangen-Holzmühle, Germany, lot 80011073). Vivacel 200® represents a material with high volume reduction during compression, while Tablettose® exhibits low volume reduction. Both materials were internally lubricated with 1% magnesium stearate (Riedel- de Haen, Seelze, Germany, lot 91320). All experiments were performed in triplicate with the second punch set only.

2.6. Data acquisition

The data acquisition was controlled by ASYST software (Vers. 4.0, Keithley Instruments, Taunton, MA, USA). With respect to the quasistatic experiments 700 sets of data were recorded at a time at a rate of 1.5 kHz. Directly after the acquisition, the mean of the 700 datapoints for each channel was calculated and only these mean values were displayed and stored. A similar procedure was used during the experiments with manual moving of the fly wheel. Instead of 700, only 100 sets of data were recorded at a time and averaged. The time span between the sampled means was 220 and 104 ms for the experiments described in Section 2.5.1 and Section 2.5.2, respectively. During dynamic measurements, 700 sets of data were recorded at a time at a rate of 1.5 kHz and stored, except for the experiments described in Section 2.4, where 1000 sets of data were acquired.

2.7. Data analysis

All data analysis was performed with ASYST software.

2.7.1. Repeatability and robustness of the calibration procedure

For the evaluation of the influence of the factors tested on the calibration results, a *t*-test ($P < 0.05$) was performed. The results of each factor were compared with the results derived from the measuring series performed at standard conditions. With respect to the experiments described in Section 2.2.3, the preliminary investigations, only the deviations of the zero readings, namely the measuring displacement at 2 mm punch separation, have to be assessed. A more comprehensive evaluation was necessary for the subsequent validation study (see Section 2.2.4 and Section 2.2.5). As the routine calibration procedure is a two-point calibration only, it seems to be useful to initially extract the respective readings from the extended measuring series. The examination of the data received at 2 and 5 mm punch separation will then provide the necessary information about the influence of the factors tested on the zero readings and on the slope of the course of the measuring displacement as a function of the punch separation. Thereafter, all measuring series were corrected for their own effects, with respect to the zero readings and the slope. The deviation of all readings from the respective straight lines was calculated, from which the influence of the factors on the shape of the curves was assessed. The measuring displacement diverged positively from linearity in the range of 3–4 mm punch separation and negatively in the range of 6–10 mm. Therefore, the shape of the curves was simplistically described by two parameters: the mean deviation from the straight line at 3 and 4 mm punch separation and the mean deviation at 6–10 mm.

2.7.2. Punch displacement as a function of loading

A linear regression was calculated for the measuring displacement as a function of the mean of the upper and lower punch force. Since the deformation response was obviously not linear at low load, the regression was repeated by omitting one low force level after the other from the data, until a sufficiently linear region was reached. Regarding the evaluation of the influence of the punch set, the rate of deformation and the application of the die, a minimum force level of 3.4 kN was selected. Before regression analysis, the dynamic data were manipulated to obtain a data structure comparable with the quasistatic experiments. The data were divided into specific intervals and the mean of each interval was calculated. Thus, the number of data points was reduced and approximately the same force levels providing steps of 1.7 kN as in quasistatic experiments were obtained. For the evaluation of the experiments performed at varying filling and upper punch penetration depths, the structure of the manipulated data was altered to obtain steps of 0.5 and 1 kN below and above a force of 2 kN, respectively, and the minimum force level for regression analysis was set to 3 kN. The influence of the factors tested was assessed from the results of the regression analysis by means of a *t*-test ($P < 0.05$), except for the evaluation of the difference between the actual and the maximum penetration depth, which was analyzed by directly comparing the measuring displacement at each force level. Regarding the latter experiments, each series was compared with its own reference series obtained at the same level of actual penetration depth, which, for the reference series, is equal to the maximum penetration depth. A comparison with a fixed reference series, namely the series derived at the selected maximum penetration depth, is also possible, but applicable only for the data obtained at the same rotational angle of the nut for the adjustment of the filling depth.

The plausibility of the experimentally derived deformation response was checked by calculating the elastic response from the dimensions and the elasticity modules of the fittings. As the exact material constant is only known for the piezo-electric load washers, elasticity modules of 200 and 220 kN/mm^2 were assumed for all other fittings. Likewise, tolerances in the dimensions of ±0.1 mm were simulated to account for the uncertainty with respect to the complex geometry of the fittings. From the theoretically derived elastic deformation, the portions which must be ascribed to the upper and lower fittings were determined to be 0.39 and 0.61, respectively, with an uncertainty of ±0.01.

2.7.3. Error summation

With respect to the evaluation of subsequent tabletting experiments, the derived measuring uncertainties must be quantified and summarized. A division of the uncertainties into four categories seems to be necessary: Firstly, one must distinguish between errors that are constant during one compression event and vary only between different compressions on the one hand, and errors that vary within one compression cycle on the other hand. The former kind of uncertainty will be called ‘between-run’, the latter ‘within-run’ error. Secondly, both error types must be subdivided into random and systematic ones. The systematic within-run errors were determined separately for the compression and decompression phases.

The random between-run error was estimated from the standard deviations of the daily two-point calibrations, during the tabletting experiments for the first punch set and of the repeatability determinations during the validation study for the second one. The standard deviations of the intercepts and slopes of the recovery-functions for the repeated punch-to-punch compressions, and the standard deviation of the determination of the mean deviation from plane-parallelism of the tablets were included.

With respect to the systematic between-run error, the accuracy of the gauge blocks and the digital micrometer used for the determination of the plane-parallelism of the tablets were considered. The mean error induced by the poor plane-parallelism with respect to punch separation was not taken into account for the error limits, as the tabletting data will be corrected for the mean deviation. In addition, unavoidable measuring errors caused by the adjustment mechanism of the upper punch penetration depth, the effects observed, when the upper punch was loaded up to 100 N against the gauge blocks, systematic effects of the rotational angle of the adjustment nut for filling depth on the punch deformation estimated from the intercepts and slopes of the recovery-functions, and the uncertainty with respect to the portions in deformation which must be ascribed to the upper and lower punch, were taken into account.

For the random within-run error the resolution of the signals during tabletting were considered.

The systematic within-run error accounts for the remaining non-linearity of the calibration of the IDTs after approximation of a polynomial function of fourth degree, as well as for the non-linearity and the hysteresis of the deformation-force curve obtained from punch-to-punch compressions. Deviations from the calibration received from the supplier, with respect to the shape of the calibration curves, and detrimental effects on the deformation-force curves induced by the rotational angle of the adjustment nut for filling depth, were included. Finally, the variability in the conversion error of the A/D-converter depending on the signal difference between two consecutive channels during tabletting was added.

In addition, all four categories contain an error with respect to punch deformation, which was calculated from error propagation of relevant errors in the force and the displacement measurement.

The measuring uncertainties were expressed as absolute or relative ones, depending on the nature of the error. For example, the intercept of a recovery-function is an absolute error, the slope a relative one. All systematic errors were summarized directly, whereas the total random variabilities were derived from the square root of the sum of squares of the single variabilities. Negative and positive error limits were added separately, the absolute and relative errors as well. For the two punch sets, only those of the experimentally determined measuring errors were considered, which were derived with the respective punch pairs. The results are listed in Table 4.

Table 4

Summary of the measuring errors as derived for both punch sets

		Punch set #1			Punch set #2		
Within-run	Random	−0.755	+0.755	%[a]	−0.574	+0.574	%[a]
		−0.7	+0.7	μm[b]	−1.0	+1.0	μm[b]
	Systematic before LTP[d]	−1.032	+0.721	%[a]	−0.056	+0.368	%[a]
		−17.7	+3.4	μm[b]	−10.9	+9.1	μm[b]
	Systematic after LTP[d]	−1.032	+0.721	%[a]	−0.056	+0.368	%[a]
		−12.1	+5.0	μm[b]	−7.8	+6.1	μm[b]
Between-run	Random	−0.245	+0.245	%[a]	−0.582	+0.582	%[a]
		−0.050	+0.050	%[c]	−0.020	+0.020	%[c]
		−4.4	+4.4	μm[b]	−3.3	+3.3	μm[b]
	Systematic	−1.380	+1.274	%[a]	−7.156	+9.561	%[a]
		−0.013	+0.023	%[c]	−0.013	+0.073	%[c]
		−5.4	+4.7	μm[b]	−12.3	+11.4	μm[b]

[a]Percentage of punch deformation.
[b]Remaining errors in punch displacement and punch deformation, which cannot be expressed as relative errors.
[c]Percentage of punch displacement (without the contribution of punch deformation).
[d]LTP, lower turning point.

3. Results and discussion

From the preliminary validation experiments, two factors can be clearly identified which influence the calibration appreciably: the direction of the setting of the upper punch penetration depth and the application of the die (Table 1). Both effects were caused by mechanical shortcomings of the tabletting machine. The influence of the direction of the adjustment of the upper punch penetration depth, can be ascribed to the deflection of the eccentric hoop relative to the eccentric sheave in the backward or frontal direction, when the adjustment direction was increasing or decreasing, respectively. Since the eccentric hoop is connected to the upper punch holder, the deflection may cause tilting of the holder within its guide. As is obvious from Fig. 1, such frontal tilting cannot be compensated by the arrangement of the two IDTs. Fig. 2b illustrates the hysteresis-like behaviour, when the direction of the adjustment of the penetration depth was altered. The hysteresis in Fig. 2a, however, is superimposed by a further problem, which presumably results from the non-compensated tilting, too. The lower ‘base line’ shows a distinct deflection, which may be caused by an irregularity in the fittings participating in the adjustment mechanism. Thus, it seems to be advisable to change the mode of instrumentation. Unfortunately, the machine frame does not allow a diagonal installation of the IDTs, as described by Dietrich [15] for a Fette EXI, which provides compensation of the frontal as well as the lateral tilting. Likewise, an instrumentation which on principle prevents the readings to be influenced by a frontal tilting, cannot be applied due to the lateral securing screw of the die. In such an arrangement, the displacement transducers are installed to the left and the right of the punches, in one line with the punches, as realized by Krumme [7] in a Korsch EK0. As both methods cannot be applied at the machine used, the only consequence is to limit the setting of the penetration depth to one direction. Additionally, the influence of irregularities in the adjustment mechanism at the selected direction must be checked in the range relevant with respect to tabletting. Only minor deviations up to 4 μm were observed in the range of 8–9 mm maximum penetration depth for both punch sets.

Besides the measuring errors induced, each tilting will also cause a real change in the measuring displacement during calibration, as a consequence of the calibration method. Using gauge blocks, the displacement of the

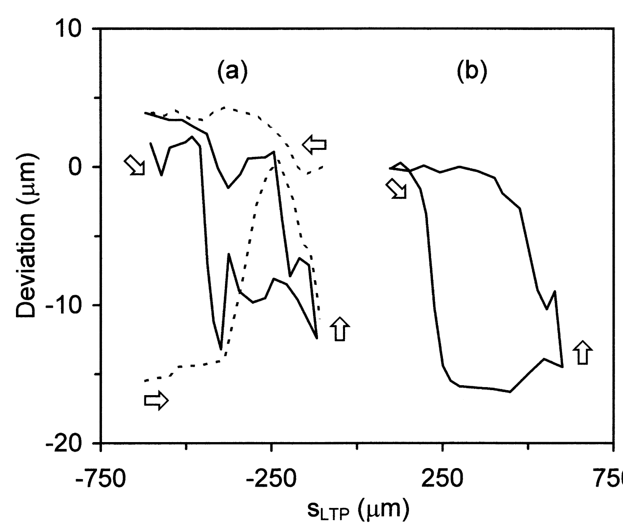

Fig. 2. Influence of the adjustment mechanism for upper punch penetration depth on the measuring displacement obtained at installation of the first punch set. The deviation of the measuring displacement from the measuring displacement at standard conditions is depicted in dependence on the displacement of the upper punch at the lower turning point (s_{LTP}). (a) The 2 mm gauge block and (b) the 3 mm gauge block were used. (—) The penetration depth was altered from increasing adjustment direction step by step in decreasing and then in increasing direction. (- - - -) Reference series with complete backward deflection (upper curve) and frontal deflection (lower curve) of the eccentric hoop.

upper punch during calibration is limited by the resistance of the steel plate. Thus, the movement of the upper punch was stopped, when the lowest point of the punch tip surface touches the gauge block with a given force. If the angle of the upper punch surface relative to the surface of the gauge block changes due to tilting, the mean displacement at contact measured by two displacement transducers in the same axis as the tilting, thus providing complete metrological compensation, must change, as the mean punch separation will change. Even if metrological compensation minimizes measuring errors during tabletting, it cannot totally preserve from systematic errors during calibration.

The application of the die provides a further example of errors induced by tilting. Ideally, the punches should be already aligned before the die is inserted. This is not the case with the machine used. As a consequence, the punches must tilt or bend during the installation of the die, in lateral as well as in frontal direction. The tilting of the punches can be made visible by means of vaseline imprints (Fig. 3). Although present with both punch sets, the expected change in the contact behaviour is clearly discernible with the second punch pair only. Note, the punch faces are by far not plane-parallel, neither before nor after the installation of the die. From the examination of the measurement of the punches and the tablets (Fig. 4), it seems that the contact behaviour without the die is determined by the punches themselves (the piezo-electric load washers and the sliding disks contribute to a minor extent), and that the situation deteriorates, when the die is installed. Thus, the deviation observed in Table 1 between the calibration with and without the die can be explained by measuring errors due to non-compensated frontal tilting, as well as calibration errors as defined above. To assure conformity between the readings during calibration and tabletting, it seems essential to conduct the calibration within the die. However, problems will arise with concave punches, as in this case the small cylindrical gauge blocks cannot be used.

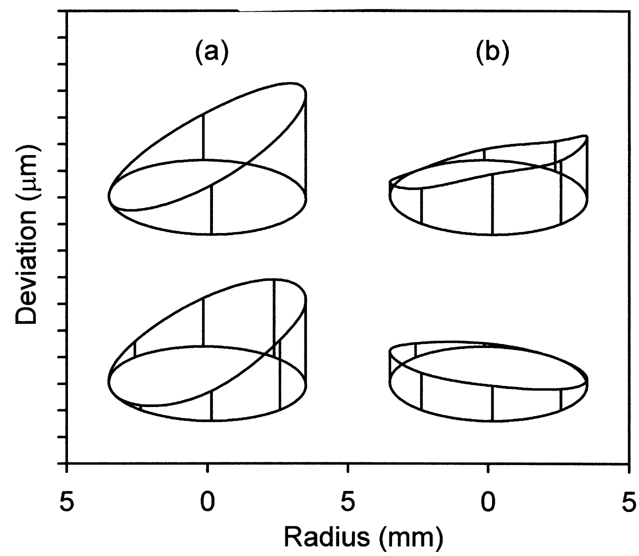

Fig. 4. Deviation from plane-parallelism of the punch faces on a radius of 3.5 mm derived from the measurements of tablets compressed to a maximum relative density of 0.85 at 3 mm minimum punch separation (upper graphs), and reconstructed from the measurements of the punches, including the piezo-electric washers and the sliding disks (lower graphs) for (a) the first punch set and (b) the second one. One interval on the ordinate corresponds to 10 μm.

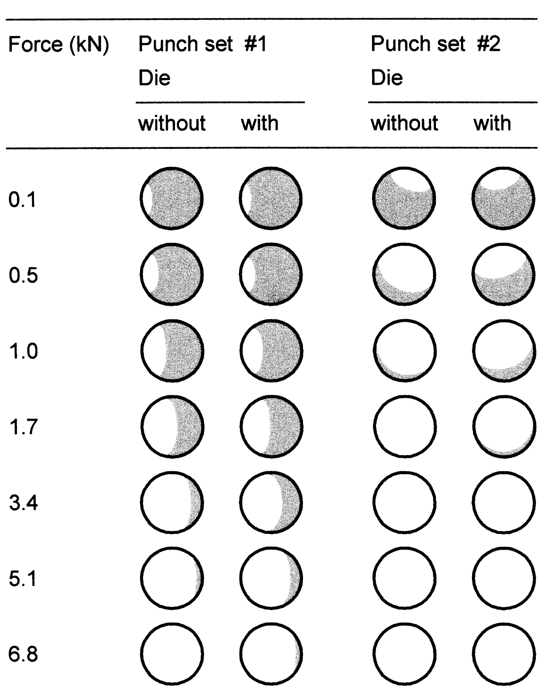

Fig. 3. Contact behaviour of the punches derived from vaseline imprints at the lower punch face (white areas) depending on the upper punch force, the punch set used, and the application of the die.

A further machine factor, the filling depth, reveals another source of variability (Table 2). From Fig. 5, the effect of the filling depth on the zero readings is obvious. A systematic change in the response of the IDTs can be observed, depending on the rotational angle of the adjustment nut. This behaviour can be explained again by tilting effects, which may arise if the drill hole of the nut is not perfectly perpendicular to the seating surface of the nut. Fig. 5 confirms a pronounced lateral tilting at specific filling depths. Non-compensated frontal tilting may participate, too. As can be inferred from Table 2, not only the zero readings, but also the slope of the measuring displacement will be partially influenced by the adjustment of the filling depth. However, the influence of the filling depth on the measuring displacement represents a problem, mainly when the die is automatically filled by the filling shoe, because it makes variations in the filling depth indispensable. As only the left IDT can be installed in this case, the effect on the response of the single IDT can, by far, be greater than that derived for the mean measuring displacement (Fig. 5).

Apart from all the unpleasant observations, the influence of which can to a great extent be eluded by limitations with respect to the settings of the machine, the standard calibra-

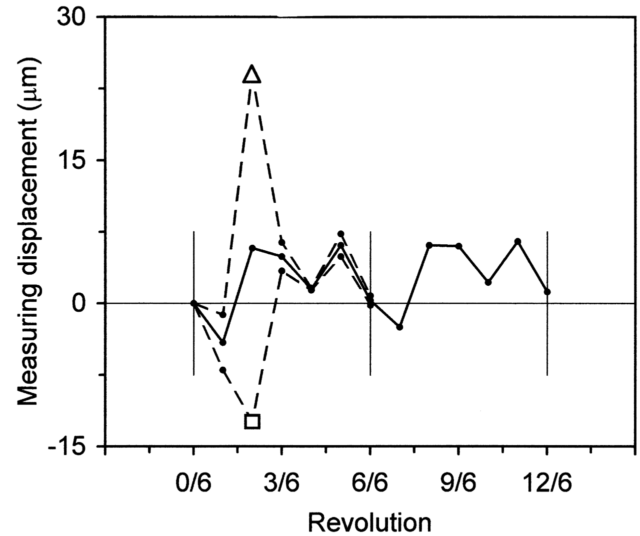

Fig. 5. Influence of the filling depth at constant setting of the penetration depth of the upper punch on the zero readings, during calibration at installation of the second punch set. Zero/6 and 12/6 revolutions of the adjustment nut correspond to 11 mm and 8 mm filling depth, respectively. (—) Mean measuring displacement. (Δ) Measuring displacement at the right and (□) at the left transducer for one full turn of the adjustment nut.

tion procedure seems to be sufficiently robust and repeatable (Table 2). That is quite an important finding, as the calibration must be checked every day during tabletting, to detect errors which may arise, for example, when the adjustment of the IDTs shifted by vibration of the running machine. Additionally, the IDTs must be reinstalled from time to time, since the amplifier cannot be balanced with the IDTs installed. Then, a high repeatability will guarantee comparability of the tabletting data and the tablets obtained over extended time periods. Furthermore, as different analysts may show slight differences in the handling, the calibration procedure must be robust at least against small variations in the performance of the calibration, to guarantee the comparability between the data received by different analysts.

In addition, the response of the IDTs seems to be quite robust against an exchange of equipment like punches and dies (Table 2, Fig. 6). Even a major change in the performance of the calibration and its setup, which can be assumed for the calibration at the manufacturers laboratory, influences the shape of the calibration curve only slightly, thus providing an indication of the reproducibility of the measurements (Table 2, Fig. 6). The comparison between the punch sets and the laboratories, however, is limited to the shape of the curves, and thus will not account for constant absolute or proportional errors in the course of the calibration curves. Such an error, which is involved definitely, is the difference between the mean punch separation and the minimum punch separation derived from calibration. From measuring the tablets, this deviation was deduced to be about 23 μm for the first and 17 μm for the second punch set, by extrapolating the values measured at 2 and 3 mm tablet height at a radius of 3.5 mm to the radius of the gauge blocks. However, the deviation may change with punch separation, e.g. as a result of the eccentric mechanism. Since the angle of the eccentric hoop relative to the upper punch holder, and with it the deflection induced on the punch holder, depends on the rotational angle of the shaft, the slope of the upper punch face may change with punch displacement. In addition, if critical factors influencing the tilting of the punches were altered, the values derived will not match the situation any more. Besides the influence on the accuracy of the calibration, the poor plane-parallelism of the punch surfaces and every change in their slopes will also affect the quality and the properties of compressed tablets, with respect to their geometry and their internal homogeneity. In practice, the density distribution within the tablets will of course be smaller than predicted from the measurement of the tablet height, as the mobility of the particles during the initial stage of compaction will level out the density gradient to some extent.

A further error inherent in the course of the calibration curves was discovered by the experiments at low forces, since the difference between the measuring displacement just at contact with the gauge block and at 100 N loading increased about linearly from 2.8 to 6.7 μm at 2 to 10 mm punch separation. A certain punch displacement during loading is not surprising, as it may be caused by flattening of surface asperities of the punches. However, a change in this displacement with punch separation cannot be explained by it. Likely, the effects observed are related to tilting, induced by the resistance of the gauge blocks which they offer to the movement of the upper punch. Relaxation by lateral or frontal tilting may change, due to an enhanced play between the upper punch and the die in the upper region of the die. This may be caused by the slightly conical upper edge of the die opening and by a reduced guidance of the upper punch tip. Additionally, lateral tilting during load-

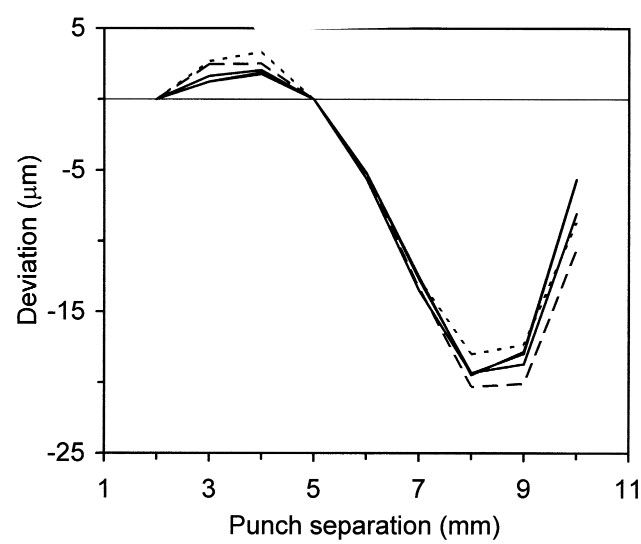

Fig. 6. Deviation from linearity for the calibration of the IDTs depending on punch separation. (—) Three repeated calibration series derived with the second punch set, (– – –) calibration series using the first punch set, (- - - -) calibration at the supplier.

ing may vary with penetration depth, as a result of an altered slope of the surface of the upper punch relative to the lower punch, caused by the eccentric mechanism as described above.

If the gauge blocks really influence the system owing to their specific resistance, the question will arise: how well will the calibration of the IDTs reflect the behaviour of the system under normal operating conditions? The experiments performed with separate acquisition of the signals of the two IDTs give an indication of the change in the response eludicated by means of the lateral tilting of the punches. Fig. 7 compares the response during an idle run, tabletting events and punch-to-punch compressions. From the results four conclusions can be drawn.

- During an idle run, the displacement of both transducers measured before the lower turning point, where they were calibrated, should not diverge from each other. However, a small deviation can be observed in Fig. 7a, which indicates that the lateral tilting of the system was slightly affected by the resistance of the gauge blocks.
- The extent of the deviation increases, when the upper punch passes the lower turning point (Fig. 7a). As the direction of tilting was reversed after the lower turning point owing to the eccentric mechanism, this observation is not surprising. As far as the tilting is metrologically compensated, the change in the response will not affect the measurement during tabletting. However, using only one IDT during automatic die filling, a systematic error in the readings must be taken into account for the tabletting data. However, the relevant range of displacement during the phase of decompression is quite small, only a few hundred micrometers.
- The behaviour of the machine changes with the magnitude of loading. A continuous change in the response can be observed up to the lower turning point, when Avicel® was compressed (Fig. 7b,c). The alteration of the direction of tilting at the lower turning point was accompanied by a sharp peak at 15 kN maximum force setting. At lower maximum upper punch force (5 kN), this peak was not observed. Besides the obvious effect on the measuring displacement, which becomes detrimental if only one IDT will be used, a change in the slope of the surface of the powder bed with punch displacement must be established. For the compression to 15 kN, a change in the slope across the punch face diameter of at most 6 μm can be deduced, considering that the punch diameter is a sixth of half the distance between the IDTs.
- Due to the small displacement during deformation, a punch-to-punch compression, from which the deformation behaviour of the punches was determined, can on principle not reflect the behaviour of the machine during tabletting (Fig. 7c–e). An examination of the deviation as a function of the force reveals, however, that the response during a punch-to-punch compression is quite similar to the response during tabletting, when the experiments were performed at the same setting of the upper punch penetration depth. However, a distinct change in the behaviour must be noted at constant filling depth. This can be inferred as well from Fig. 7, on examination of the peak height. Looking again at the events within the die, the differences between tabletting and punch-to-punch compression are limited to about 2 μm.

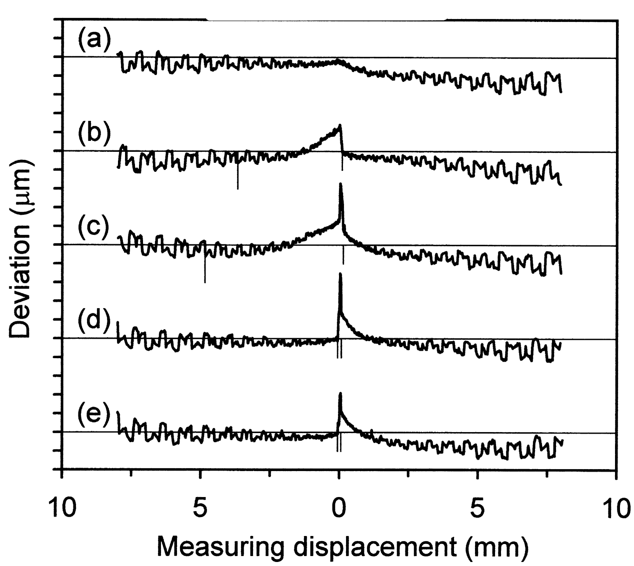

Fig. 7. Deviation of the measuring displacement at the left IDT from the mean measuring displacement in dependence on the mean measuring displacement (a) for an idle run, for tabletting of Avicel PH101® to (b) 5 kN and (c) 15 kN maximum upper punch force, and for (d) and (e) punch-to-punch compressions to 15 kN maximum force. Filling depth: (a–c,e) 11 mm, (d) 9 mm. Maximum penetration depth of the upper punch: (a–d) 9 mm, (e) 11 mm. Vertical lines below the base lines indicate the contact time during which the upper punch force exceeds 79 N, corresponding to 1 MPa in the tabletting experiments, where the force is more evenly distributed over the punch surface. One interval on the ordinate corresponds to 10 μm. The deviation has to be assessed with reference to the respective horizontal base lines.

Such a conformity between the response at tabletting and punch-to-punch compression is, however, somewhat surprising and perhaps a result of the interaction of several factors. For a punch-to-punch compression, not only an altered penetration depth of the upper punch at a given force must be stated, but also an altered stress distribution across the punch faces must be assumed. During tabletting the stress exerted on the punches is mediated by a powder bed. The initial mobility of the particles may level out the inhomogeneity of the stress distribution at the punch faces, which must be expected according to Fig. 3 for a punch-to-punch compression as a result of the poor plane-parallelism. Such an uneven stress distribution will promote tilting and bending as well as enhanced deformation of the punch tips touching, which in turn reduces the constraint to tilting. However, tilting effects, which are conceivable theoretically, will be restricted in practice by the clearance in the bearings.

However, at least the change in the deformation of the touching punch tips will question the transferability of the response during punch-to-punch loading to tabletting, since it inevitably influences the mean measuring displacement. In Fig. 8a the detrimental effect is clearly reflected in the non-linear behaviour at low forces, which increases with the deviation from plane-parallelism. Tilting and bending may participate in the initial non-linearity. Besides the major effect exerted by the punch set used, the setting of the filling depth influences the initial portion of the curves (Fig. 8b). Again, the rotational angle of the adjustment nut dominates the behaviour.

However, the slope of the curves derived from regression analysis was less influenced by the variation in the experimental conditions, because tilting effects may already occur in the initial phase of compression and since the force spreads over the whole punch face area at higher loads. Neither the punch set used, nor the rate of deformation exerts a significant effect on the slope. The rotational angle of the adjustment nut as well as the filling depth at constant rotational angle, significantly affected the slope in some cases only, although a systematic effect of the rotational angle is clearly detectable. Since the validation of the calibration of the lower punch force transducer identified the filling depth as a critical factor [13], the variability seen is not only a result of the displacement measurement or the deformation of the punches. However, all effects are small compared with the significant influence of the application of the die. Fig. 8a illustrates the change in the response, when the die is removed. Differences in the contact behaviour (Fig. 3) cannot explain the effects seen, as this difference is much more pronounced between the punch sets. The confidence intervals of the derived slopes were compared with the theoretically determined range of 3.84 to 4.56 μm/kN. All experiments performed within the die show an overlapping of the confidence intervals with the theoretical range, while the confidence intervals of the other experiments are well below this range. Therefore, the results derived from measurements within the die seem to be more plausible.

From Fig. 8a,b, a more or less pronounced hysteresis can be observed in the course of the deformation of the punches. Such a phenomenon was described in literature for various instrumentations [5–7,15,16]. Two main reasons for this behaviour are conceivable. Firstly, the hysteresis may be caused by the deficient dynamic response of the transducers or amplifiers [5,16]. Comparing the hysteresis of the dynamic and quasistatic experiments (Fig. 8a), it seems that the dynamic hysteresis of the transducer systems, the force and the displacement measuring systems, are either both small in reality or they are large but cancel each other out. Secondly, the hysteresis may be of mechanical nature. If only one IDT had been used, the hysteresis might be ascribed to the change in the direction of tilting after the lower turning point [16]. However, the application of two IDTs should actually compensate for this effect. It seems to be more likely that the change in the uneven stress distribution, as a result of the altered direction of tilting, induces a

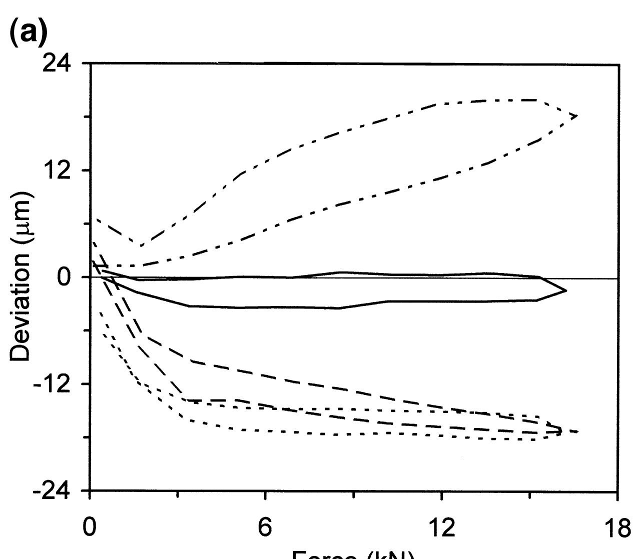

Fig. 8. Deviation of the measuring displacement from the displacement calculated by the slope of the regression function of the repeated punch-to-punch compressions at varying installation of the IDTs, using the second punch set at a filling depth of 11 mm. (a) Influence of the punch set, the rate of deformation, and the application of the die at 11 mm filling depth: (—) second punch set, dynamically, with the die, third of the repeated series, (– – –) first punch set, quasistatically, with the die, (– - - –) first punch set, quasistatically, without the die, (- - - -) first punch set, dynamically, with the die. (b) Influence of the filling depth for the second punch set at dynamic loading within the die: (—) 8.00 mm filling depth, (– – –) 8.75 mm, (- - - -) 9.00 mm. All dynamic experiments were performed at 30 strokes/min.

real change in the deformation of the punches. Furthermore, the mechanical hysteresis of the piezo-electric force transducers [13] will participate in the hysteresis seen, but can by far not account for the total extent.

As mentioned above, a punch-to-punch compression, on principle, cannot simulate the behaviour during tabletting, owing to the small displacement during deformation. The results of the experiments performed at low forces up to 100 N had demonstrated that the behaviour of the system can change with the penetration depth of the upper punch. At higher forces, systematic trends can be observed too, since the deviation in the response increased with the difference between the actual and the maximum penetration depth and with force, as illustrated in Fig. 9. However, all significant effects are out of the region of interest, which is marked in Fig. 9 by some tabletting data. The experiments at 8 mm maximum penetration depth and at low maximum upper punch force show similar results, as well as a comparison at constant rotational angle of the adjustment nut for filling depth with a fixed reference series (series at the respective maximum penetration depth). So, it can be concluded that a simple punch-to-punch compression, performed at a single location within the die, can in principle reflect the response of the machine before the lower turning point in the region of interest. Unfortunately, the behaviour of the IDTs cannot be examined for the decompression phase after the lower turning point at high differences between the actual and the maximum penetration depth. Since the decompression displacement during tabletting exceeds the deformation displacement of the punches only to a comparatively slight extent, this phase may be sufficiently represented by a simple punch-to-punch compression, also.

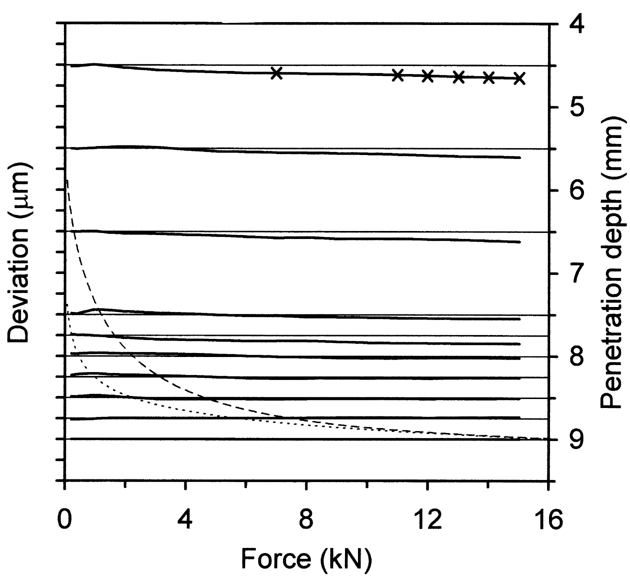

Fig. 9. Influence of the difference between the actual and the maximum penetration depth on the measuring displacement, during punch-to-punch compressions to 16.5 kN maximum upper punch force and 9 mm maximum penetration depth. The deviation of the actual measuring displacement from the respective reference series is illustrated depending on the loading and the actual penetration depth. The deviation (bold lines) has to be assessed with reference to the respective base lines (thin lines) drawn at the penetration depths where the data were obtained. (×) Significant deviations. One interval on the left ordinate corresponds to 10 μm. The region of interest, namely the range of forces in dependence on the penetration depth, is marked by tabletting data: (– – –) Vivacel 200®, (- - - -) Tablettose®.

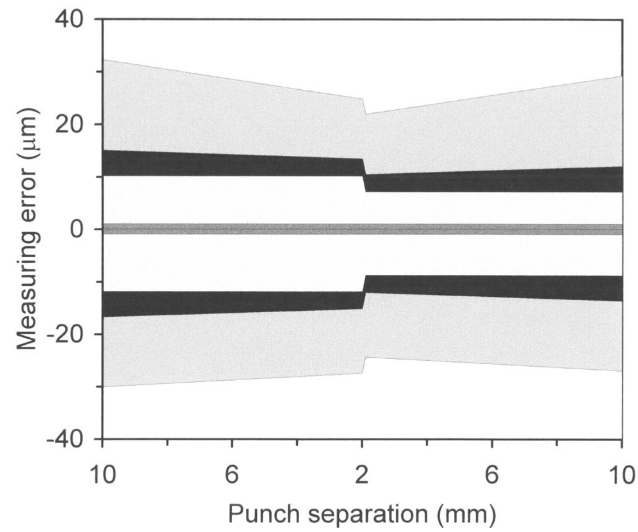

Fig. 10. Measuring errors of the punch separation for the second punch set used before and after the lower turning point, without the contribution of proportional errors related to punch deformation. Error (from central to outer region): (dark grey shaded) random within-run, (light grey shaded) systematic within-run, (black shaded) random between-run, (medium-grey shaded) systematic between-run.

The unavoidable random and systematic errors involved in the determination of punch separation are summarized in Table 4. A direct comparison of the errors with respect to the two punch sets used is, however, not possible, as some influence factors were not experimentally examined for the first one. Fig. 10 illustrates the contribution of the four error categories to the total error, which comes up to 33 μm for both punch pairs when simply added. The total contribution of the proportional errors with respect to punch deformation can be assessed to be up to 3 and 7 μm at 16 kN maximum force for the first and the second punch set, respectively. Concerning a compression of a pharmaceutical material to 16 kN maximum force with a resulting minimum punch separation of 2 mm, a percentage error of 1.6% can be estimated for the minimum tablet height. This seems to be acceptable, even if a better quality was originally assumed. However, this study does not lay claim to complete detection of all possible errors and their total extent, owing to the complex behaviour of the system. So, the true measuring uncertainty may exceed the error limits experimentally derived.

4. Conclusions

This study presents an example of how easily the measuring displacement can be influenced by machine parameters. The reasons can be found in shortcomings of the tabletting machine used, accompanied by a deficiency in the instrumentation, which is again a consequence of the construction of the machine.

The validation of the calibration procedure and the response of the machine at loading will provide valuable information on limits in the machine settings which should be kept in order to minimize the measuring uncertainty and the effects on tablet quality. Both, measuring uncertainty and variability in tablet quality, cannot only result from measuring or calibration errors, but also from a real change in the behaviour of the machine. A validation will also provide a measure of unavoidable measuring errors and variability, the knowledge of which will be necessary to assess the quality of the data derived from tabletting experiments.

Even if the construction of other machines and instrumentations will suggest less pronounced effects on punch separation as described in this article, the existence and the extent of the influence of machine factors should be experimentally investigated, to assure the quality of analytical results.

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