European Journal of Pharmaceutics and Biopharmaceutics 46 (1998) 381–395

European Journal of Pharmaceutics and Biopharmaceutics

Research paper

The tabletting machine as an analytical instrument: qualification of the measurement devices for punch forces and validation of the calibration procedures

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Received 21 August 1997; accepted 16 February 1998

Abstract

The quality of force measurement in an eccentric tabletting machine equipped with piezo-electric load washers mounted under pre-stress at the upper and lower punches, and the reliability of their calibration in situ and under working conditions were 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 the repeatability under standard conditions and the robustness against variations in machine settings, installation conditions, equipment and handling were evaluated. Two differently constructed reference load cells equipped with strain gauges were used for the calibration of the upper punch sensor. The lower punch sensor was calibrated against the upper one. Except for a mechanical hysteresis, owing to uneven stress distribution over the piezo-electric sensors, the results of the quasistatic measurements are assessed to be satisfactory. In addition, dynamic calibrations were performed. One of the strain-gauged load cells was used in addition to two piezo-electric load washers installed without pre-stress. The dynamic behaviour of all the transducers used is deficient. While for the piezo-electric sensors a significant change in the slope of the calibration function with respect to the quasistatic behaviour was observed, for the strain-gauged load cell a pronounced hysteresis must be noted. Comparing the dynamic behaviour at different profiles of rates of force development generated by variations in machine speed and by maximum force setting, the variability in the sensitivity of the upper and lower punch piezo-electric load washers is comparatively small. © 1998 Elsevier Science B.V. All rights reserved

Keywords: Upper and lower punch force; Eccentric tabletting machine; Piezo-electric washers; Strain-gauged load cell; Quasistatic calibration; Dynamic calibration; Qualification; Validation

1. Introduction

Instrumented tabletting machines are used in production, development and research. While in the former case the instrumentation is mainly used to ensure constant tablet quality, in the latter application the instrumented machine is quite often adopted as an 'analytical instrument' for the thorough physical characterization of the compression properties of pharmaceutical materials.

There will be different demands with respect to the precision and the accuracy of the measurements depending on the purpose for which the collected data are intended. In many cases, e.g. using only one machine with particular fittings and constant machine settings by the same operator, a high repeatability may be sufficient. In other cases, a high reproducibility will be necessary, e.g. to allow for the production of equivalent tablets or for the comparison of compression data obtained from different machines of the same or different type with the same or different instrumentation.

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PII S0939-6411(98)00027-7

Using the tabletting machine as an analytical instrument, high precision as well as high accuracy should be invariably expected, although it might not be essential for the object of the study. In all cases, the manufacturer specifications of the measurement devices themselves will not necessarily be representative of the accuracy and response of the transducers after mounting [1], a calibration of instrumented fittings outside of the machine no less [2]. While the machine is optimized by the manufacturer for production, the analyst quite often has to improve or develop measuring systems within a given geometrical and mechanical system. Thus, the quality and characteristics of the measuring system in situ may be influenced by the location and the method of instrumentation [3,4], as well as the design of fittings [5,6]. Deficiencies of individual machines [7] may also be involved. Distortion, tilting, bending of the instrumented fittings, induced by the mechanisms of the machine, or parallel connection of forces to securing screws may affect the response.

For the measurement of the upper and lower punch force, piezo-electric load washers have been used [1,2,8,9], mounted between the punch and the punch holder. Since the load cells are directly coupled to the punches, exchange of punches was accompanied by a reinstallation of the sensors. This may alter the response of the transducers and therefore makes recalibration necessary. Then, also the calibration procedures must be at least of high repeatability, besides the output of the measuring chain. In addition, the robustness of the calibration method should be investigated, as variations in the settings of a conventional tabletting machine as well as in the installation conditions of the fittings and the handling may not only influence the signals of the installed sensors, but also the response of the force reference utilized for calibration. As a force reference, only another more or less perfect load cell can be applied, which in turn has to be calibrated against a force standard according to conventional procedures. This load cell should be as robust as possible against non-axial, eccentric and uneven induction of forces in order to minimize errors during its application. However, the space for the installation of the reference is quite often limited, so that the choice of the reference cannot only be based on its quality.

After a suitable reference has been considered, the next dilemma will arise: which calibration procedure should be selected? Load cells are usually calibrated under static conditions. Only a few attempts have been made to develop dynamic calibration methods [10,11], and these are not yet common procedures. In this regard, a static procedure close to the convention seems to be the method of choice. On the other hand, the installed sensors are loaded dynamically during tabletting and therefore it appears to be more close to reality to conduct the calibration under normal motion. Leitritz et al. [12] compared the static and dynamic calibration at a rotary tabletting machine and found deviations of about 4% between the results of both methods. However, as long as the dynamic response of the load reference is not known with certainty, the application of this load cell in dynamic mode as a secondary load standard is questionable. Moreover, irrespective of the dynamic quality of the reference, the circumstances during normal pharmaceutical tabletting will not be sufficiently reflected in the collision of the punches and fittings during dynamic calibration. Furthermore, not only the machine speed but also the properties of the powder bed will affect the rate of development of force, the duration of load and the cushioning of the frequency response.

Therefore, a quasistatic calibration procedure following the DIN 51301 was chosen for the calibration of the piezo-electric force transducers in a small eccentric tabletting machine. As the machine is used as an analytical instrument, the calibration procedure is carefully validated with respect to its repeatability and robustness. Additionally, the dynamic sensitivity of the instrumentation is investigated. Different reference sensors are used to get an impression of the reliability of the results.

2. Methods

2.1. Equipment and installation

An eccentric tabletting machine (Hanseaten Exacta E1, W. Fette, Schwarzenbek, Germany) was instrumented with two piezo-electric load washers (labelled UP and LP, respectively, both type 9021, Kistler, Winterthur, Switzerland) with a measuring range of 35 kN. The sensors were mounted between specially designed lower and upper punches and punch holders under a pre-stress of 10 kN with the aid of a stretching screw spanning the punch holder. The construction was principally taken from [8] and is described in detail elsewhere [13]. Flat, sharp-edged punches of 10 mm diameter were used. The output signals of the load cells were processed by charge amplifiers (type 5054 A, Kistler), digitized by an interface with a 14 bit A/D-converter (System 500, Keithley Instruments, Cleveland, OH, USA) and fed to a computer (DECpc 333, Digital).

To perform the calibration of the piezo-electric load cell fitted to the upper punch, the lower punch and punch holder must be removed. Then, the reference load cell can be installed into the empty cavity between the machine frame and the die table. A simultaneous calibration of the upper and lower piezo-electric transducers (UP, LP) was not possible with a suitably constructed reference. Unfortunately, the LP can only be calibrated against the UP.

Two sensors, equipped with strain gauges, were used as force references for the quasistatic calibration of the UP: a small-dimensioned load cell (type 8431–40 000, Burster, Gernsbach, Germany) with a capacity of 40 kN (RC1) and a robustly constructed load cell (type K-6kN, GTM, Seeheim-Jugenheim, Germany) with a range of only 6 kN (RC2). The transducers were connected to a 5 kHz carrier frequency amplifier (KWS 3082 A, Hottinger Baldwin Messtechnik, Darmstadt, Germany). The calibration set-up is depicted in Fig. 1a,b.

For the dynamic experiments, only the RC1 was used as shown in Fig. 1a and linked to a DC amplifier (MGC-MC10, Hottinger Baldwin Messtechnik). Additionally, two piezo-electric force washers were utilized: a small one (type 9011, Kistler) with a range of 15 kN (RP1) and the piezo-electric load cell usually applied to the measurement of the lower punch force (RP2). Both piezo-systems were installed without pre-stress according to Fig. 1c. The piezo-electric sensor, the sliding disks and the calibration cap were gently fixed to one another with an adhesive tape applicated at their outside. The output signals were conditioned as described above. For the investigation of the influence of the time constant of the charge amplifier on the dynamic behaviour, an amplifier (type 5001, Kistler) with selectable time constants was used in combination with the UP.

2.2. Calibration of the reference load cells

The RC1 was calibrated at the PTB (Physikalisch-Technische Bundesanstalt, Braunschweig, Germany) according to DIN 51301 up to a maximum force of 20 kN. Additionally, experiments were conducted to investigate creep during loading and unloading. The error due to creeping 1 min after loading up to 10 kN or unloading from 10 kN was determined to be 0.007%.

The calibration of the RC2 was performed in the GTM-laboratories up to a maximum load of 5.25 kN, especially including low force levels of 50, 100, 150, 250 N.

The piezo-electric load cells used as dynamic references were quasistatically calibrated in situ against the RC1.

2.3. Calibration of the amplifiers and the acquisition board

The carrier frequency and DC amplifiers used for the reference load cells were calibrated against a special calibration device (K 3607, Hottinger Baldwin Messtechnik), which provides stepwise selectable resistors and thus simulates strain gauges. Each of the measuring ranges of the amplifiers used was calibrated in steps of 10%. The calibration was checked in time intervals of a few days.

A separate calibration of the acquisition board as well as the charge amplifiers was not necessary, as the characteristics of these components are included in the calibrated measuring chains. A charge calibrator (5351, Kistler) was only used to test the response of the amplifier to a rectangular signal.

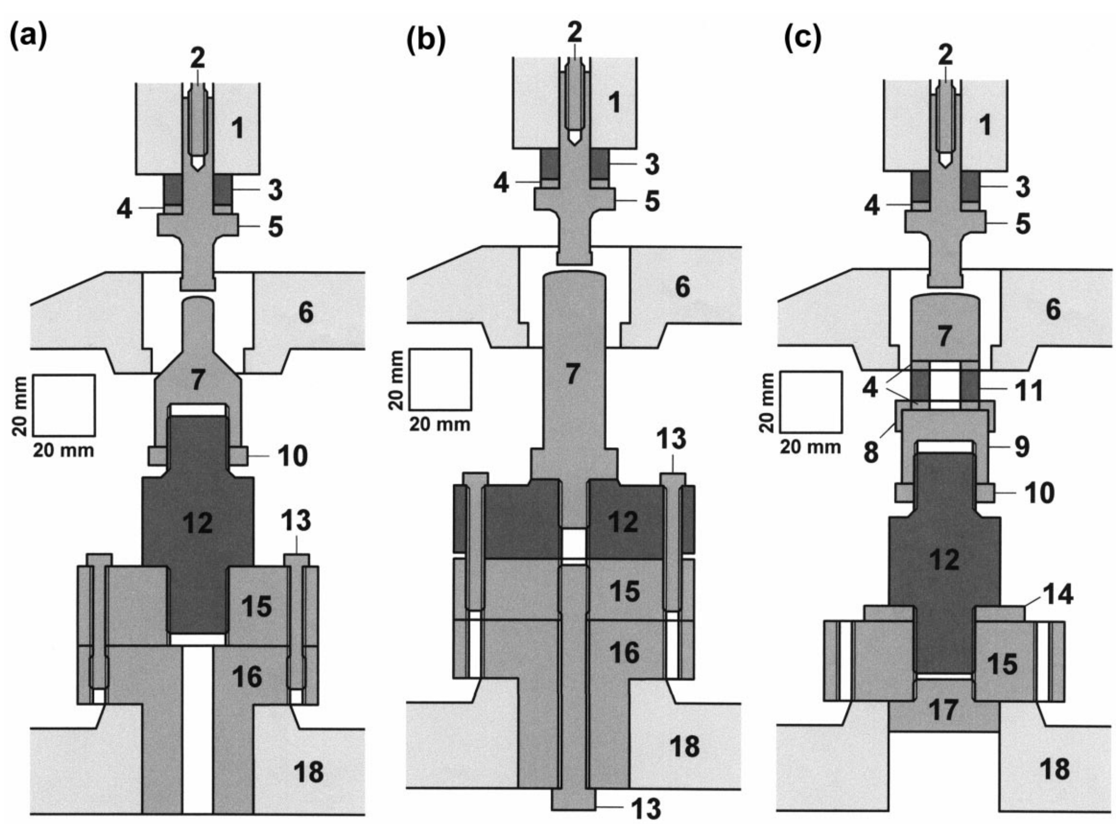

Fig. 1. Experimental setup of the (a) quasistatic and dynamic calibration with the RC1, (b) quasistatic calibration with the RC2, and (c) dynamic calibration with the RP1 and RP2. (1) Upper punch holder, (2) stretching screw, (3) UP, (4) sliding disk, (5) upper punch, (6) die table, (7) calibration punch, (8) centering ring, (9) bracket cap, (10) counter nut, (11) reference piezo-electric load washer, (12) reference load cell, (13) fixing screw, (14) washer, (15) load cell support, (16) base plate, (17) guide pilot, (18) machine frame.

2.4. Quasistatic experiments

2.4.1. General procedures

The calibration procedure was in principle in accordance with DIN 51301. Divergent from the instructions, the transducers had to be unloaded when changing the force levels, to allow for a reset of the charge amplifier. Otherwise, the drift of the amplifier would have increasingly distorted the readings. As a suitable compromise, a comparatively short loading period of 1 min was selected. During this period, the output signals change by about +1 to −3 N.

Before each measuring series, the upper punch penetration depth was adjusted to the maximum force level and the sensors were pre-loaded three times for 1 min with the selected maximum load. Between each loading phase, the sensors were unloaded for 3 min. Three minutes after the last pre-loading, the zero value was taken and then the measurement cycle was started: The transducers were loaded for 1 min at the desired level, the reading captured, then they were unloaded for 1 min, after which the next loading-unloading cycle was initiated. During the loading phase, the target force was reached within 10–30 s and then held constant, as far as possible adjusting the fly wheel by hand. The release of force was attained within 10 s maximally. At least 10 force levels per series were realized. Each series was repeated three times at different days, except for the experiments described in Section 2.4.5, where triplicate runs were carried out in succession. The sequence of the load levels was strictly ascending, when the calibration was performed before the lower turning point, and strictly descending, when calibrated after the lower turning point.

2.4.2. Factors influencing the results

The main object of validating the quasistatic calibration was the investigation of the influence of machine settings, installation conditions, equipment and handling 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 table. To hold the maximum force level constant, the penetration depth of the calibration punch was altered.
'maximum force': maximum penetration depth of the upper punch into the die table at a fixed penetration depth of the calibration punch.
'adjustment direction': direction of the adjustment of the upper punch penetration depth, namely in the direction of increasing or decreasing penetration depth.
'filling depth': penetration depth of the lower punch into the die table. To maintain the maximum force level, the penetration depth of the upper punch was altered with the filling depth.
'position relative to lower turning point (LTP)': position of the upper punch regarding its movement, namely application of the load before or after the LTP of the upper punch travel.
'position calibration punch': installation angle of the calibration punch relative to its standard positions with respect to the load cell. The installation angle of the RC1 calibration punch cannot be varied without changing the penetration depth. A full turn of the calibration punch results in an increase of its height of 1.5 mm. The penetration depth of the upper punch was altered to keep the maximum force at its standard level.
'position calibration cap': installation angle of the calibration cap of the lower punch relative to its standard positions with respect to the lower punch. The influence of the installation angle relative to the lower punch was also checked.
'position load cell': installation angle of the load cell relative to its standard positions as well as its centricity relative to the upper punch. To simulate eccentricity, the load cell was shifted by about 0.5 mm to the left or to the back.
'position base plate': installation angle of the base plate relative to its standard positions with respect to the load cell.
'position sliding disk': installation angle of the sliding disk relative to its standard position.
'position UP': position of the UP relative to its standard position.
'calibration punch': utilization of another calibration punch.
'sliding disk': application of another sliding disk.
'piezo': application of another piezo-electric load cell. Instead of the UP the LP was installed.
'upper punch': application of two other punches: one with the same tip diameter as the standard punch, and another with a diameter of 14 mm, respectively.
'calibration cap': calibration of the LP without the cap.
'die': installation of a die.
'load cell': utilization of the RC1. The maximum force and the force levels are chosen equivalent to the RC2 series.
'pre-stress': level of pre-stress of the piezo-electric transducer.
'sequence of force levels': sequence of the different force levels, namely in strictly increasing or decreasing order, both before the LTP.
'constance of force': manually applied forces cannot be held exactly constant over an extended time period. Variations of up to 20 N were observed. Therefore, only a situation worse than under the operator's 'normal' handling was simulated by slightly loosening the counterpressure after reaching the desired load level, leading to a decrease in force of up to 60 N.

Only one factor was varied at a time. All other factors were held constant at their standard levels. The measuring series were conducted in random order.

2.4.3. 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 of 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 procedures, to attain a representative characteristic of the system.

Therefore, in this first phase, several factors were investigated at coarse levels. The factors tested as well as their standard and variation levels are summarized in Table 1. Each factor was checked in triplicate.

2.4.4. Repeatability and robustness at constant installation of the upper punch

From the results of phase one it was concluded, that the main procedure was generally suitable for the calibration of the UP. Only the position of the reference load cell and the position relative to the LTP must be taken into consideration. Therefore the method was altered slightly: Firstly, the position of the reference was varied between the three measuring series. The installation angle for the RC1 and the RC2 was set to 0°, –120°, +120° and to 0°, –90°, +90°, respectively. Secondly, each measuring series was performed at first before the LTP and, immediately afterwards, after the LTP, each in at least 10 steps.

Due to the alterations in the calibration procedure, some factors already investigated during the preceding experiments had to be checked once again. However, the main topic of this second validation phase was the robustness of the chosen procedure against unavoidable variations in machine settings, small variations of the installation conditions of the fittings, and the handling as well as the repeatability under the ‘normal’ operator variability. This then may give an indication of the reproducibility. The factors tested and their levels are summarized in Table 2. The repeatability was checked under standard conditions in triplicate.

2.4.5. Repeatability and robustness at varying installation of the upper punch

Whereas the experiments described above were con-

Table 1

Influence factors, standard and variation levels, and results of the *t*-test for the first phase of the validation of the UP

Factor	Level			Significance of effect	
	RC1	RC2		RC1[a]	RC2[b]
Penetration depth (mm)	8.5	8.3	SL		
	7.0	6.3		+	–
		5.3			–
		4.1			–
Maximum force (kN)	16.5	6.0	SL		
	11.0	4.5		–	–
	6.0	3.0		–	–
Adjustment direction	Increasing	Increasing	SL		
	Decreasing	Decreasing		–	–
Position relative to LTP	Before	Before	SL		
	After	After		+	+
Position calibration punch	0°	0°	SL		
	–90°			–	
	–180°			–	
	–270°			–	
Position load cell	0°	0°	SL		
	–90°	–90°		–	–
	–120°			+	
	+120°			–	
	+90°	+90°		–	–
Position base plate	0°	0°	SL		
	–120°	–90°		–	–
	+120°	+90°		–	–
Die	Without	Without	SL		
	With			+	
Sequence of force levels	Increasing	Increasing	SL		
	Decreasing	Decreasing		–	–

[a]RC1, reference load cell 40 kN.
[b]RC2, reference load cell 6 kN.
SL, standard level.
+, significantly different from the standard ($P < 0.05$); –, not significantly different from the standard ($P < 0.05$).

Table 2

Influence factors, variation levels, results of the *t*-test and recovery for the second phase of the validation of the UP at constant installation of the upper punch

Factor	Level		Significance of effect		Recovery (%)	
	RC1	RC2	RC1	RC2	RC1[a]	RC2[b]
Penetration depth (mm)	7.0	6.0	–	–	100.07	100.04
Maximum force (kN)	8.5	3.0	+	+	99.65	99.66
	8.5	3.0	+	–	99.81	100.05[c]
Adjustment direction	Decreasing	Decreasing	–	–	99.92	100.02
Position calibration punch	–10°		–		99.96	
	+10°		–		99.97	
Position load cell	–10°	–10°	–	–	99.93	100.02
	+10°	+10°	–	–	99.97	99.99
	Left shift	Left shift	–	–	99.99	100.04
	Backward shift	Backward shift	–	–	100.03	100.04
Position base plate		–10°		–		100.00
		+10°		–		100.04
Calibration punch	#2	#2	–	–	99.98	100.00
Load cell		RC1		+		99.57
Constance of force	Worse	Worse	–	–	99.99	100.02
Repeatability	#1	#1	–	+	100.03	99.69
	#2	#2	–	–	99.96	100.00
	#3	#3	–	–	100.00	99.99

[a]RC1, reference load cell 40 kN.
[b]RC2, reference load cell 6 kN.
[c]*t*-test and recovery were calculated without the data of the maximum load level.
+, significantly different from the standard ($P < 0.05$); –, not significantly different from the standard ($P < 0.05$).

ducted during fixed installation of the upper punch, now the upper punch was removed and reinstalled several times in the course of this phase. The robustness of the characteristic of the UP against small variations in the installation conditions of the fittings and the interchange of components was thus examined. Additionally, the repeatability under nearly the same circumstances as prior to the first removal of the upper punch, adopted as the standard conditions, was checked in triplicate. From the results, the necessity of recalibration after punch exchange can be assessed. The factors tested and their levels are summarized in Table 3.

2.4.6. Repeatability and robustness at constant installation of the lower punch

The calibration procedure described in Section 2.4.4 was adopted for the calibration of the LP. The installation angle of the calibration cap was varied between the three measuring series to 0°, –120°, +120°.

The robustness of the calibration to variations in machine settings, installation conditions, and handling was investigated. The repeatability was checked in triplicate. The factors tested as well as their standard and variation levels are summarized in Table 4.

2.5. Dynamic experiments

The dynamic characteristics of the UP and LP, and the suitability of the references used (see Section 2.1) for a proposed dynamic calibration were investigated.

Before and after the dynamic measurements, the piezoelectric load cells were calibrated quasistatically against the RC1, according to the quasistatic standard procedure described above (Section 2.4.1 and Section 2.4.4). Owing to the lack of space, the installation angle of the RP1 and RP2 must be held constant between the triplicate measuring series. Only the installation angles of the force-distributing cap and the sliding disk were varied according to the positioning angles of the RC1. At each installation two quasistatic series were performed.

Table 3

Influence factors, variation levels, results of the *t*-test and recovery for the second phase of the validation of the UP at varying installation of the upper punch

Factor	Level	Significance of effect		Recovery (%)	
		RC1	RC2	RC1[a]	RC2[b]
Position sliding disk	–90°	–	+	100.19	100.52
	+90°	–	+	99.82	100.11
Position UP	–5°	–	+	100.07	100.35
	+5°	+	+	100.30	100.45
Sliding disk	#2	–	+	100.14	100.51
Piezo	LP	+	+	106.39	107.16
Upper punch	#2	+	+	100.32	100.61
	#3	–	+	99.85	99.59
Pre-stress (kN)	9.07	–	–	99.99	100.20
	10.03	–	+	100.18	99.92
Repeatability	#1	–	–	100.16	99.96
	#2	–	+	100.11	100.40
	#3	+	–	99.73	99.60

[a]RC1, reference load cell 40 kN.
[b]RC2, reference load cell 6 kN.
+, significantly different from the standard ($P < 0.05$); –, not significantly different from the standard ($P < 0.05$).

Table 4

Influence factors, standard and variation levels, results of the *t*-test and recovery for the second phase of the validation of the LP at constant installation of the lower punch

Factor	Level		Significance of effect	Recovery (%)
Maximum force (kN)	15.5	SL		
	8.0		–	99.91
	8.0		–	99.98[a]
Adjustment direction	Increasing	SL	–	
	Decreasing		–	100.03
Filling depth	11.05		–	99.94
	11.00	SL		
	10.95		–	99.92
	10.5		+	99.74
	9.5		–	99.83
	8.0		–	99.92
Position calibration cap	0°	SL		
	–20°		–	99.99
	+20°		–	99.96
	–120° only		–	100.01
	0° only		–	100.01
	+120° only		–	99.97
Calibration cap	With	SL		
	Without		–	99.92
Constance of force	Normal	SL		
	Worse		–	99.95
Repeatability	#1		–	100.06
	#2		–	100.00
	#3		–	99.94

[a] *t*-test and recovery were calculated without the data of the maximum load level.

SL, standard level.

+, significantly different from the standard ($P < 0.05$); –, not significantly different from the standard ($P < 0.05$).

As before, the LP must be calibrated against the UP. Therefore, the dynamic behaviour of the LP can only be assessed relative to the behaviour of the UP. However, the utilization of the LP without pre-stress as a dynamic reference for the calibration of the UP may give information about the influence of the stretching screw between punch and piston on the dynamic behaviour of the sensor.

The dynamic experiments were performed at machine speeds of 17 and 30 strokes/min. The speed was set electronically via a frequency converter (type 613 E1C, Lenze Aerzen GmbH, Hameln, Germany). The maximum loads of the quasistatic series were fixed at 6 and 12 kN. The machine settings were maintained during the dynamic loading, leading to an increase in maximum force up to about 1 kN. Between the two respective quasistatic calibrations, two dynamic data sets per speed level were sampled. Thus, six runs were obtained for each condition.

As a result of both the variation in machine speed and in maximum load, a comparatively broad 'velocity' spectrum with respect to the force development was obtained as depicted in Fig. 2a. Of course, none of the profiles created will reflect the asymmetrical behaviour during the compression of pharmaceutical materials. Therefore, asymmetrical force-time profiles were created by the following procedure. The upper punch was placed closely above the calibration punch to prevent the normal acceleration of the movable machine parts before the punches come into contact. As the frequency converter mode caused intensive noise in the recorded data when started directly before the acquisition, the machine was run in its normal operation mode at its pre-setting of 25 strokes/min. For comparison, data were generated by the standard procedure, namely by arresting the upper punch at its upper turning point before starting the machine. The modified profile shown in Fig. 2b is of course more comparable to the force development during tabletting, but it can represent at best one of the scores of possible variations. Unfortunately, the results of the regression analysis of these data will become questionable, as not only the duration but also the number of datapoints varied considerably between the loading and the unloading phase. However, the structure of the dynamic data with its uneven frequency distribution of the force levels is a general problem with respect to the regression analysis.

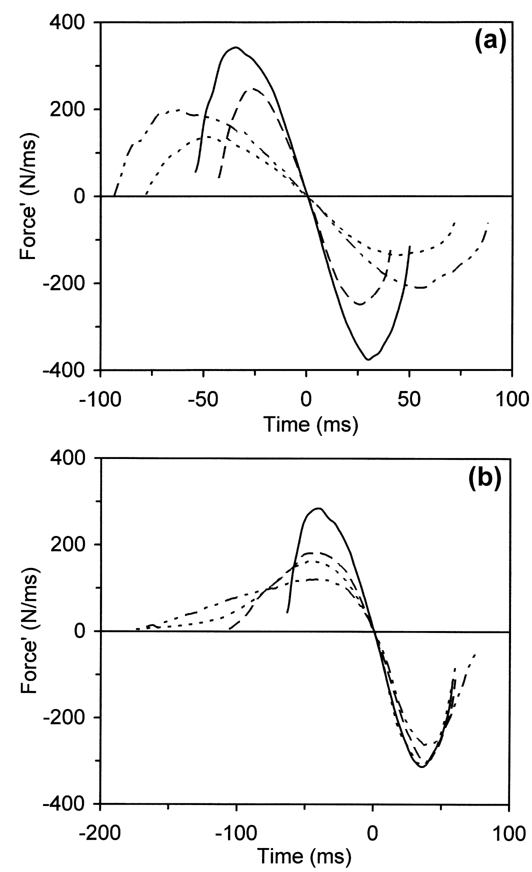

Fig. 2. First derivative of the force (force′) calculated from the signal of the RP1 during dynamic loading at different settings of machine speed and maximum force. For clarity, only the data between the end of the initial yield of the bearings and the take-off of the upper punch are shown. Data were smoothed. (a) (——) 30 min^{-1}, 12 kN; (– – –) 30 min^{-1}, 6 kN; (– - - –) 17 min^{-1}, 12 kN; (- - -) 17 min^{-1}, 6 kN. (b) 25 min^{-1}, 12 kN: (——) upper punch positioned at its upper turning point before starting the machine, (– – –), upper punch positioned closely above the calibration punch before starting the machine, (– - - –) compaction of 300 mg Starch 1500®, (- - -) compaction of 300 mg Parmcompress® (Dicalciumphospate dihydrate).

2.6. Data acquisition

The data acquisition was controlled by ASYST software (Keithley Instruments, Taunton, MA, USA). For the calibration of the amplifiers and for the quasistatic calibration experiments 700 sets of data were recorded at each level at a rate of 1.5 kHz. Directly after the acquisition, the mean of 700 datapoints for each channel was calculated and only these mean values were displayed and stored. Thus, the random error due to the noise of the signals was minimized, since the number of the data sets created, about 20 levels in force, is small. During the dynamic measurements 700 sets of data were recorded a time at a rate of 1.5 kHz and stored.

2.7. Data analysis

All data analysis was performed with ASYST software.

2.7.1. Regression analysis

In general, polynomials of the third degree were used for the regression of the quasistatic calibration data, as the characteristics of the UP and LP obviously were non-linear. For the calibration of the amplifiers linear regression was sufficient in most cases. Considering the increasing complexity of the inverse function, necessary for further data processing, with increasing polynomial degree, the regression was carried out with the reference as the dependent variable.

2.7.2. Quasistatic experiments

For the evaluation of the significance of the influence of the factors tested and their quantitative effects on the calibration results, the recovery was estimated by linear regression through the force calculated as a function of the reference force. The conversion of the UP or LP signals into the 'calculated force' was performed with the sensitivity derived from the data sets regarding the repeatability under standard conditions. Normally all nine repeated runs were used, except for the experiments with the RC2 described in Section 2.4.4, where only the last six series were included. The recovery was calculated separately for each measuring series. From the results, the means and the confidence intervals ($P < 0.05$) of the regression coefficients for the triplicate determinations were obtained. The confidence interval derived for each coefficient was compared with the respective confidence interval calculated from the measuring series under standard conditions. The influence was considered to be significant, when only one coefficient, the intercept or the slope, was significantly different from the respective coefficient of the standard calibration.

2.7.3. Dynamic experiments

Firstly, the quasistatic sensitivity was calculated for the systems: RP1(UP), RP2(UP), RP1(RC1), RP2(RC1), RC1(UP) and UP(LP) (function: $y(x)$).

The dynamic data were treated with a median filter to eliminate sharp noise peaks caused by the frequency converter, the data were corrected for the conversion delay between the consecutive acquisition channels, and the force was calculated using the quasistatic sensitivity. For the calculation of the recovery only the data ≥1 kN and equal or lower the maximum force level of the respective quasistatic data (6 or 12 kN) were selected. The recovery of the quasistatic data was determined within in the same range. The linear regression was performed for each data set separately, and the means and the confidence intervals ($P < 0.05$) of the slopes and intercepts of six such data sets were determined.

2.7.4. Error summation

With respect to the evaluation of subsequent tabletting experiments, the derived measuring uncertainties of the several devices used 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 errors were estimated as the standard deviation (SD) between the intercepts and slopes of the recovery-function from repeated measurement series. The calibration of the reference load cells, the carrier frequency amplifier, and the installed piezo-electric force transducers were considered.

With respect to the systematic between-run error, six kinds of errors were taken into account: (1) the rotational symmetry, namely the variability in dependence on the installation angle of the RC1 during their calibration and during the calibration of the UP; (2) significant effects with respect to the robustness of the quasistatic calibration of the UP and LP at constant installation, where the variability of both, items (1) and (2), was derived from the recovery as the maximum positive and negative deviations of the intercept and slope; (3) the dynamic error received from the intercept and slope of the recovery of the dynamic experiments at 30 strokes/min and 12 kN with respect to the RC1; (4) the mean drift of the UP and the LP during quasistatic calibration; (5) the conversion error of the A/D-converter in dependence of the signal difference between two consecutive channels during the calibration of the UP, LP and carrier frequency amplifier, determined to be 0.01%, which can be assumed to be nearly constant during a calibration run; (6) the accuracy of the amplifier calibrator, adopted from the manufacturer specifications.

The random within-run variability includes the resolution of the signals during calibration of the RC1, UP, LP and carrier frequency amplifier and during tabletting. Addition-

Table 5

Summary of the measuring errors with regard to the calibration of the upper and lower punch force; at low force (1 MPa) and in the total selected measuring range

		UP			UP			LP		
		'1 MPa'			Total range			Total range		
Within-run	Random	–2.4	+2.4	N	–4.3	+4.3	N	–5.3	+5.3	N
		–0.060	+0.060	%	–0.006	+0.006	%	–0.006	+0.006	%
	Systematic	–5.0	+1.8	N	–47.9	+2.6	N	–25.0	+49.0	N
	Before LTP	–0.000	+0.010	%	–0.003	+0.012	%	–0.012	+0.003	%
	Systematic	–0.1	+8.3	N	–35.9	+44.0	N	–43.8	+57.0	N
	After LTP	–0.000	+0.021	%	–0.003	+0.014	%	–0.014	+0.003	%
Between-run	Random	–0.1	+0.1	N	–0.6	+0.6	N	–1.5	+1.5	N
		–0.019	+0.019	%	–0.043	+0.043	%	–0.074	+0.074	%
	Systematic	–7.7	+10.9	N	–3.0	+19.2	N	–9.9	+22.7	N
		–0.025	+0.035	%	–1.287	+0.063	%	–0.762	+0.398	%

ally, the SDs between the mean residuals of the respective recovery functions were determined from repeated measuring series. The variability in the drift was also considered for the quasistatic calibration of the UP and the LP.

The systematic within-run error accounts for the hysteresis and the remaining non-linearity with respect to the chosen polynomial function derived from the calibration of the four measurement devices. The maximum and minimum residuals of the regression were selected. Detrimental effects on hysteresis and non-linearity by variations in the calibration procedure (robustness, rotational symmetry) of the UP and LP were not included since they were not significant. Finally, the variability in the above mentioned conversion error during tabletting must be taken into consideration.

All systematic errors were summarized directly, whereas the total random variability was derived from the squareroot of the sum of squares of the single variabilities. Negative and positive error limits were added separately, the absolute and relative errors as well. The results are listed in Table 5. The measuring error at a low upper punch force corresponding to about 1 MPa necessary for the determination of the contact time of a tabletting event was determined separately. The quasistatic calibration results of the respective RC2 series at 50 and 100 N were used instead of the RC1 series.

3. Results and discussion

3.1. Quasistatic experiments

As is obvious from Table 1, the main problem associated with the measurement of the upper punch force is the deviation between the data obtained before and after the LTP. In Fig. 3, distinct hysteresis between the readings before and after the LTP is discernible. As both calibrations with RC1 and RC2, respectively, in spite of the large differences in their construction, demonstrate nearly the same extent of hysteresis, one may assume, that this phenomenon is mainly attributable to the UP. This is confirmed by the fact, that the width of the hysteresis changes with the installation of the UP, as evident from Fig. 4c. From the latter, another conclusion can be drawn. Creeping or thermodynamic effects cannot be exclusively responsible for the hysteresis. Presumably, the differences before and after the LTP may to a great extent be based on mechanical effects owing to an uneven loading of the UP. When the upper punch passes the LTP, the stress distribution on the UP may be altered due to slight tilting effects caused by the characteristic mode of motion of the eccentric shaft. This then may lead to a change in sensitivity. The observed effects are not artefacts of the UP or the mode of installation, as the LP is also susceptible to this source of error, irrespective of whether it was installed at the upper or lower punch holder or used without pre-stress. When indeed this hysteresis is caused by mechanical shortcomings of the piezo-electric transducers used, then not only the calibration but also the measurements during tabletting will be affected. However, the magnitude of the influence may change under tabletting conditions. Firstly, the application of a die may decrease the tilting proposed. Indeed, it can be observed, that the hysteresis diminishes when the calibration is performed

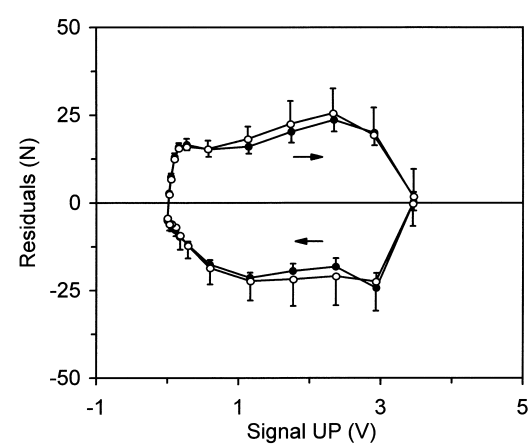

Fig. 3. Mean residuals of the regression analysis of quasistatic calibration data of the UP. At each force level the confidence intervals ($P < 0.05$) of six measuring values are shown. The regression was performed separately for the RC1 and RC2 series. Reference load cell: (○) RC1, (●) RC2.

with a die as illustrated in Fig. 4b. Concurrently, the overall sensitivity is altered (to about 0.2%). Whether these effects result from parallel connection by friction of the upper punch to the die or from the response of the UP to a more homogeneous stress distribution, remains open. Secondly, during powder compaction, the force induction to the upper punch is not exerted by a selective small contact area with a bulged steel cap (Fig. 1(7)) but by a more or less flexible powder bed. This may alter the stress distribution and the tilting of the punch. Therefore, transferring the response of the UP at calibration to the response during real tabletting without restrictions is questionable.

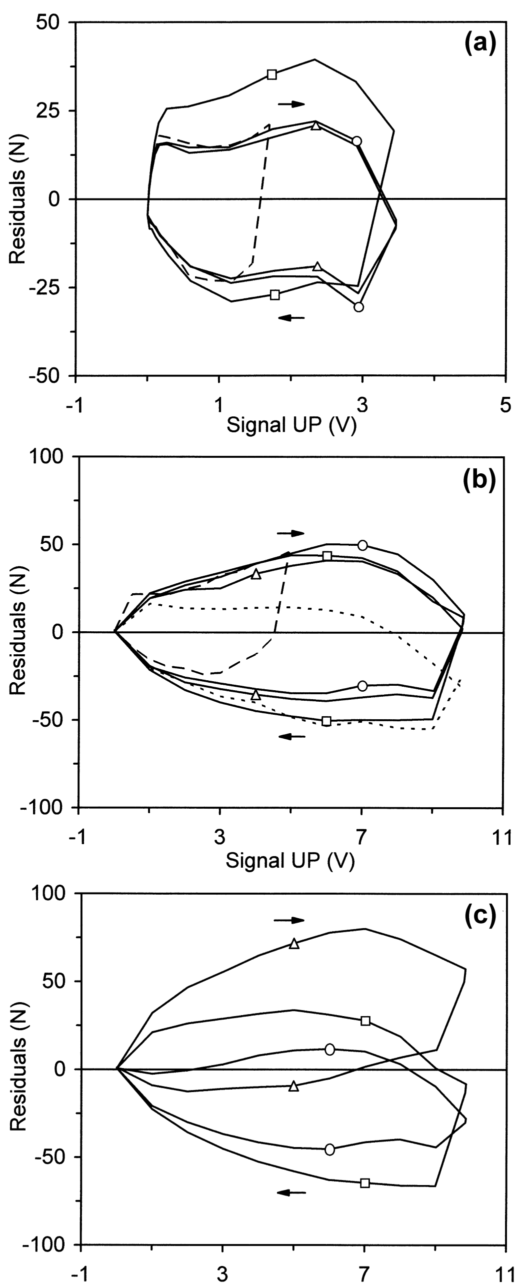

Fig. 4. Mean residuals of the regression analysis of the repeated quasistatic calibration experiments of the UP. The means of three measurements per force level are connected with lines. (a) RC2 series at constant installation of the upper punch, (b) RC1 series at constant installation of the upper punch, and (c) RC1 series at varying installation of the upper punch. (—□—) First series of repeatability, (—○—) second series, (—△—) third series, (– – –) half maximum force, (- - -) with a die.

Further, the course of the hysteresis can change with the adjustment of the maximum load as is evident from Fig. 4b. At lower maximum force settings, the width of the hysteresis remains nearly constant (Fig. 4a). Reducing the maximum force further, the width of hysteresis decreases again. In the former case, the changes do not proceed symmetrically to the bisector of the width, leading to variations in the mean sensitivity with the setting of maximum load. The estimate of the extent of influence by means of the recovery leads to some serious results, especially in case of the RC2 series as obvious from Table 2. This can be explained by the structure of the data. At maximum force two readings are taken, as at the other load levels too, but both maximum values lie on the ascending hysteresis, thus distorting the recovery. Excluding the maximum levels from the regression, the results conform well with the visual observations. Provided that the course of hysteresis is similar during tabletting, the mean sensitivity of the UP derived from the calibration will not necessarily be representative for lower maximum force settings. As five measuring ranges are available on the charge amplifier, each one calibrated separately, the resulting error will be small, when the measuring ranges are selected carefully during tabletting.

Although the hysteresis measured with both references is comparable and therefore the influence of tilting effects on these load cells seems to be small, there exist distinct qualitative differences between the two load cells, which become evident from the confidence intervals shown in Fig. 3. The random error and the sensitivity to variations in the installation angle is noticeably smaller for the RC2. This was expected owing to its high rotational symmetry, which makes the RC2 robust against variations in the mode of force induction. From Table 2 another difference between the two force standards must be established: The overall sensitivity with respect to the signal of the UP differs by about 0.4%. Regarding the discussion above, the results obtained with the RC2 seem to be more reliable. On the other hand, it must be considered, that the bridge resistance of the amplifier calibration device agrees with the resistance of the RC1 but not with that of the RC2. Therefore, the response of the carrier frequency amplifier to the RC2 may not be correctly determined. However, these findings provide an insight into the accuracy of the calibration, which is difficult to assess, when imperfect reference devices must be used.

Apart from the aim to prove for the accuracy of the calibration, the RC2 was used in particular, to determine the behaviour of the UP at low forces. In contrast to chemical analytics, where the method can be adopted to the required concentration range, in the evaluation of the compaction behaviour of pharmaceutical materials the response of the sensor must be known from zero load up to 10-folds of kilo

Newtons. However, the use of a load reference with an adequate range for the measurement of maximum forces will not necessarily be suitable to calibrate forces of only a few Newtons. Usually, load cells only meet their specifications when loaded with forces greater than 10% of their capacity. Therefore, one must choose an appropriate reference before the measurement of low force can be assessed. For this purpose the RC2 was used, which was specially calibrated at low forces. Comparing the results of the calibration of the UP obtained with the RC2 at low forces with the findings from the respective RC1 series, the differences in the response of both reference load cells are quite small (about 1% at a load of 50 N) compared with the deviations associated with the problems due to the hysteresis of the UP, which caused a span of 25% at 50 N load level. The only conclusion that can be drawn is that the quality of the UP in the present mode of installation is not sufficient to measure extremely small forces at high settings of the maximum load. Unfortunately, this cannot be avoided, except for the case when only the maximum pressure is the property of interest. For the sake of completeness it should be mentioned, that the accuracy of the quasistatic calibration of low forces is negatively affected in addition by the drift of the charge amplifier. The absolute magnitude of the drift is of course small, but its relative contribution becomes more pronounced at low forces.

A further problem associated with the sensitivity of the UP to uneven load induction should not be omitted: the change in the width of the hysteresis accompanied by a change in the overall sensitivity when, as proposed, the UP was not loaded high enough after its installation. From Fig. 4a,b it is evident, that this problem is only clearly detectable with the RC2. The phenomenon can also be observed with the RC1 series performed with a maximum force of 6 kN. This corroborates the presumption that, after mounting the UP, a sufficient high load must be applied to achieve a stabilization of the position of the UP and the sliding disk. Thereafter, the response of the UP remains acceptably constant during the period of validation, irrespective whether the calibration was repeated under standard conditions or performed with variations in the installation positions, machine settings and handling (Table 2).

Comparing the results obtained at constant installation of the UP (Fig. 4b) with the calibration curves derived under variation of its installation (Fig. 4c), the necessity of a recalibration after punch exchange is obvious. Nevertheless, the variability with respect to the overall sensitivity is less than ±0.3% and ±0.6% for the calibration against the RC1 and the RC2, respectively, as derived from the calculation of the recovery summarized in Table 3. No remarkable influence of the parameter settings tested at punch exchange on the calibration can be observed, except for the use of the LP instead of the UP. As the nominal sensitivities of both sensors are different from each other, this should not surprise.

For the LP the same problems as discussed for the UP must be taken into consideration. Additionally, a further problem will arise: the influence of the filling depth, as is obvious from Table 4. Therefore, when alterations of the filling depth during tabletting experiments are unavoidable, the variation of the filling depth should be included in the standard calibration procedure. When the die is hand-filled, the filling depth is usually fixed at a preset level. Then it will be sufficient to calibrate the LP at this setting. Except for this fault, the repeatability and robustness are satisfactory.

3.2. Dynamic experiments

In Fig. 5 the results of the recovery as a measure of change in mean sensitivity are presented graphically. As the change in the response due to dynamic loading is accompanied by a slight change in the linearity, this parameter will provide only a rough measure. Most conspicuous is the deviation of the dynamic sensitivity of the UP from the quasistatic response, obvious with respect to all three reference load cells used. 'Only' the extent varied from reference to reference, which becomes more pronounced at high maximum load levels. From the latter it must be concluded, that each of the references may have its own dynamic shortcomings. So, the question will arise: which sensor is the most reliable one? As the true dynamic force obviously is not known, we must elucidate the experimental data more thoroughly.

One aspect for the assessment of the dynamic suitability is the incidence of a dynamic hysteresis. In all three systems, where piezo-electric sensors are combined with each other, the dynamic hysteresis is quite similar to the quasistatic one, as inferred from Fig. 6a,b. This does not mean, that there is no additional dynamic hysteresis in the behaviour of the single transducers, as the hysteresis of these similarly constructed sensors may cancel each other out.

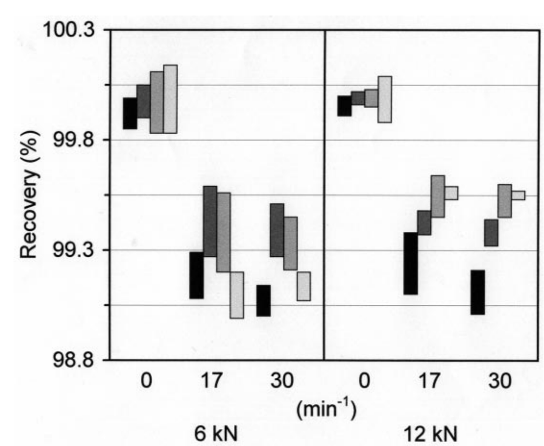

Fig. 5. Confidence intervals ($P < 0.05$) of the percentage recovery of the dynamic experiments with respect to the quasistatic experiments at 17 and 30 strokes/min, 6 and 12 kN maximum load level and for different calibration systems. The recovery of the quasistatic experiments is included at 0 min^{-1}. Calibration function ($y(x)$): (black shaded bar) RC1(UP), (dark grey shaded bar) RP1(UP), (medium grey shaded bar) RP2(UP), (light grey shaded bar) LP(UP).

Comparing, on the other hand, the RC1 with the piezo-electric systems, a pronounced hysteresis must be attributed to the RC1 (Fig. 6c). As the direction of the dynamic hysteresis of the UP-RC1 system is opposite to the quasistatic one, the magnitude of the dynamic deviations inferred from Fig. 6c is underestimated. The hysteresis of the RC1 has a marked characteristic. It follows the rate of force development quite precisely as evident from Fig. 7. As a result, the width of the hysteresis varies not only considerably during a compression event, but is also highly dependent on machine speed

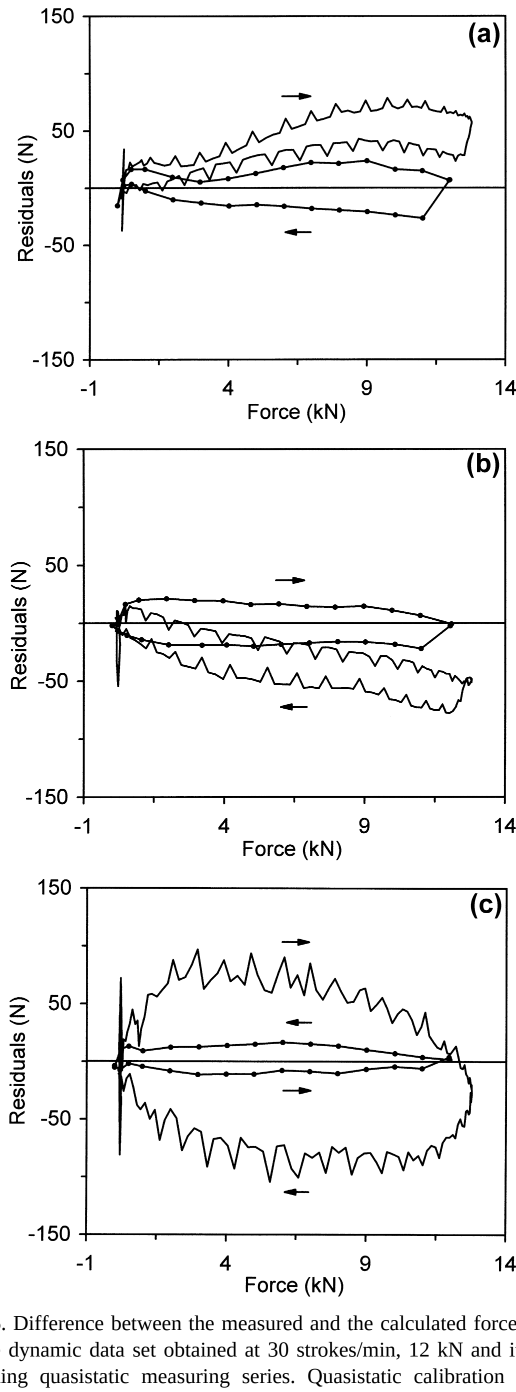

Fig. 6. Difference between the measured and the calculated force of each single dynamic data set obtained at 30 strokes/min, 12 kN and its corresponding quasistatic measuring series. Quasistatic calibration function (*y*(*x*)): (a) RP2(UP), (b) UP(LP), and (c) RP2(RC1). (—●—) quasistatic data, (—) dynamic data.

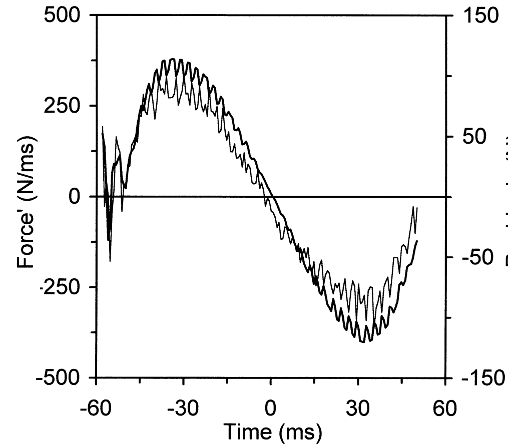

Fig. 7. First derivative of the force (force′) calculated from the signal of the RP1 during dynamic loading at 30 strokes/min and 12 kN maximum force level, and difference between the force measured at the RP1 and the calculated force of the RC1 (quasistatic calibration function: RP1(RC1)). (thick black line) force′, (thin black line) residuals.

and maximum force settings, which alter the loading profiles according to Fig. 2a,b. However, when in an ideal case a simple correlation exists between the velocity and the hysteresis, the deviation will become zero at maximum force and the hysteresis will take a symmetrical course. Then, the mean sensitivity of the system will not be affected by dynamic loading.

This short-term creeping of the RC1 is in opposite to a distinct long-term creeping of the piezo-electric transducers. This kind of creeping becomes evident, once the unloading phase is completed. Fig. 8 compares the residual signals of the RC1, UP, and RP1. The behaviour of the RP2 and LP is comparable to that of the UP. Now the question is, whether the change in sensitivity at dynamic loading can be ascribed to this long-term creeping of the piezo-electric sensors? The proposed interrelation was checked considering the viscoelastic theory. Both the observed characteristic dynamic behaviour of the piezo-electric load cells as well as that of the RC1 can be qua-

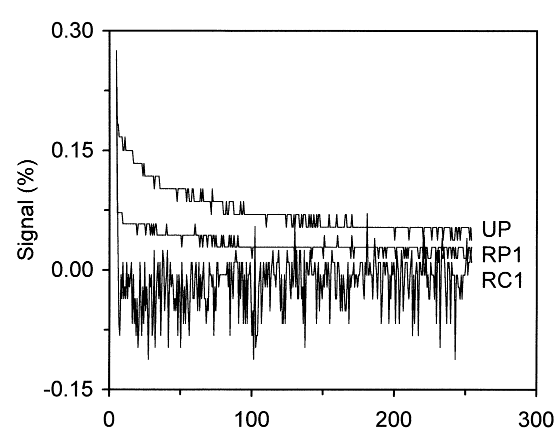

Fig. 8. Remaining signal after dynamic loading at 30 strokes/min and 12 kN maximum force level, normalized with respect to the maximum signal.

litatively modelled with a simple system, a spring and a Kelvin-element connected in series. (To try a quantitative description is doomed to failure as long as the true force is not known.) Although the dynamic properties can be simulated by viscoelastic models, their origin must not necessarily or solely be of mechanical nature. The behaviour of the electrical circumference, e.g. the amplifiers, may at least contribute to the effects seen.

As far as possible, the influence of the amplifiers on the dynamic response was checked. Firstly, the long-term creeping after unloading was examined. Instead of the piezo-electric sensors a charge calibrator was connected to the charge amplifier and a rectangular signal generated. A long-term creeping was not observed. Secondly, the influence of the time constant of the charge amplifier was evaluated. A charge amplifier with selectable time constant was connected to the UP and the dynamic responses at 30 strokes/min using the ‘short’, ‘medium’, and ‘long’ settings were investigated. Compared to the ‘long’ setting, which was normally used during all the calibration experiments, no significant difference in the response was obtained at the ‘medium’ setting. Using the ‘short’ constant, the amplifier signals were clearly distorted by the charge leakage and are therefore poorly expressive. From these results it can be concluded, that long-term creeping is most probably not caused by the charge amplifier. For the investigation of the dynamic behaviour of the DC amplifier no reference was available. The dynamic error of the DC amplifier in the slow frequency range of a calibration event can be assumed to be less relevant [14]. To get an impression of the dynamic variability in the force measurement with the RC1, the carrier frequency amplifier normally used only for the quasistatic experiments was linked to the RC1 instead of the DC amplifier. The deviation between the quasistatic and the dynamic response of the UP-RC1 system decreased from 0.9%, as obtained with the DC amplifier, to 0.7% when the carrier frequency amplifier was utilized at 30 strokes/min and high maximum force. Simultaneously, the hysteresis is widened. Such differences in the course of the hysteresis were already observed by Krumme [15]. Of course, from these experiments the accuracy of the dynamic force derived from the RC1 measuring chain cannot be estimated. But it is obvious, that the response of the RC1 can easily be affected by the kind of amplifier used during dynamic calibration.

Another important aspect with regard to the dynamic behaviour is the frequency response of the system. The knowledge of the resonance frequency of the sensors themselves provided by the manufacturer specifications will not necessarily conform with the resonance in situ, as the masses of additional fittings, e.g. calibration punches or force distribution caps, will influence the response. Then, also the resonances during calibration and tabletting will become different. The resonance of the electrical circumference will further contribute to the resonance frequency of the whole system. A simple ‘hammer blow test’ [16], namely a stroke with a hammer, e.g. on the eccentric during static loading, will provide useful information about the frequency behaviour of the entire system in situ. Such a test was carried out with the UP linked to the RC1. But as only a maximum acquisition rate of 1.5 kHz can be realized with the present acquisition system, the informational content of these experiments is quite limited. After a sharp peak of the stroke, only increased noise is detectable, from which the resonance frequency could not be estimated. However, owing to the low dynamic masses (the masses between the sensors and the dynamically effective masses of the sensors) and the moderate accelerations at the selected machine speeds, it should be assumed that the frequency response influences the calibration and tabletting experiments only to a minor extent.

In summary, deficiencies in the time dependent behaviour of all the sensor systems tested seem to dominate the differences seen between the quasistatic and dynamic calibration. Owing to the long-term creeping of the piezo-electric systems, the RC1 seems to be the most reliable dynamic reference, as far as only knowledge of the mean dynamic sensitivity is of interest, as in the case of a calibration.

Compared to the marked deviations between the results of the quasistatic and the dynamic calibration method, the behaviour of the UP is only little influenced by variations in the course of force development within the range tested (Figs. 2a and 5). Differences of up to 0.2% can be observed for the UP. This will also apply to the simulation of asymmetrical profiles. But, as mentioned above, quantitative estimates must be handled with caution in the case of asymmetrical data. However, from these results it can be concluded, that the comparability of the data received during tabletting will be only slightly restricted as long as the variation in the velocity profiles is moderate. But it should be emphasized, that such variations are not only caused by the setting of the machine speed, but also by the compaction resistance of the powder bed.

As the LP can only be calibrated against the UP, its dynamic properties are difficult to assess in detail. The only conclusion that can be drawn is that its dynamic behaviour is superior to the UP. At low maximum load level, its dynamic error may be extremely small, as only the deficiency of the UP is reflected in the calibration results (Fig. 5). At high maximum forces, the mean error increases to about half of that estimated for the UP.

Comparing now the results between the UP-LP with the UP-RP2 system, the influence of the installation under prestress on the dynamic behaviour of the piezo-electric sensor should be assessable. From the recovery depicted in Fig. 5 it is evident, that the influence diminishes with increasing load. No dramatic effects with respect to a change in slope or dynamic hysteresis (Figs. 5 and 6a,b) can be observed. As the instrumentation of the upper and lower punch is similar in principle, a minor influence of the installation under pre-stress on the dynamic response can also be assumed for the UP.

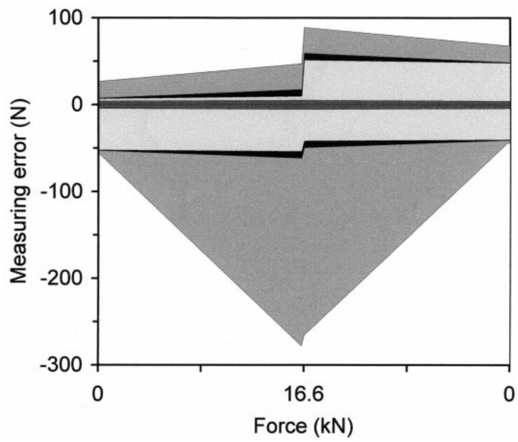

Fig. 9. Measuring errors of the upper punch force before and after the lower turning point up to a maximum upper punch force of 16.6 kN. Error: (dark grey shaded area) random within-run, (light grey shaded area) systematic within-run, (black shaded area) random between-run, (medium grey shaded area) systematic between-run.

3.3. Error summation

From the discussion above it becomes evident, that at least two main sources of error are involved in the accuracy of the force measurement, both of systematic nature: the deviation owing to dynamic loading on the one hand, and the hysteresis effects on the other hand. In an ideal case, systematic errors should be eliminated by corrections in the mode of instrumentation or reduced to solely random ones by application of proper mathematical models. In practice, this is only partially possible due to their complex nature. Therefore, the remaining systematic errors must be included into the tolerances of the measuring system.

An examination of Table 5 reveals that the systematic errors are of about one order of magnitude higher than the random variability. However, the summation of the systematic errors is handled in a worst case mode, that is, the possibility that different errors can compensate each other is ignored. On the other hand, there will remain uncertainties, the extent of which cannot be assessed as, e.g. the dynamic hysteresis of the piezo-electric washers. Other factors such as the interaction of machine settings, installation conditions, equipment and handling checked during the quasi-static validation phase only in a simple non-interacting mode may additionally contribute to a broadening of the tolerances of the system. The transferability of the variability obtained from calibration experiments to real tabletting is a further element of uncertainty with respect to the formulation of such error limits.

The graphical representation of the errors in the measurement of the upper punch force (Fig. 9) illustrates not only the magnitude of the systematic contributions, but also shows the importance of the between-run errors. However, the systematic within-run errors will be relevant too. This means, that the course of the force measured during tabletting could not only be shifted or stretched, but also distorted to a appreciable extent with respect to the true behaviour.

4. Conclusions

The force measurement by the installed transducers as well as their calibration in situ and under working conditions is accompanied by several problems, as not only the quality of the installed sensors but also the response of the references is influenced by the functioning of the tabletting machine. Sometimes it is difficult to assess, whether a deficiency is caused by the mounted transducers or by the force reference. The choice of as many variations as possible not only in the machine setting or installation conditions, but also in the measuring devices will be helpful in discovering sources of error, in assessing their relevance for the calibration or the subsequent measurement during real tabletting, and in estimating the reliability of the measuring system and the data derived from tabletting experiments. Thus, the use of such comprehensive methods seems to be advisable if not necessary to assure the quality of the analytical results.

Acknowledgements

The authors would like to thank Dr. A. Sawla and Mr. R. Kumme, Physikalisch-Technische Bundesanstalt, Braunschweig, for the valuable discussions and the efforts with the calibration of the reference load cell, and Mr. Ruth, Institute of Physical Chemistry, University of Hamburg, for the manufacture of the calibration fittings.

References

[1] M.J. Waring, H. Sen, J.W. Forrester, J.R. Salom, Instrumented and computer interfaced single tablet press for the rapid evaluation of compression and lubrication behaviour, Drug Dev. Ind. Pharm. 12 (1986) 1847–1867.

[2] K.-J. Steffens, Die physikalischen Eigenschaften von Magnesiumstearat und ihr Einfluss auf das tribologische Verhalten bei der Tablettierung, Ph.D. thesis, University of Marburg, Germany, 1978.

[3] F.W. Goodhart, G. Mayorga, M.N. Mills, F.C. Ninger, Instrumentation of a rotary tablet machine, J. Pharm. Sci. 57 (1968) 1770–1775.

[4] P.C. Schmidt, H. Koch, Vergleich einer Einzelstempelinstrumentierung mit piezoelektrischem Kraftaufnehmer mit einer Dehnungsmeßstreifen – Instrumentierung am Hebelarm bei der Aufnahme von Preßkraft-Zeit-Kurven, Pharm. Ind. 53 (1991) 508–511.

[5] B.W. Müller, K.-J. Steffens, P.H. List, Tribologische Gesetzmäßigkeiten und Erkenntnisse in der Tablettentechnologie, Pharm. Ind. 43 (1981) 665–671.

[6] R.F. Lammens, J. Poldermann, C.J. de Blaey, Evaluation of force-displacement measurements during powder compaction. Part I: precision and accuracy of force measurements, Int. J. Pharm. Tech. Prod. Mfr. 1 (1) (1979) 26–35.

[7] P. Ridgway Watt, Tablet Machine Instrumentation in Pharmaceutics: Principles and Practise, Ellis Horwood, Chichester, 1988, pp. 242–244.

[8] P.C. Schmidt, U. Tenter, J. Hocke, Preßkraft- und Weg-Zeit-Char-

akteristik von Rundlauftablettenpressen, Pharm. Ind. 48 (1986) 1546–1553.

[9] N.-O. Lindberg, Instrumentation of a single punch tablet machine, Acta Pharm. Suecica 9 (1972) 135–140.

[10] A. Sawla, R. Kumme, Dynamic behaviour of strain-gauge force transducers in fatigue testing, Proceedings of the IFToMM-jc international symposium on theory of machines and mechanisms, Nagoya, Japan, 24–26 September, 1992.

[11] R. Kumme, M.J. Dixon, The results of comparisons between two different dynamic force measurement systems, Measurement 10 (1992) 140–144.

[12] M. Leitritz, M. Krumme, P.C. Schmidt, Vergleich von statischer und dynamischer Kraftkalibrierung bei einer Rundlauftablettenpresse, Pharm. Ind. 57 (1995) 1033–1038.

[13] P.H. Krause, Einflüsse des Geschwindigkeitsverlaufs in Exzenter – Tablettiermaschinen auf die Verdichtungseigenschaften von pharmazeutischen Haufwerken, Ph.D. thesis, University of Hamburg, Germany, 1991.

[14] R. Kumme, Influence of measuring amplifiers on dynamic force measurement, Proceedings of the 13th international conference on force and mass measurement, Helsinki, Finland, 10–14 May, 1993.

[15] M. Krumme, Entwicklung rechnergestützter Verfahren zur Kompressions- und Festigkeitsanalyse von Tabletten, Ph.D. thesis, University of Berlin, Germany, 1992.

[16] A. Bauer, Untersuchungen zur Prozessdatengewinnung, Viskoelastizität und Struktur von Tabletten, Ph.D. thesis, University of Bonn, Germany, 1990.