Investigation and Optimisation of the Presster – A Linear Compaction Simulator for Rotary Tablet Presses

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ZUR ERLANGUNG DES DOKTORGRADES (DR. RER. NAT.)

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Das Schönste, was wir entdecken können, ist das Geheimnisvolle.

(Albert Einstein)

Contents

1 Introduction and Objectives

More than 160 years ago, since the patent for `Shaping pills, lozenges, and blacklead by pressure in a die` was granted to William Brockedon in 1843, tablets started their evolution to become the most frequently used pharmaceutical dosage form.

Both eccentric and rotary tablet presses had been developed by 1874 (Rubinstein, 1996). Nevertheless, it took almost a century before Brake (1951) and Higuchi (1952, 1953 and 1954) described the instrumentation of tablet presses using strain gauges.

This was the beginning of preliminary investigations of the physics of powder compression. Instrumented tablet presses became the fundamental tool in tablet research and development. Instrumentation of tablet presses has been progressing since then.

A review of different techniques applicable to perform force measurements on tablet presses was published by Erdem (1982).

More detailed information about the physics of powder compression have been collected by additionally monitoring the vertical displacement of both the upper and lower punch during the compression event using preferably linear variable displacement transducers (LVDT´s) (Watt, 1988).

Instrumentation of modern single to triple sided rotary tablet presses, realising a production capacity up to one and a half million tablets per hour, often showed to be difficult and sometimes inaccurate (Bateman, 1987).

Anyhow, process data obtained from instrumented production scale rotary tablet presses will always be necessary to control and adapt the compression process. Therefore tablet press manufacturers try to continuously optimise their machine instrumentation as well as the machines in order to improve the precision and accuracy and thus to minimise the quantity of waste produced.

Nevertheless, the predominant utilisation of rotary tablet presses is still in the field of production. This is due to the rather large amount of powder required for operation which is often not available in the very early stages of a new formulation development.

For this reason new formulations are often developed using either small scale rotary tablet presses or even eccentric presses in order to be able to gather preliminary compaction data as early as possible.

Due to fundamental differences between eccentric and rotary tablet presses as well as small scale and production size rotary tablet presses, results and the subsequently developed formulations may not be easily transferable from one machine to another (Palmieri, 2005).

Varying dwell time, magnitude and rate of applied forces, as they can be found for different brands of machines of the same working principle, may cause major differences in tablet properties as well.

Compaction simulators, requiring only small amounts of powder while running at comparable working principles as rotary tablet presses are therefore the most appropriate to gather compaction data during the early stages of development.

A comparison of the compaction simulator with various other methods in the field of pharmaceutical formulation development is shown by Tab. 1-1.

The first device for simulating the compression conditions of rotary tablet presses was developed by Cole (1971). Two-sided powder compression was realised on a testing device, which was similar in design to a single stroke tablet press, by moving the die downwards during the compaction event to simulate the upward movement of the lower punch. The whole compression process was therefore somewhat closer to the machines to be simulated.

Mechanical testing machines, based on a rotating screw drive to compress materials in a single punch and die set, have often been used for fundamental investigations (Bateman, 1987), but due to their different working principle, the data produced on this machines showed a similar lack of transferability to rotary presses as known from eccentric tablet presses.

Tab. 1-1 Comparison of equipment for tableting studies (after Çelik et al., 1989)

Feature	**Single Station Press**	**Multi-Station Press**	**Punch and Die Set**	**Compaction Simulators**
Model production conditions	no	yes	maybe	yes
Model other presses	no	no	maybe	yes
Require small amount of material	yes	no	yes	yes
Easy to instrument	yes	no	yes	yes
Useful for stress/strain studies	no	no	yes	yes
Easy to set up	yes	no	maybe	maybe
Equipment inexpensive	yes	no	yes	no
Useful for scale-up	no	yes	maybe	yes

As a consequence of constant rising development expenses and mainly to solve the afore mentioned problems of poor transferable data another simulation device was developed by Rees (1972), but this was limited by design to relatively slow compression speed settings.

The first high speed compression simulator, with maximum compression rates of 400 mms^{-1} and able to reproduce the multiple compression and ejection cycle, was presented a few years later by Hunter (1976). In the following years other small different types of compaction simulators were been developed (Rubinstein, 1996).

Similar in design and construction (Nokhodchi, 1996) and often working on a hydraulic principle they operated either under punch displacement or force control.

By the use of the original tooling and compression rollers in the same dimensions as used on the rotary tablet presses to be simulated, differences between compaction simulators and rotary tablet presses were minimised.

The linear compaction simulator Presster, developed by MCC (Metropolitan Computing Corporation, USA), has been the first compaction simulator to mimic both, punch displacement and force application rate curve at the same time (Levin, 2000).

With respect to the reliable application of the Presster within any formulation development, the objectives of this work have been as follows:

Estimation of the specifications and measurement systems of the Presster in its original state, simulating a Fette P1200 (Fette, Germany) rotary tablet press.

In case of proven necessity the Presster might be improved in order to obtain an easy to use and powerful tool for research and development purposes.

Furthermore, the quality of improvements had to be verified simulating a Fette P1200 rotary tablet press with respect to the precision and accuracy required for the various force and displacement measurements.

Finally the quality and validity of data gained using the improved measurement systems had to be evaluated in consideration of conceivable applications in Pharmaceutical Research and Development.

2 Theoretical Aspects and Analysis of Powder Compaction Behaviour

The processes and principles of powder compaction behaviour cause issues for Pharmacists in both formulation development as well as production.
Although the first tablet machine instrumentation was performed in 1954 (Higuchi) the multifaceted processes of powder compaction are still not categorically understood today.
Missing or inadequate instrumentation on tablet presses seems to be one reason for the above mentioned lack of knowledge. Therefore, concerted efforts have been undertaken throughout the last few years to enhance the precision and accuracy of tablet machine instrumentation as well as data processing.

Nevertheless, problems like low tablet strength, capping or even batch variability still exist in the large scale production of tablets. These can cause the rejection of whole batches for quality and safety reasons. Many of these problems could be avoided by proper investigations of powder compaction behaviour using high precision instrumented tablet presses or compaction simulators either in advance of or isochronous to any formulation development.

Some commonly used measurements and assessments are discussed below along with their effect on the final compact.

2.1 Compactibility

The compactability, i.e. the ability of a powder bed to form a compact of a specific strength by the application of pressure, gives, in combination with the compressibility, essential information about the tabletability of (pharmaceutical) materials and thus successful tablet production.
Usually, the compactibility is described in terms of tablet tensile strength as

a function of the applied compaction pressure. As the tensile strength is affected by various process parameters such as machine settings, time period of storage and storage conditions between the compaction event and the strength analysis, type of compaction tester and its working principle etc., the experimental setup has to be kept constant to be able to generate comparable results.

Furthermore, particulate characteristics of the uncompacted particles, such as particle size distribution and particle shape of the powder to be compressed also affect the compactibility of any powder.

Due to multiple variations in the setup of investigations, a large number of the findings presented in literature are unfortunately not comparable.

2.2 Tensile Strength

In addition to the determination of compaction force, tablet mass, height and diameter, the evaluation of tablet crushing force, using tablet compression testers, is one of the most common methods for the determination of tablet properties with respect to the stability of the compact during subsequent processing steps such as film coating or packaging.

Crushing force values of tablets of different size and shape obtained by the diametral compression test (Fig. 2-1) are not directly comparable to each other due to inconsistent dimensions of the fractional surface.

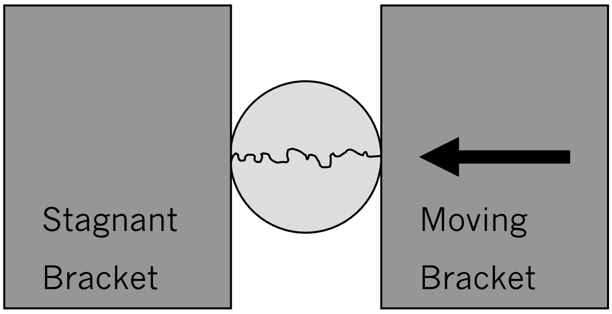


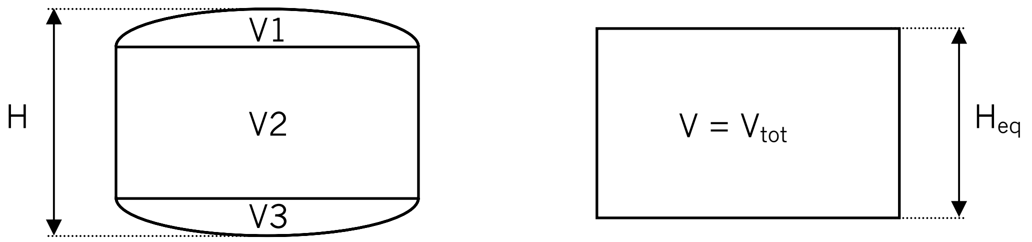
Fig. 2-1 Determination of diametral crushing force

Therefore Fell and Newton (1970) established the Tensile Stength (Eq. 2-1) as a size and shape independent character to describe tablet properties, strictly valid for round and flat tablets only.

$$TS = \frac{2 \cdot F}{\pi \cdot D \cdot t} \qquad \text{Eq. 2-1}$$

TS	Tensile Stength [Nmm^{-2}]
F	diametral crushing force [N]
D	tablet diameter [mm]
t	tablet thickness [mm]

In order to compare properties of round, non flat tablets with each other, the height of any non flat tablet can be converted to the height of a flat tablet having the same volume. The calculation of the Tensile Strength is then carried out using this equivalent height value (Fig. 2-2)



$$V_{tot} = V1 + V2 + V3$$

Fig. 2-2 Determination of the equivalent height H_{eq} of a flat tablet having the same total volume V_{tot} as a curved tablet of the same diameter.

2.3 Compressibility

In most cases, the chemical properties of both Active Pharmaceutical Ingredients (API´s) and pharmaceutical excipients of a new tablet formulation are well defined as necessary for quality assurance purposes. However, the physical behaviour in terms of powder compaction behaviour of both the individual ingredients, especially of the API´s, and the final formulation is often not known sufficiently.

As the properties of the compact finally depend on the physical properties of both the single ingredients and the final blend it should therefore be studied in greater detail.
Hence, individual ingredients, and blends of them, are often compressed in order to evaluate their ability to be compressed or reduced in volume due to the application of a given stress, representing their compressibility c [Pa^{-1}] (Eq. 2-2),

$$c = \frac{\Delta V}{V \cdot \Delta P} \qquad \text{Eq. 2-2}$$

where the ratio of ΔV over V gives the relative change in the volume of the compact due to a certain change in the effective pressure ΔP [Pa].
The compressibility as well as the following compactability characterise the tabletability of any (pharmaceutical) material.

2.4 Compaction Pressure vs. In-Die-Tablet-Height Plot

As the compressibility describes the ability of a material to be deformed under pressure, compaction pressure vs. in-die tablet height plots gives us one feasible graphical representation of these investigations. In contrast to the evaluation of the compactability by compaction pressure vs. tensile strength plots, which requires the subsequent determination of tablet properties such as crushing force, height and diameter on devices different from the tablet press, the compaction pressure vs. in-die tablet height plot is generated by signals from the instrumented tablet press and is therefore dedicated to the real time in-process-control of any tableting process.
Critical or missing precision of the displacement measurement system of many tablet presses, based on whatever working principle, might be the

reason for the seldom use of this plot.

The well known Heckel-plot, i.e. used for the investigation of the materials deformation behaviour, is a modification of this compaction pressure vs. in-die tablet height plot but is, due to the missing information of the final mass of the compact, not applicable with respect to real time process control purposes.

2.5 Porosity

Tablet properties like tensile strength, friability, disintegration and dissolution time depend mainly on the porosity of tablets. Therefore, the information about the actual in-die-porosity of tablets at a certain pressure is precious information during development stages.

Based on precise and accurate punch displacement measurements, the recent in-die-porosity and therefore the degree of densification at each point during the compression cycle can be calculated using the following Eq. 2-3:

$$\varepsilon\,[\%] = 100 \cdot \left[1 - \frac{V_t}{V_c}\right] \qquad \text{Eq. 2-3}$$

where $\varepsilon\,[\%]$ is the percentage porosity of the compact, V_t is the "true" volume of the powdered material (determined by helium pycnometric measurement) and V_c is the volume of the compact at a certain pressure.

In most cases, alterations of compact properties, e.g. in terms of tablet strength, might be observed as a consequence of any variation in the compacts porosity.

The information obtained by the measurement of the in-die-porosity of course exceeds the information of out-of-die measurements as the latter give no information about any elastic recovery, equalizing an increasing porosity during decompression. To guarantee constant tablets properties, the in-die porosity during compaction must be kept constant.

The reliable and accurate investigation of porosity alterations during compaction is furthermore most important for the evaluation of the compaction behaviour in terms of Heckel-plots.

2.6 Heckel-Plot

The examination of volume reduction of the particle bed inside the die under pressure, i.e. the compressibility, is one of the most commonly used methods to investigate and evaluate powder compression behaviour and particle deformation mechanisms. Different empirical models, based on the relative density of the compact under pressure have been established by Walker (1923), Kawakita (1971), Cooper (1962), Heckel (1961a, 1961b) and some others.

The model of Heckel, given by Eq. 2-4, is the most universally accepted one to describe the volume reduction of a powder bed under pressure.

$$\ln\left(\frac{1}{1-\rho_r}\right) = KP + A \qquad \text{Eq. 2-4}$$

ρ_r represents the relative density of the compact at pressure P while K reflects the slope of the linear part of the compaction phase. A gives the intercept of the extrapolated linear part of the compaction phase with the ordinate and hereby some small information about the bulk density inside the die prior to the compaction event.

The Heckel equation, following first order kinetics, is strictly valid only for the linear part of the compaction phase. However, the nonlinear parts of the compaction phase at low or high pressures gives some further information about the behaviour of the powder during particle rearrangement and strain hardening respectively (Gabaude, 1999).

The reciprocal of K from the Heckel equation describes the resistance of the (pharmaceutical) material against persisting deformation, equalizing the mean yield pressure P_y of the material, which finally represents the ability of the material to deform plastically.

An alternative method for the calculation of P_y, suggested by Sonnergaard (1999) is given by Eq. 2-5. If the coefficient of correlation (r^2) of the linear regression was found to be smaller than 0.95, this model of Sonnergard was found to provide better results (Dressler, 2002) in the calculation of P_y.

$$P_y = \frac{r^2}{K} \qquad \text{Eq. 2-5}$$

In the present work the standard calculation of P_y was used due to the comparability of measurements obtained by the Presster with data from literature.

Several parameters influencing the quality and validity of Heckel-plots and finally the calculation of P_y have to be taken into consideration. These are machine parameters such as densification speed, contact time, dwell time and the applied compaction pressure. Also specifications of the materials used are critical, e.g. its humidity, particle size and distribution.

Furthermore the quality and validity of the determination of the in-die-tablet-height by punch displacement measurements as well as the determination of the true density of the material carried out by helium pycnometric measurements have a major influence with respect to the validity of Heckel-plots (Krumme, 2000; Sonnergaard, 2000).

Therefore, with respect to the comparison of Heckel data, data from literature has to be handled with care in order to prevent estimation errors based on varying machine settings and operational techniques.

Comparisons between Heckel data, which have been either obtained by the in-die method, as described above, or the out-of-die method, where the height of the tablet is measured by a sliding calliper after the compact has been ejected out of the die, are more than critical and finally misleading.

Nevertheless, the out-of-die method for the determination of the height of the compact is still often used, as a highly precise punch displacement measurement system for in-die measurements is often not available.

To generate Heckel-plots according to the out-of-die method several tablets have to be produced at varying pressure levels. Therefore the amount of material required to set up this plot is comparably larger. This has considerable time and cost implications to the overall development process. Beyond that, the out-of-die method gives no information about pressure relaxation (Rx) and elastic recovery (ER) of the compact, which might indicate to capping or lamination tendencies.

Therefore, Heckel-plots generated by the out-of-die method only consist of the compression slope.

2.7 Dwell Time

Beside the maximum compaction force the according dwell time, which is by definition the time over which the flat portion of the punch head is in contact with the compression roller, has a major effect on tablet properties. As the dwell time is affected only by machine parameters and settings it can be calculated for any tablet press by Eq. 2-6 and 2-7 respectively.

$$DT = \frac{D \cdot NP \cdot 3{,}600{,}000}{\pi \cdot PCD \cdot TPH} \tag*{Eq. 2-6}$$

$$DT = \frac{D}{LS} = \frac{D \cdot 60{,}000}{\pi \cdot PCD \cdot RPM} \tag*{Eq. 2-7}$$

DT	Dwell Time [ms]
D	Diameter of the flat portion of the punch head [mm]
NP	Number of punch stations
PCD	Pitch circle diameter [mm]
TPH	Tablets per hour
LS	Linear Speed [ms^{-1}]
RPM	Revolutions per minute

In connection with the dwell time, two further parameters influencing tablet properties have to be defined.

First, the contact time, which is the time over which the punch head of both the upper and lower punch is in contact with the appropriate compression roller (Fig. 2-3). It depends mainly on the outer dimension of the compression roller and on the vertical position of the punch in relation to the vertical position of the compression roller, while the first is affected by the depth of fill and the pre-compression level.

Secondly, the vertical punch velocity (Seitz, 1965; David, 1977; Pitt, 1987), equalising the compression or densification speed, which, for a certain speed setting of the turret, depends mainly on the outer diameter of the compression roller.

The smaller the difference between both contact time and dwell time, the larger the resulting densification speed at a given compaction pressure.

The investigation of dwell time effects on compact properties might at least be worthwhile for mainly plastically deforming materials and formulations.

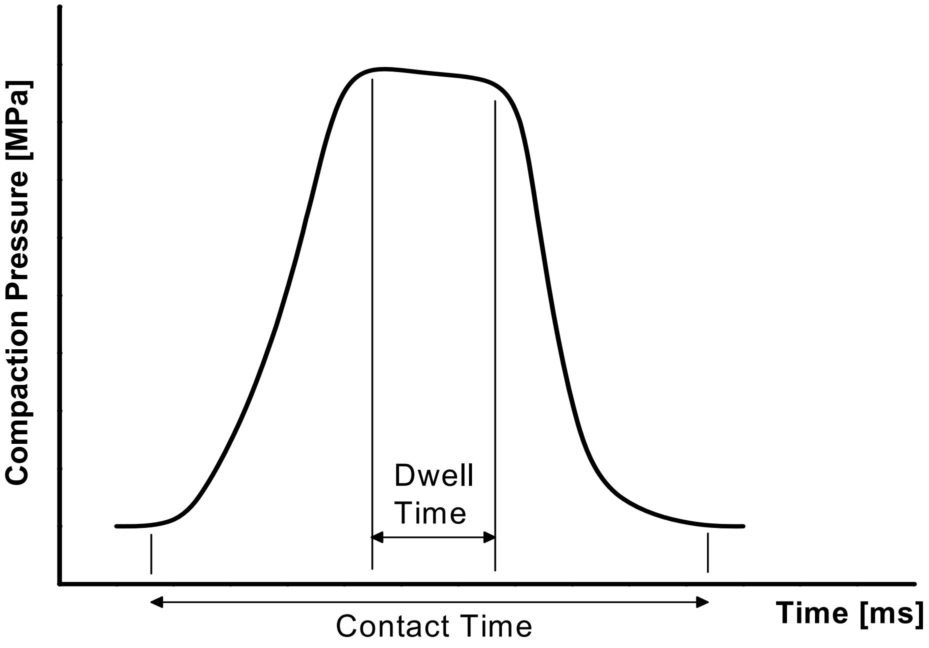


Fig. 2-3 Contact time and dwell time of a compaction event

3 The Presster - A Linear Compaction Simulator

Due to the different working principles between rotary tablet presses and any commercially available compaction simulation device, the Presster, a linear tablet press simulator was designed by MCC (Levin, 2000) during the late 1990th.

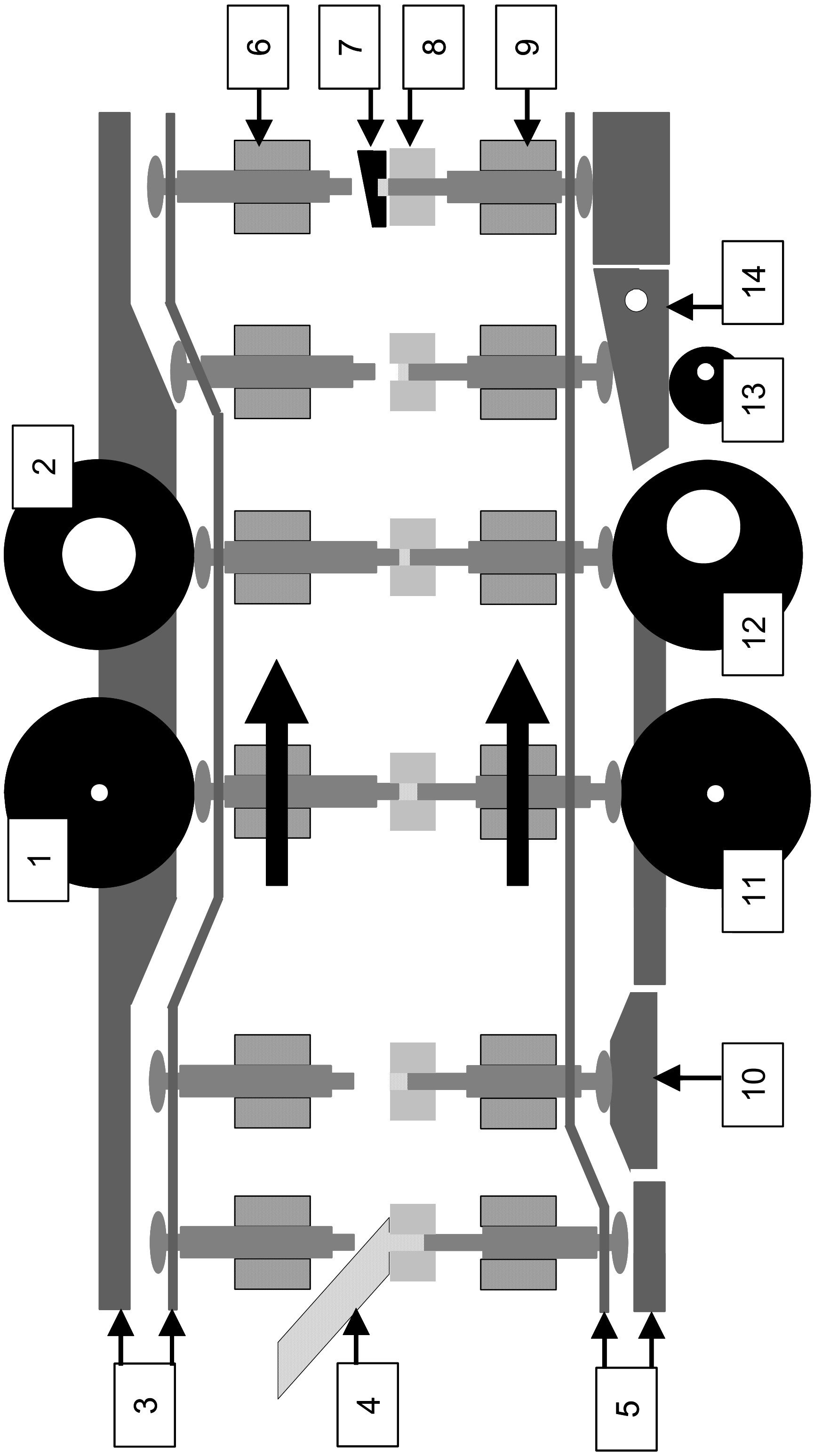
Basically, its design resembles a single station rotary tablet press with all its individual sections (Fig. 3-1), which are in this case not arranged on a circular path but on a straight line.

In contrast to almost any rotary tablet press the Presster operates with just one pair of punches and one single die. The tablet tooling is installed in a turret-analogue carriage, which is driven by a drive belt on a horizontal line through the whole machine passing successively the dosing cam, the upper and lower rollers of the pre- and main compaction station and finally the ejection cam and the take off bar. As the punches on the Presster are guided by punch cams similar to the ones used on rotary tablet presses the geometrical path of the punches on both types of machines is quite close.

Standard tooling, identical with those used on the machines to be simulated, is used on the Presster. Different punch formats, as e.g. EU B and EU D can be used as there are interchangeable carriages comparable to different turrets on rotary tablet presses. Compaction rollers of different diameters from 7.5” to 15.4” (equals about 190 to 390 mm). are applicable.

In order to simulate a Fette P1200 rotary tablet press, the compaction rollers of the Presster were selected to have a diameter of 250 mm for this research study.

Die feeding takes place either manually or by use of a gravity force feed shoe mechanism, which has been fixed to the carriage. Depth of fill, tablet thickness and machine speed are all adjustable by computer control.



1 – Upper Precompaction Roller
2 – Upper Main Compaction Roller
3 – Upper Punch Cam
4 – Hopper
5 – Lower Punch Cam
6 – Upper Punch Bushing
7 – Take-Off Bar
8 – Die
9 – Lower Punch Bushing
10 – Dosing Cam
11 – Lower Precompaction Roller
12 – Lower Main Compaction Roller
13 – Adjustment for Ejection Angle
14 – Ejection Cam

Fig. 3-1 Schematical drawing of the functional compaction cycle assemblies of the Presster

According to the specifications of the Presster (MCC, USA), provided by the supplier, the speed of the carriage in horizontal plane covers the range from 0.055 up to 2.2 ms^{-1}, while 4 tablets per minute represent the maximum tablet output using an optional enforced feed shoe system. Therefore, dwell times in the range from 5.8 to 230 ms (based on calculations using a tooling with a flat portion of the punch head of 12.65 mm in diameter) can be achieved.

Tablets are collected in a tablet container attached to the carriage. Maximum forces applicable by the sets of pre- and main compaction rollers are 10 and 50 kN respectively.

Compression forces are monitored by strain gauge instrumented compression roller pins, which are fixed on one side to the machine frame. Ejection forces are observed using strain gauge instrumented bolts, with which the mounting of the ejection cam is held inside the machine frame. The ejection cam itself is not directly instrumented.

The adaptation of the ejection angle to the one present on the machine to be simulated is performed by computer control of an eccentric actuation within the range of 5° to 15.6°. Take-off forces are monitored by a unilateral mounted, strain gauge instrumented take-off bar.

To control the vertical punch movement during compression the core of one LVDT is attached to each punch by a bracket, whilst its body is clamped to the carriage in the height of the punch bushing.

The mounting positions of the displacement transducers are in rectangular orientation to the moving direction of the carriage next to the punches.

The software package delivered with the Presster is used for both operating the Presster as well as for data acquisition.

The horizontal movements as well as the horizontal speed of the carriage are observed by proximity switches, which are passed by the carriage during each compaction cycle. The software and data acquisition board are limited to a fixed number of 5000 data points per channel and compaction cycle.

At our request, the manufacturer of the Presster provided all the signals of the individual instrumentation in this Presster, serial number 107 by parallel wiring, in order to allow collection of all the measurement data of the Presster using a data acquisition system separate to the original one.

4 Results and Discussion

The investigation of powder compaction behaviour requires reliable and accurate measurements of compaction cycle related forces and punch movements.

Prior to any investigation of this kind, the measurement systems of the various equipment used during these trials has to be examined properly in order to guarantee the qualification of these measurement systems with respect to their reliable precision and accuracy.

Therefore, the various measurement systems of the Presster as well as the uninstrumented machine parts, which also have an influence on tablet properties, have been investigated with respect to the accurate simulation of a Fette P1200 rotary tablet press.

In case of proven necessity, the individual systems have been improved in order to guarantee accurate and reliable results.

In the following the results of the investigations of the linear compaction simulator Presster, the finally implemented modifications and a comparison between the measured results of both the original and the improved systems are presented.

4.1 Data Acquisition System

4.1.1 Original Presster Data Acquisition System

The original Presster data acquisition system was designed to collect a fixed number of 5000 data points per channel during each compaction cycle. The physical length of the compaction cycle equals a fixed distance of 1.354 m, bounded to both sides by proximity switches.
As the time, required to cover this distance depends on the horizontal speed of the carriage, a variable sample rate, computable by Eq. 4-1, has been obtained.

$$\frac{NODP\ \ per\ CC}{Time\ of\ \ CC\ [s]} = \frac{5000\ [S]}{Time\ of\ \ CC\ [s]} = Sample\ Rate\ [S\ /\ s] \qquad Eq.\ 4\text{-}1$$

NODP Number of data points [Samples S]
CC Compaction Cycle

Hence, dependent on the achieved horizontal speed of the carriage within the range of 0.4 and 2.0 ms^{-1}, the resulting sample rate was found to be within the range of about 1.5 to 7.4 kHz.

This implies, that a take-off (TO) force peak, if it has been measured properly having a peak time of e.g. 100 µs, would be represented by less than one data point while operating the Presster at maximum speed conditions.
Therefore, referring to the examined sample rate, this original data acquisition system delivered with the Presster was by design not suited to monitor any compaction cycle measurement with the exception of rather slow signals, as e.g. compaction forces.

Additionally, measurement signals of the various instrumentations of the Presster were amplified by strain gauge input signal conditioners

(DSCA38-05, Dataforth, USA). Both the voltage raw data as well as the processed data were monitored by the original data acquisition system of the Presster.

To ensure a signal processing without any distortion of the signal amplitude, the signal frequency should not exceed 50 % of the cut-off frequency of a certain measurement system. This frequency range might be used as long as a possible signal phase shift has no effect on the validity of measurements.

If it is even necessary to prevent any signal phase shift, the signal frequency should be below the twentieth part of the cut-off frequency of the measurement system used (Hoffmann, 1995).

Therefore, the cut-off frequency of the DSCA38-05 amplifiers has been investigated by the application of a unit step function using a function generator (HM 8130, HAMEG, Germany). An example result of these trials is shown by Fig. 4-1.

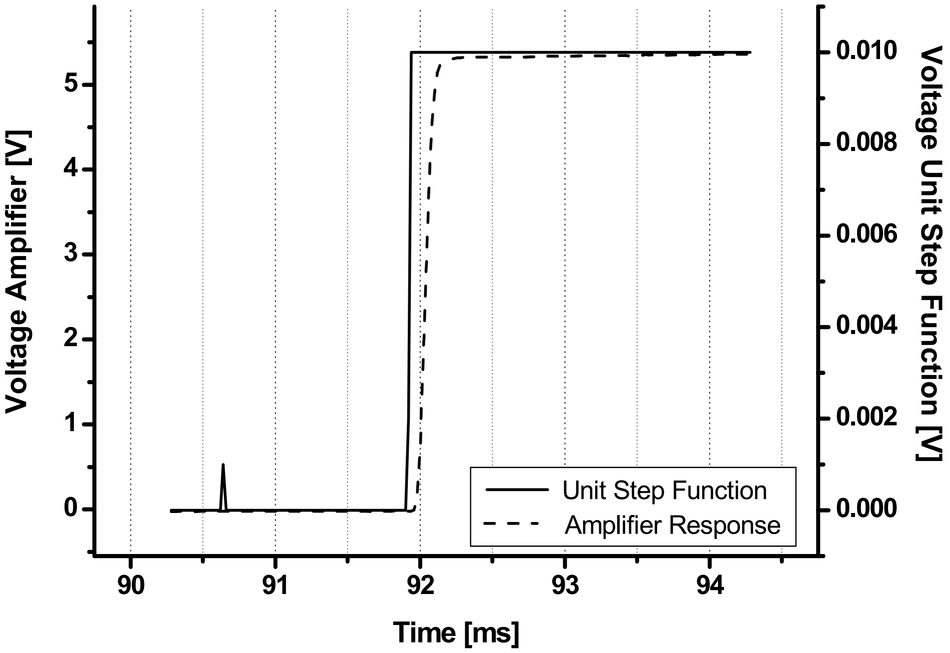


Fig. 4-1 Unit step function and amplifier voltage signal of DSCA38-05 amplifier to investigate its cut-off frequency

After the determination of the rise time, which is the time it takes for the voltage to rise from 10 % to 90 % of its peak value, the cut-off frequency of the individual measurement systems is calculated according to Eq. 4-2.

$$f_g = \frac{\ln 9}{2 \cdot \pi \cdot t_a} \cong \frac{0{,}35}{t_a} \qquad \text{Eq. 4-2}$$

f_g cut-off frequency [kHz]

t_a rise time [ms]; time interval between $t_{10\,\%}$ and $t_{90\,\%}$

Therefore, the cut-off frequency of the DSCA38-05 amplifiers, used by the original Presster data acquisition system, was found to be about 3.25 kHz, confirming the specification of 3 kHz.

The amplifier response time of about 60 µs present in Fig. 4-1 and the missing response to the small noise peak, located at 90.62 ms, indicates to a low pass filter characteristic of the amplifier.

Therefore, high frequency signals as well as high frequency noise are not monitored by this type of amplifier.

In conclusion, the amplifiers used in the Presster are sufficient for the measurement of pre- and main compaction force signals, as their frequency is in general smaller than 0.1 kHz.

Due to the incomparable larger frequency of especially take-off force signals, which will be presented in the following, these signals can not be captured sufficiently using this type of amplifier.

Therefore not only the limitation in the number of data points per compaction cycle and channel by design of the data acquisition system itself but also the too small cut-off frequency of the original amplifiers restricts the applicability of the original data acquisition system to rather low frequency signals as pre- and main compaction force signals and impeded the reliable investigation of any higher frequency signals, like ejection force and TO force signals.

4.1.2 Presster-Independent Data Acquisition System DAQ4

Initially in order to qualify the original data acquisition system of the Presster but finally to be able to reliably monitor the whole compaction cycle or just parts of it at an acceptable user selectable sample rate, the independent data acquisition system DAQ4 (Hucke Software, Germany) was connected to the Presster.

In the first instance, the DAQ4 has been connected to the Presster using electrically isolating amplifiers (DSCA49, Dataforth, USA), which have been preinstalled for this application by the manufacturer for the purpose of preventing any electronic interference between the DAQ4 and the Presster system.

Unfortunately, the input signal for the DSCA49-05 amplifiers has been found to be the output signal of the DSCA38-05 amplifier and not the original signal from the force or displacement sensors (Fig. 4-2).

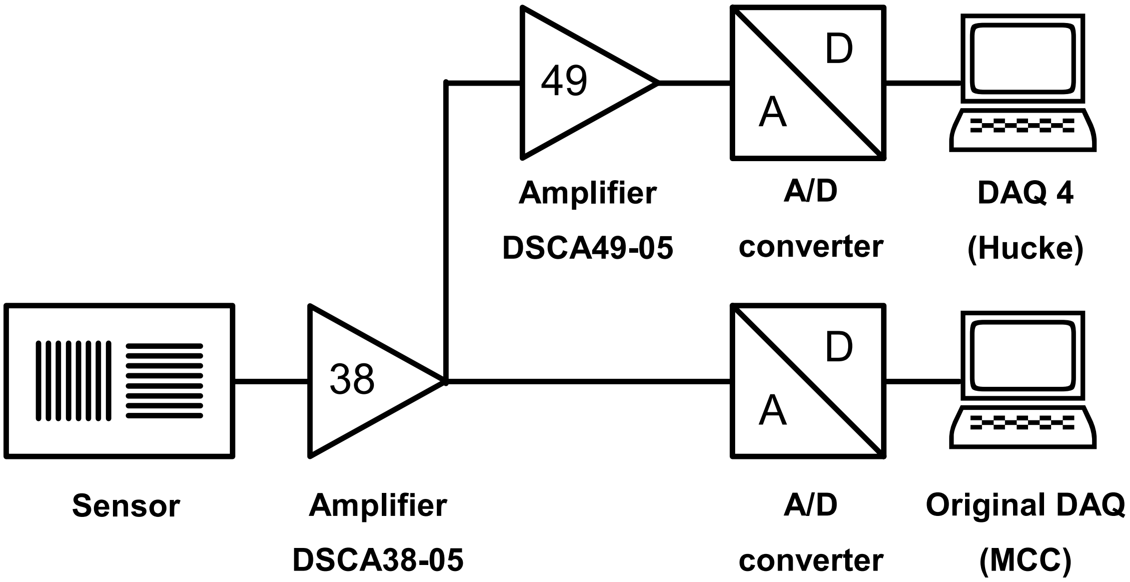


Fig. 4-2 Scheme of the signal processing on the Presster

Therefore, the input signal of the DSCA49-05 isolating amplifiers was not equal to the original signal from the individual sensor, but represented a pre-treated copy, filtered and smoothed by the DSCA38-05 amplifiers.

Hence, the output signals of the DSCA49-05 amplifiers had to be evaluated carefully.

The investigation of the cut-off frequency (-3 dB) of these DSCA49-05 isolating amplifiers, performed by the method described previously, confirmed the specification of a cut-off frequency of about 1 kHz (Fig. 4-3).

Therefore, the investigation of signals up to only 50 Hz is possible without the risk of any signal phase shift (Hoffmann, 1995).

To prove this assumption, a sine wave of 50 Hz has been applied to the DSCA49-05 amplifier. Unfortunately and in contrast to this assumption, the amplifier response to the 50 Hz sine wave signal showed the presence of a slight phase shift (Fig. 4-4).

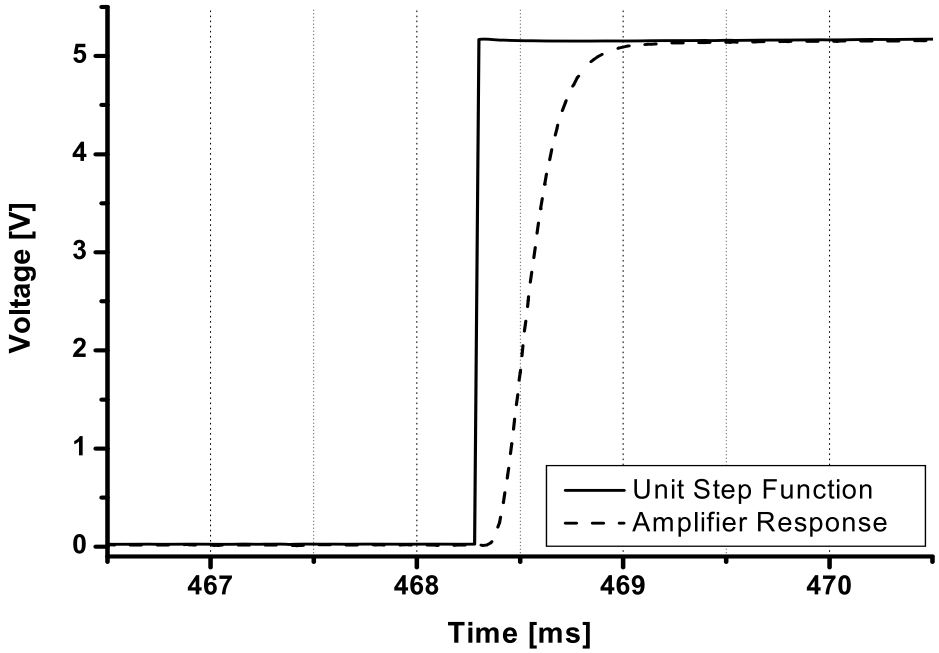


Fig. 4-3 Unit step function and amplifier voltage signal of amplifier DSCA49-05 to investigate its cut-off frequency

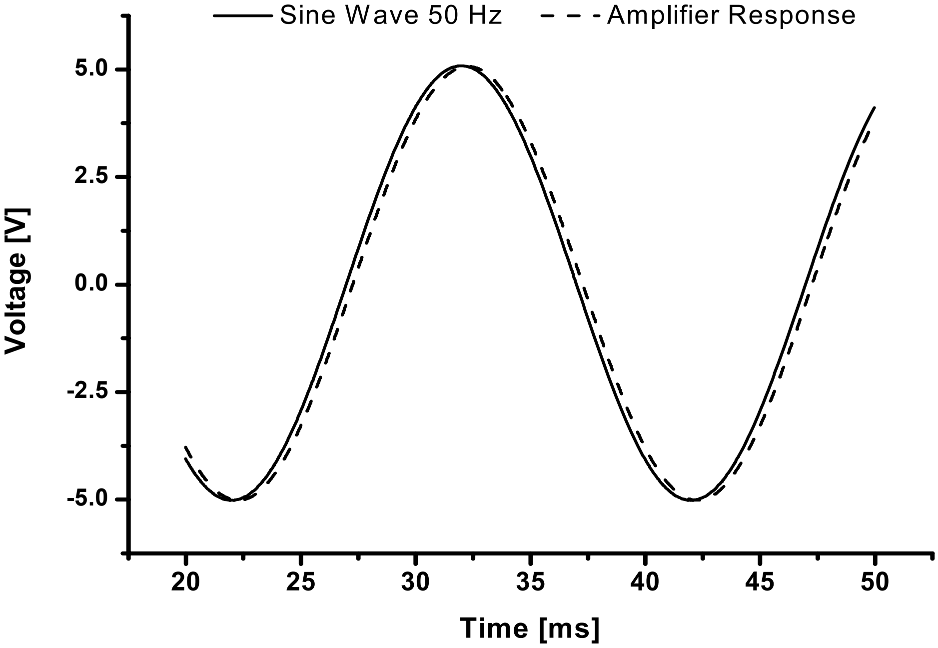


Fig. 4-4 Signal phase shift at 50 Hz sine wave monitored by the amplifier DSCA49-05

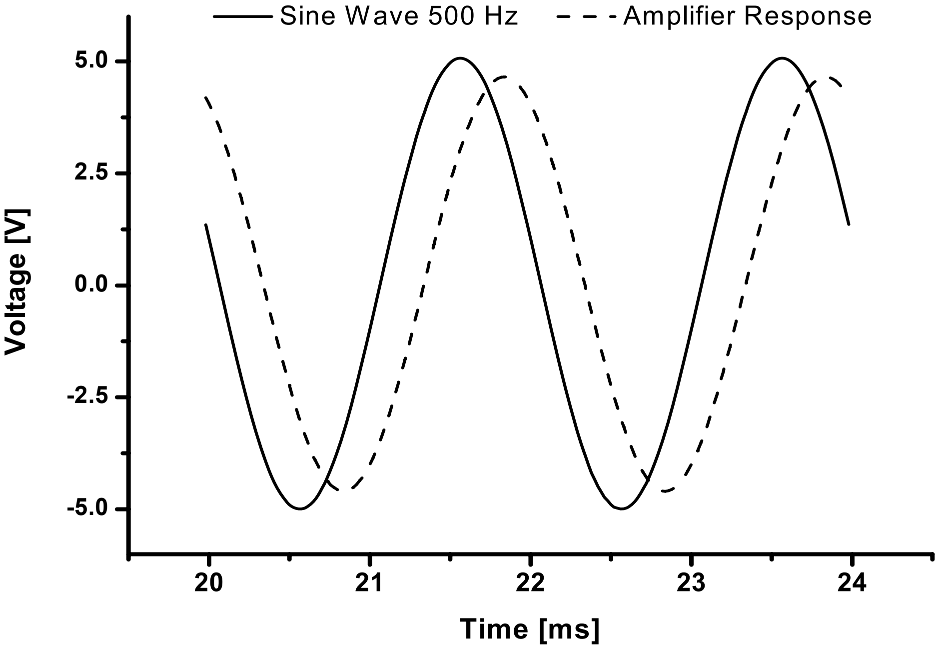


Fig. 4-5 Signal phase shift and distortion of the amplitude at 500 Hz sine wave monitored by the amplifier DSCA49-05

Additionally, by the application of a sine wave of 0.5 kHz to the DSCA49-05 amplifier, a more significant distortion of the amplitude was found (Fig. 4-5). Amplitude distortion was present in the amplifier response at sine wave signals ≥ 250 Hz.

As a signal phase shift is less critical for standard investigations of compaction forces compared to the distortion of the amplitude, the performance of the DSCA49-05 amplifier is sufficient for the examination of low frequent signals up to about 250 Hz, as long as only the magnitude of this amplitude is of importance and not its value as a function of time.

Therefore, taking care of a possible signal phase shift, the examined frequency range of both types of amplifiers has been found to be adequate for most of the investigation of compaction forces.
Faster signals, e.g. the ejection force and take-off force signals can not be monitored reliably using either the DSCA38-05 or the DSCA49-05 type of amplifier.
The circumstances of essential revision of some of the instrumentation, as presented in the following, demanded concurrently the revision of the associated amplifiers. All the improved measurement systems have been comprehensibly installed independently of the original data acquisition system of the Presster. Therefore, the reliable observation of all compaction cycle associated signals has been ensured at a user selectable sample rate up to 1.25 MHz using the independent data acquisition system DAQ4.

As a consequence, the original system of the Presster is no longer used for any data acquisition purposes.

4.1.3 Summary

The reliable and accurate investigation of powder compaction behaviour, as well as compaction related processes, require a data acquisition system providing a sample rate which exceeds the signal frequency at least by 100 %, in order to avoid any distortion of the signal amplitude as measured by the amplifiers.

Due to the cut-off frequency of the original amplifiers of the Presster, accurate data acquisition has been limited to signals having a frequency below 1.5 kHz. Using the manufacturer provided parallel wiring, signal distortion has already been found for signals having a frequency larger than 0.25 kHz.

Therefore the original data acquisition system of the Presster was found to be inadequate as the speed dependant sample rate in the range of 1.5 and 7.4 kHz worked only for slow signals e.g. pre- and main compaction force signals.

It was been found to be unsuitable to monitor rather high frequency signals, e.g. those of the TO event.

In order to reliably monitor all the signals of the Presster properly without any limitations and at a user selectable sample rate, the independent data acquisition system DAQ4 has been used in all subsequent data capture.

Therefore, the original system of the Presster became redundant except for control aspects.

4.2 Compaction Force Measurement Systems

The evaluation of the process of powder compaction in terms of compactibility requires an accurate determination of the compaction pressure over the entire contact time between punch and compaction roller.

In contrast to the standard instrumentation of just the lower pre- and main compaction rollers on research and production size rotary tablet presses, both the upper and lower pre- and main compaction forces have been monitored on the Presster.

With respect to the simulation of a Fette P1200 rotary tablet press the lower pre- and main compaction forces of the Presster have been investigated, since on a Fette P1200 only the lower pre- and main compaction forces are displayed.

4.2.1 Techniques for Force Measurements

On the field of tableting mainly two different technologies, strain gauges and piezoelectric transducers, are in use for the measurement of the applied compaction forces.

The most popular way until today is the use of strain gauges applied to different machine parts (Watt, 1988; Bauer-Brandl, 1998), as Higuchi and co-workers previously had in 1952.

As a consequence of the mechanical design of these strain gauge transducers and their need for linear bending or shearing machine parts, their resonance frequency is limited to lower frequencies (Fig. 4-6).

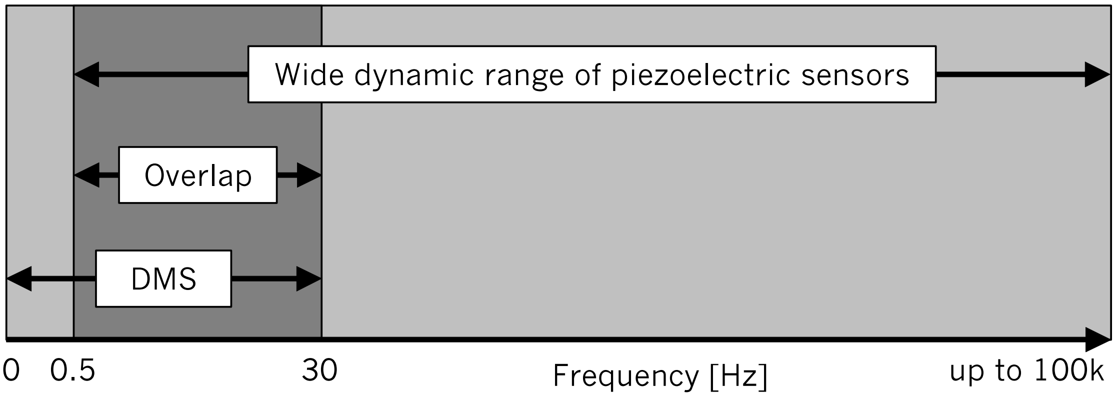


Fig. 4-6 Frequency ranges of strain gauge and piezoelectric sensors (according to force sensor selection guide, PCB, USA)

Hence, strain gauge transducers are designated for the measurement of static and less dynamic forces.

Furthermore, dependent on the point of application of the strain gauges, the resulting resonance frequencies of the different systems may vary, as the bending of machine parts requires the movement of these machine parts and therefore their associated mass.

This is comparable to the situation known for piezoelectric instrumentation, as their resonance frequency decreases with increasing mass attached to the system, resulting in a smoothing effect.

The measurement of compaction forces as close as possible to the tip of the punch, using an instrumented punch, is the most precise method.

Different systems of single instrumented punches have been developed in the last few years (Tab. 4-1), while the DigiPunch (PST, Rheinbach, Germany) represents the most actual development.

As the method of calibration of compaction force instrumentations has an effect on the precision and accuracy of the obtained compaction force data (Leitritz, 1995), these instrumented punches are at least a very highly precise calibration tool, applicable on any press working with the particular type of tooling.

Tab. 4-1 Various models of instrumented punches

Brand	**Supplier**
Portable Press Analyzer	Puuman Oy, Kuopio, Finland
Telemetric Punch	University of Bonn, Germany
The Punch	SMI, Whitehouse, New Jersey, USA
DigiPunch	PST, Rheinbach, Germany

Especially with scale-up problems or the comparability between presses of different brands or size, the dynamic calibration of tablet presses may help to identify and finally minimise calibration induced discrepancies and is therefore the calibration method of choice.

4.2.2 Investigation of the Original Presster Pre- and Main Compaction Force Measurement Systems

In case of the Presster, the strain gauges (Tab. 4-2) have been placed on the compaction roller pins.

Each single strain gauge works as a Wheatstone bridge, is fully active and temperature compensated.

Tab. 4-2 Strain gauges used for compression roller pin instrumentation on the Presster

Point of Application	**Type of strain gauge**	**Supplier**
Upper and lower pre-compression roll pin	N2A-06-T031P-350	Vishay
Upper and lower main compression roll pin	TK-06-S145R-10C	Vishay

The investigation of the compactibility of different excipients simulating a Fette P1200 rotary tablet press has been performed to evaluate the comparability of tablets produced on both the Presster and the Fette P1200 at similar compression pressure settings.

On both presses a 9R15 Euro B tooling has been used. The Fette P1200 has been equipped with a full set of this type of punches and dies.

Depending on the deformation behaviour of any pharmaceutical material, the densification speed is known to have a major influence on tablet properties (Roberts, 1985). Therefore, the diameter of both the pre- and main compaction rollers used on the Presster have been selected to match the diameters of the compaction rollers of the Fette P1200 (all 250 mm).

Excipients and lubricants used within this investigation have been blended in a 20 l metal vessel using a lab-scale free fall blender (Bohle, Germany).

As the vessel had been filled by a maximum of 5 kg, the remaining space was sufficient for the blending process. The lubricant has been placed in between two fractions of the individual excipients inside the vessel, in order to minimise lubricant adhesion to the inner wall of the blending vessel. Blending time was set to 3 minutes at 60 RPM, while the direction of rotation of the blending vessel was changed every 30 seconds.

The results of the first investigations of the compactability of Flowlac 100 and Neosorb P60W blends showed some major differences in the resulting compactability profiles obtained for the Fette P1200 and the Presster (Fig. 4-7 and 4-8), present over the entire compaction pressure range.

Tablets made at the same compaction pressure level showed larger tensile strength values on the Presster compared to those made on the Fette P1200.

Despite both the Presster and the Fette P1200 being calibrated by the individual manufacturer, the most likely reason for these differences in the compactibility profiles had been assumed to be a difference in the calibration of the force measurement systems of one or even both machines, as the machine settings and process parameters had been harmonised as far as possible for the two machines.

Therefore, a dynamic calibration was performed on the Presster and the Fette P1200 using the DigiPunch.

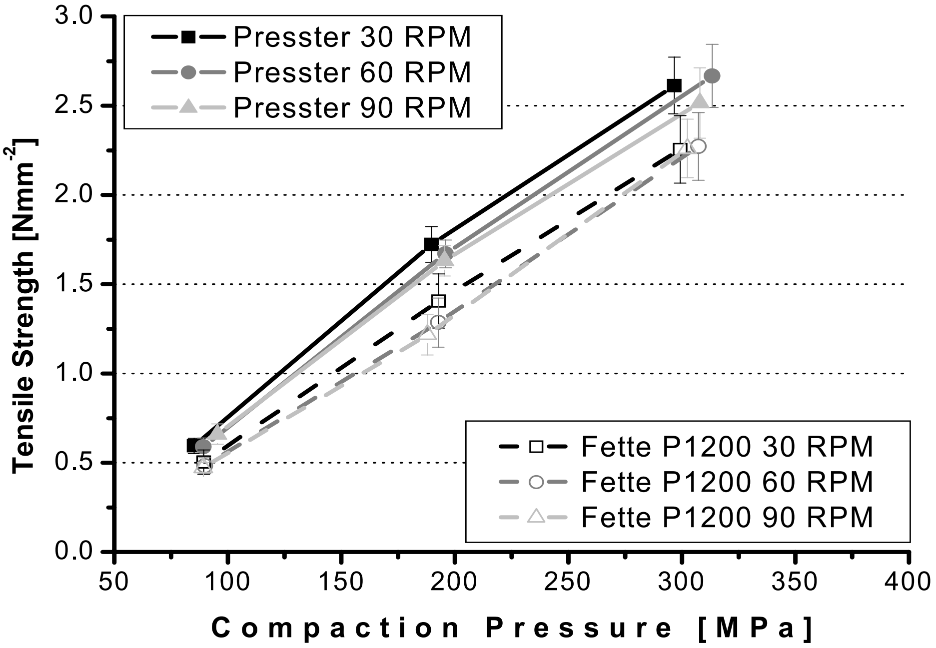


Fig. 4-7 Compactibility profiles of a blend of Flowlac 100 and magnesium stearate (99:1)

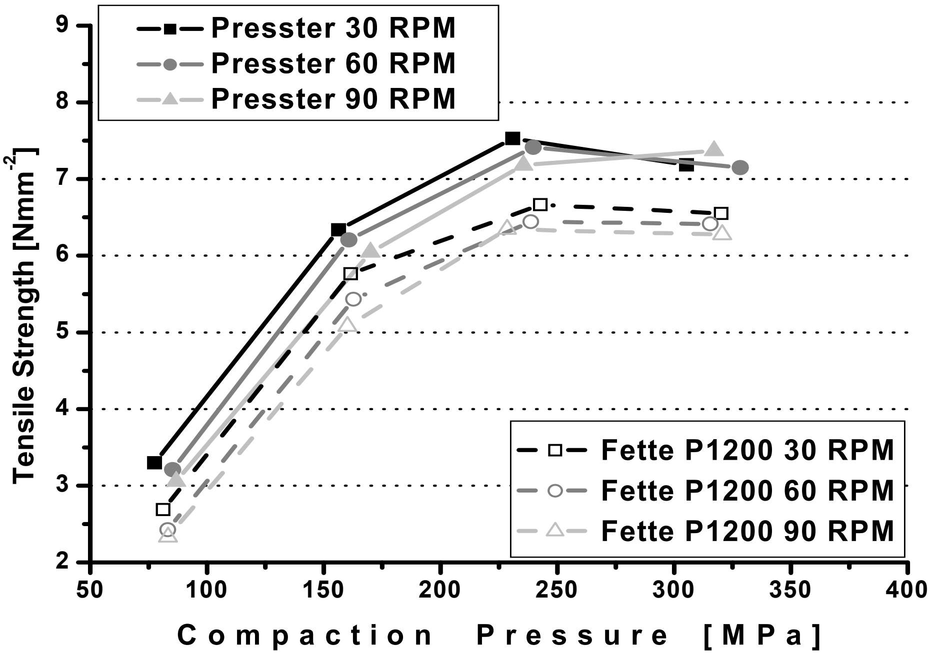


Fig. 4-8 Compactibility profiles of a blend of Neosorb P60W and magnesium stearate (98.5:1.5)

4.2.3 Dynamic Calibration of the Original Pre- and Main Compaction Force Measurement Systems

Differences between static and dynamic calibrations of tablet presses have been shown by Leitritz (1995). Therefore, to calibrate the Presster pre- and main compaction force measurement instrumentations, a dynamic calibration method was preferred.

After all the amplifiers have been warmed up for minimum 1 hour, at least 10 tablets of Emcompress have been made at the load settings of the final calibration runs, before the dynamic calibration has been performed at a horizontal speed of 1.2 ms^{-1}.

The compaction forces monitored by the instrumented punch DigiPunch (PST, Germany) during the calibration runs were used as the reference force in order to calibrate the original pre- and main compaction force measurement systems, of which the voltage output has been monitored by the DAQ4 system.

Both data sets were analyzed using the CaliDat software (Hucke Software, Solingen, Germany).

As long as the residuals of the linear fit of the data points of the calibration run described a mathematical function, polynomial fits have been used to adequately characterise the data sets.

The degree of the polynomial function has been increased up to the maximum of a forth degree, until the residuals of the following polynomial degree either became more narrow or had been spread randomly around the fit. If none of these two demands had been fulfilled by the following polynomial degree the smaller one had been accepted.

The calibration function of the lower main compaction force measurement system of the Presster as well as the corresponding residual plot is given by Fig. 4-9 and 4-10, respectively, which have been significantly different to the ones preset by the manufacturer within the original data acquisition system.

The 95 % confidence and prediction intervals are shown tenfold enhanced for better recognisability.

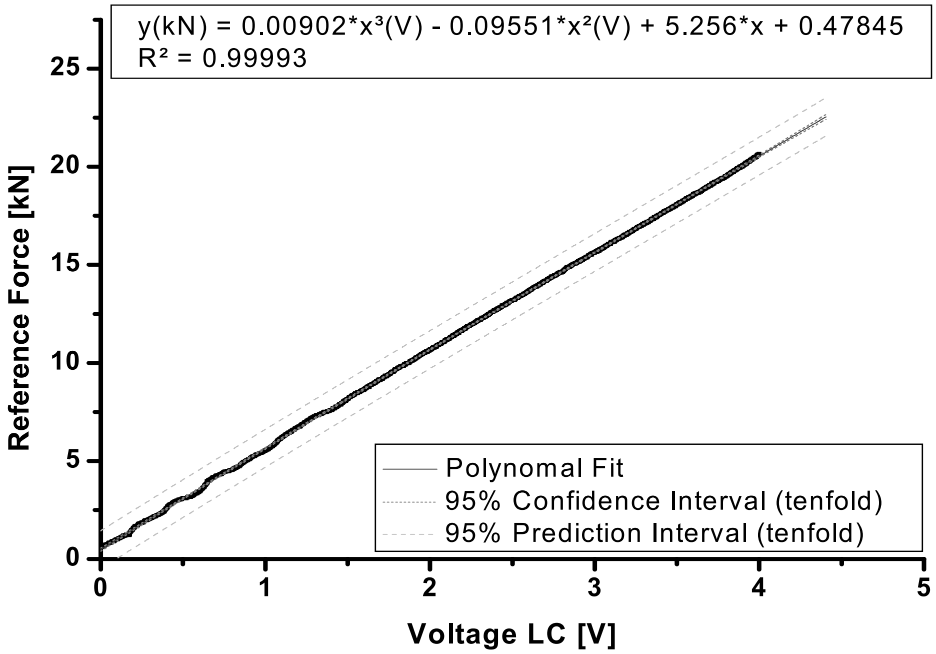


Fig. 4-9 Calibration of force measurement system exemplarily shown for the lower main compression force measurement system

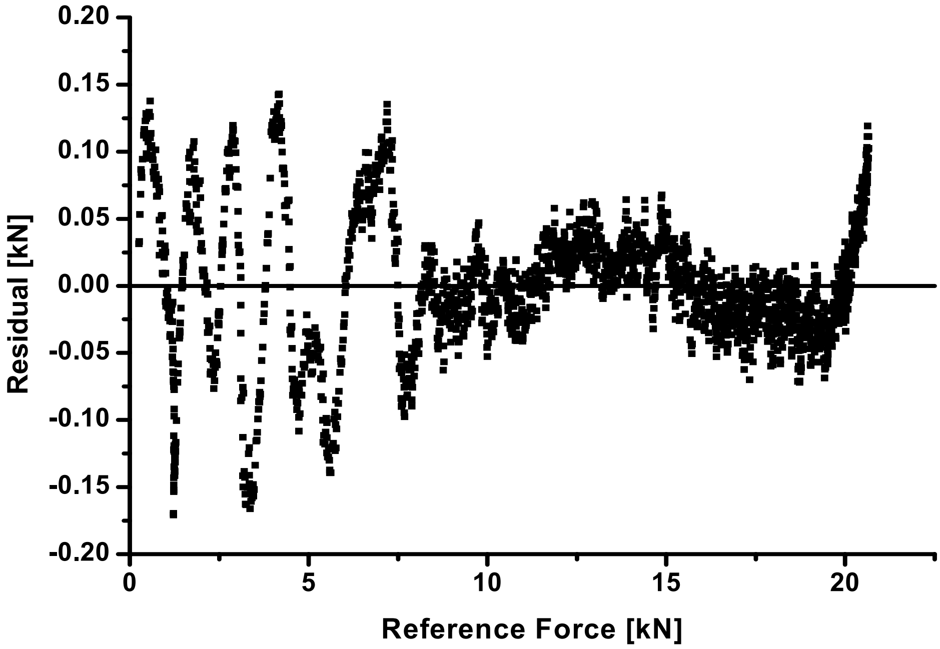


Fig. 4-10 Residual plot of the calibration of the lower main compression force measurement system

After recalibration of the Presster force measurement instrumentations the new calibration functions (Tab. 4-3) have been implemented to the independent data acquisition system DAQ4.

Tab. 4-3 Calibration functions of the compaction force measurement systems of the Presster

Measurement System	**Calibration Function**	**COD**
Upper Pre-Compaction	$y \text{ [kN]} = -0.02029{*}x^2 \text{ [V]} + 1.39425{*}x \text{ [V]} - 0.13157$	0.99979
Lower Pre-Compaction	$y \text{ [kN]} = -0.01383{*}x^3 \text{ [V]} - 0.07857{*}x^2 \text{ [V]} + 1.22689{*}x \text{ [V]} - 0.10027$	0.99991
Upper Main Compaction	$y \text{ [kN]} = 0.04293{*}x^3 \text{ [V]} - 0.34545{*}x^2 \text{ [V]} + 6.19811{*}x \text{ [V]} - 2.2337$	0.99978
Lower Main Compaction	$y \text{ [kN]} = 0.00902{*}x^3 \text{ [V]} - 0.09551{*}x^2 \text{ [V]} + 5.256{*}x \text{ [V]} + 0.47845$	0.99993

Due to the recalibration, the residuals of all upper and lower pre- and main compaction force measurement systems have never been found to exceed ± 5 MPa.

4.2.4 Compactibility Studies Simulating a Fette P1200 Rotary Tablet Press

After the recalibration of the compaction force measurement systems, the results of the previously performed investigations on the comparability of compactibility profiles have been converted by the new calibration functions. The compactability of the blend of Flowlac 100 and 1 % magnesium stearate, processed on both the Presster and the Fette P1200, now turnes out to be much more reproducible (Fig. 4-11).

The error in the previously used calibration functions of the compaction force measurement system of the Presster is obvious by the difference in the compaction pressure levels between the two machines.

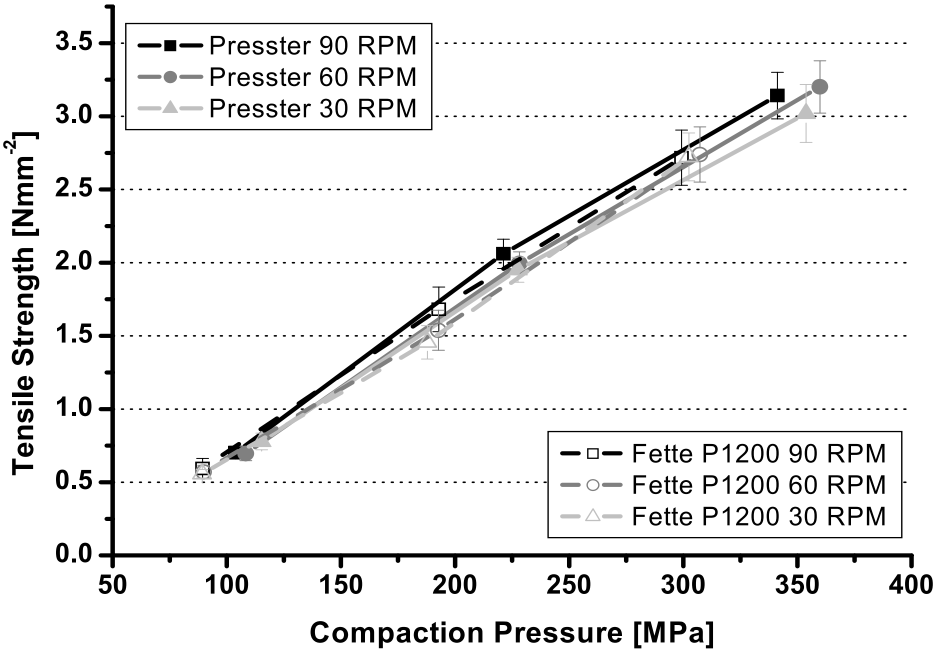


Fig. 4-11 Compactibility profiles of a blend of Flowlac 100 and magnesium sterarate (99:1)

A different situation has been found for the blend of Neosorb P60W and 1.5 % of magnesium state (Fig. 4-12). A satisfying conformity for the compactibility profiles obtained by the two machines has been obtained up to a compaction pressure level of about 175 MPa and a tensile strength of about 6 Nmm^{-2}. At higher compaction pressures, the tensile strength of tablets made on the Presster exceeded those made on the Fette P1200.

As all the accessible and adaptable machine parameters had been harmonised between the two machines prior to the investigation, the origin of this effect is caused by some inadaptable and varying machine parameters between the two machines as the die feeding process or the lag time between the pre- and main compaction station.

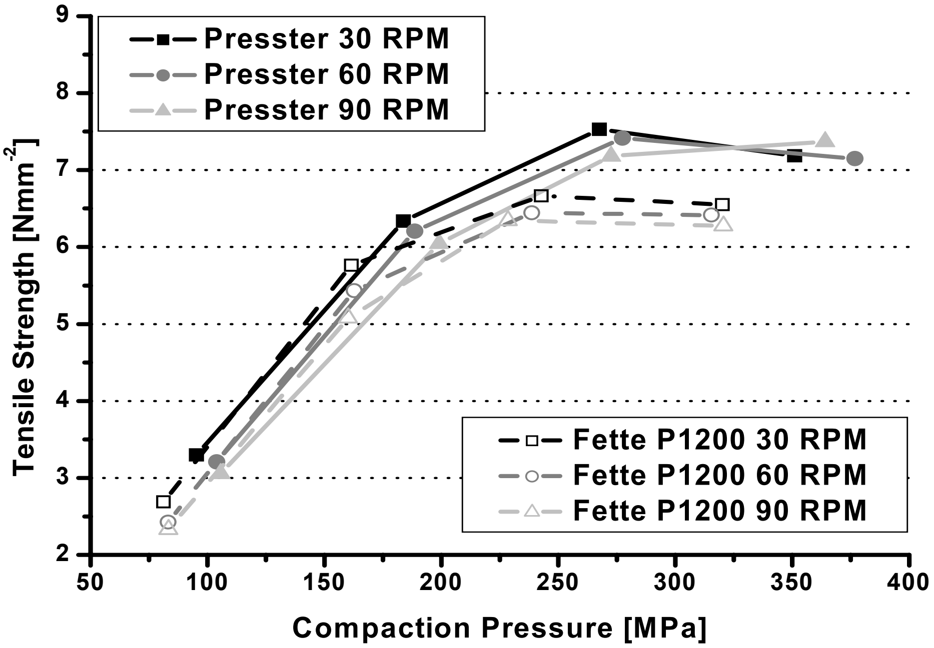


Fig. 4-12 Compactibility profiles of a blend of Neosorb P60W and magnesium sterarate (98.5:1.5)

The production and investigation of sorbitol tablets, having a tensile strength larger than 5 to 6 Nmm^{-2}, is quite unusual and of rather limited practical interest, as those large tensile strength values in most cases will have an adverse effect on disintegration and dissolution profiles.

The conformity of the compactibility profiles over the range of practical use for production, including the consistency for the observed speed dependency, predominates the deviation in the range above 175 MPa or rather 5-6 Nmm^{-2}.

As the compactibility profiles of other blends did not show any obscurity in the upper compaction pressure ranges, it might be suggested, that the reason for this difference has to be located in the determination of the crushing force of the tablets and the particular hardness tester.

As the crushing force of tablets of both machines have been investigated on the same type of hardness tester (Multicheck Turbo III, Erweka, Germany) this assumption is unlikely and it’s a true difference.

The repetition of the investigation of the compactibility of Neosorb P60W did not show any significant variation compared to Fig. 4-12.

Finally, the same investigation has been performed for a blend of Di-Cafos and 1 % magnesium stearate (Fig. 4-13).

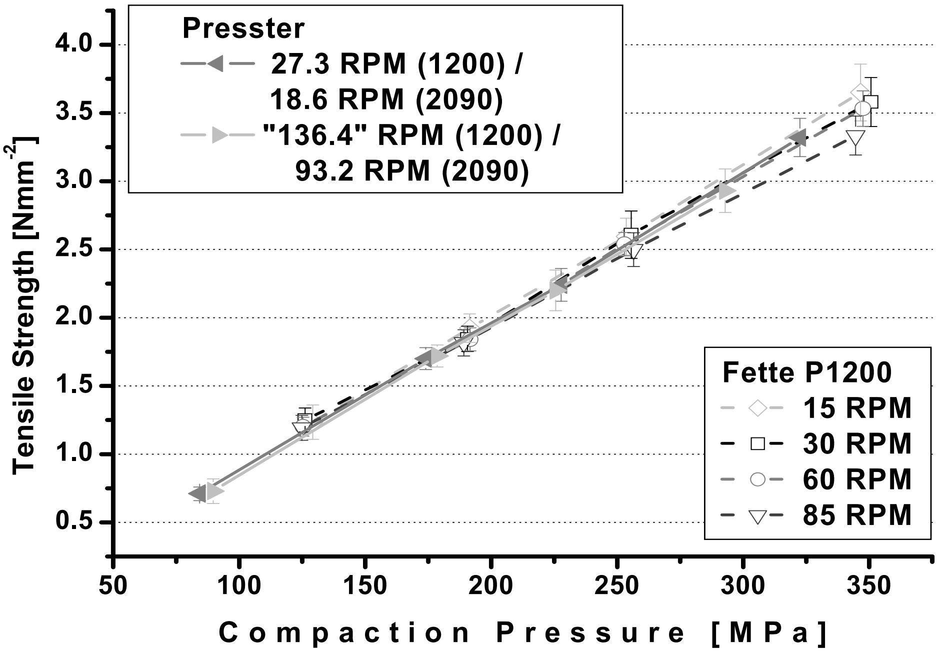


Fig. 4-13 Compaction Pressure vs. Tensile Strength Profile of a blend of Di-Cafos and Magnesium Sterarate (99:1)

Due to the brittle nature of dicalcium phosphate dihydrates it has been expected, that the tensile strength of tablets of Di-Cafos are hardly affected by an increase in tableting speed (Armstrong, 1989; Rees, 1978).

Therefore, the set speed values of the Presster have been selected to match its minimum and maximum achievable speed conditions. As the maximum horizontal speed of the Presster exceeds the speed range of the Fette P1200 a Fette 2090 has been simulated, while the Fette P1200 has been operated at four different speed settings of 15, 30, 60 and 90 RPM.

The resulting compactibility profiles obtained by both the Presster and the Fette P1200 complied sufficiently with each other and finally confirmed the more or less speed independent compactibility of dicalcium phosphates.

4.2.5 Summary

The compaction force measurement systems of the Presster have been investigated in order to ensure reliable compaction force measurements during compressibility and compactibility studies.

Comparable pressure levels on both the Presster and the Fette P1200 should result in compacts having similar properties.

Therefore, compactibility profiles of three different blends of pharmaceutical excipients have been investigated at different speed settings on both the Presster and the Fette P1200 rotary tablet press, revealing major differences, in particular at higher pressure levels.

A dynamic recalibration of both the Fette P1200 and the Presster finally disclosed a wrong calibration of the compaction force measurement systems of the Presster.

Hence, after recalibration, compactibility profiles of the blends of Flowlac 100 and Di-Cafos complied satisfyingly between the two machines, while the blend of Neosorb P60W still showed some inconsistency at compaction pressure levels larger than 175 MPa and tensile strength values of the compact of about 6 Nmm^{-2} respectively.

As the compaction cycle on both the Presster and the Fette P1200 has been harmonised as far as possible, the remaining, inaccessible variations in the compaction process of the two machines, as e.g. the die feeding system and the lag time between pre- and main compaction stations, account for these discrepancies.

Therefore, compactibility data obtained at compaction pressure levels beyond 175 MPa or accompanying tensile strength values larger than 6 Nmm^{-2} have to be handled carefully, while a general rejection of compaction data obtained at pressure levels beyond 175 MPa has not been indicated due to the consistency in the results observed for the blends of Flowlac 100 and Di-Cafos.

Nevertheless, the production of tablets, having tensile strength values above 6 Nmm^{-2} is rather seldom due to the increasing number of adverse effects like unsatisfying disintegration time or lacking divisibility of tablets. Therefore, the compaction force measurement systems of the Presster have finally been applicable to monitor compression forces reliably.

4.3 Ejection Force Measurement System

The ejection force in general represents the maximum force necessary to overcome the friction of the tablet at the beginning of the ejection phase.

It has often been found to be unequal to the overall maximum force of the ejection event (Herzog, 1991).

The maximum, as well as the shape of the ejection force signal, sometimes in combination with the residual force (Hanssen, 1970), are commonly used to estimate the necessary lubrication of tableting blends with respect to preventing friction and sticking problems.

Sticking tablets and increasing friction between tablets and punches and/or dies are often first recognised by increasing ejection forces. Therefore, the monitoring of these signals during research and development as well as during production activities is recommended.

Investigations on this topic have been first published by Nelson (1954).

The instrumentation of the ejection cam of rotary tablet presses proved to be more complex compared to the situation present on eccentric tablet presses.

Knoechel (1967) placed the ejection cam of a rotary tablet press on two strain-gauge instrumented bolts. The interpretation of ejection force signals was quite difficult, as always more than one punch has been in contact with the ejection cam at the same time. Therefore, a reduced number of punches had to be used to eliminate this problem. To avoid any dependency between the location of the punch on the cam and the measured load, the ejection cam had to be supported on three widely spread transducers, whose outputs have been summed (Williams, 1984).

Marshall (1983) suggested a segmented ejection cam in order to be able to use a full set of punches on rotary tablet presses. Furthermore, the ejection cams of rotary tablet presses have been shortened and, at the same time, the width of the gauged section has been designed to be narrower.

Influences of the tablet band height as well as the machine speed on the maximum height of the ejection peak have been found by Führer (1970), using an instrumented eccentric tablet press.

As the quality of ejection force signals gained by an instrumented cam has often been affected by various issues e.g. the friction between the punch barrel and the punch bushing or machine vibrations, the instrumentation of individual punches using strain gauges has been implemented (Shotton, 1963; Wiederkehr-von Vincenz, 1977).

A predominance of quartz load cell instrumentation compared to strain gauges, especially while used in the range of small forces, has been seen (Steffens, 1978; Schmidt, 1989).

With respect to dynamic force measurements, further advantages of piezoelectric force transducers in comparison to strain gauge transducers are shown in Table 4-4.

Tab. 4-4 Advantages of piezoelectric force transducers regarding dynamic force measurements

Aspect	**Advantage**
Measurement range	Up to 10 times larger
Rigidity	Typical 10 times more rigid
Stability of sensitivity	No altering effects, therefore more stable as no moving parts
Calibration interval	Longer

The instrumentation of a lower punch of an eccentric press using a quartz load cell finally enhanced the quality of ejection force signals for practical measurements (Steffens, 1982).

An instrumented EU19 punch has been used by Reisen (1987) to measure ejection forces on a Manesty Rotapress MKII at an ejection speed of 82 $\mathrm{mms^{-1}}$ and to compare these signals with those of an eccentric tablet press. Despite the presence of interfering effects on the signals of the quartz load cell instrumented eccentric press, its signals were obviously smoother.

Gullatz (1996) used a quartz load cell instrumented EU19 punch to monitor ejection forces on a Kilian T 200 (Kilian, Cologne, Germany). Signals have been transferred from the punch to a receiver outside the tablet press by radio telemetry. Therefore, the only limitation to the feasible number of revolutions of the turret of the tablet press has been given by the voltage supplying battery.

As these instrumented punches have not been connected to the tablet press as completely as the ejection cams the interfering noise has been much smaller and therefore the quality of ejection force signals exceeded the most standard instrumentation of rotary tablet presses.

Despite the well known differences in the frequency ranges of strain gauge and quartz load cell instrumentation (Fig. 5-2-2), strain gauge instrumented bolts or beams are still widely used to measure ejection forces.

The ejection force measurements of most current rotary tablet presses do still not represent the force required to eject one single punch including its tablet, as there are in most cases, depending on the type of tooling, still at least two adjacent punches simultaneously in contact with the ejection cam.

Therefore, the ejection force measurements of rotary tablet presses working with a full set of punches have to be evaluated carefully.

Nevertheless, as the ejection force of one of the punches being in contact with the ejection cam at the same time is always smaller than the actual measured total ejection force, the accuracy of this measurement might be sufficient in those cases, where the ejection force is used only to either monitor changes in the motility of the punches and the proper functionality of the individual rotary tablet press or with respect to relative measurements.

As soon as the ejection force should be further investigated with respect to e.g. the optimization of the amount of lubrication of an actual powder blend it might be interesting to measure individual ejection forces for each single punch and compact. Due to the above mentioned situation on rotary tablet presses, this is still only possible while working with a reduced number of punches.

This has been the situation for the simulated Fette P1200 rotary tablet press whether a turret of 24 or 30 EU19 stations has been used.

Therefore, the ejection force signals finally presented for the Fette P1200 have been obtained using just 1 of the 24 pairs of punches on the Fette P1200, which was operated using a special galenic operation mode.

4.3.1 Investigation of the Original Presster Ejection Force Measurement System

The ejection cam of the Presster has been placed inside a small frame, which has been hung up into the Presster using three strain gauge instrumented bolts (Fig. 4-14).

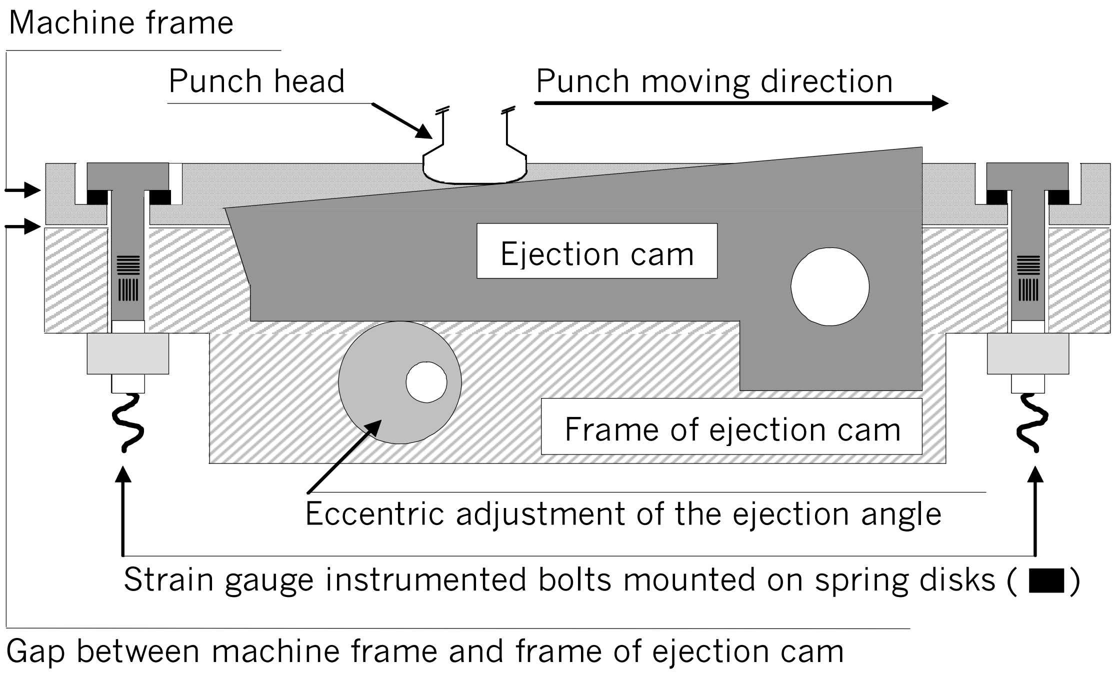


Fig. 4-14 Scheme of the original ejection cam of the Presster

Within the nominal range of 5° to 15.6°, the ejection angle of the ejection cam of the Presster is adaptable to the conditions of the simulated rotary tablet press by an eccentric drive.

The frame of the ejection cam has not been connected directly and therefore rigidly to the machine frame of the Presster but has been supported on three

sets of disk springs, one at each mounting point, working as an overload protection for the ejection cam.
As the ejection cam was designed to be not directly instrumented by itself, the ejection force measured by this system equals the extension of the instrumented bolts.

The signals of the three strain gauge instrumented bolts have been summed up to one signal, which has been processed by the associated amplifier (DSCA38-05, Dataforth, USA) before being sent to the data acquisition system.

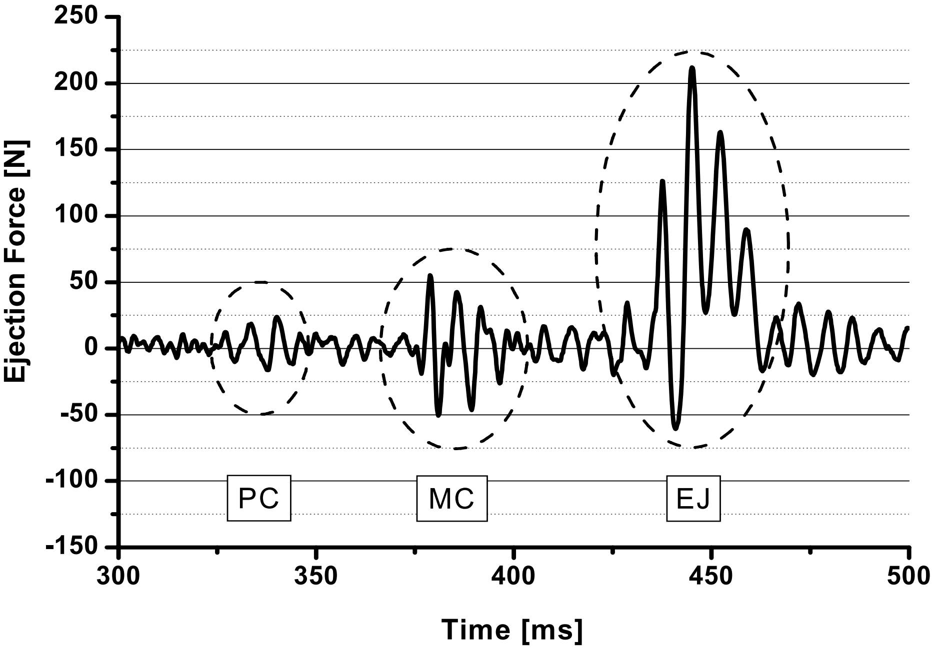


Fig. 4-15 Ejection force signal gained by the original instrumentation of the Presster

The already previously mentioned, rather loose supporting of the frame of the ejection cam on disk springs with respect to an overload protection, being more than obvious due to the presence of a small gap in between the two frames, was supposed to be responsible for the quite noisy signal monitored by the ejection (EJ) force measurement system (Fig. 4-15).

Early parts of the ejection force signal could be clearly associated to the previous pre- and main compaction events (PC and MC in Fig. 4-15).

These observations would resemble the behaviour of the ejection force measurement system of a Korsch PH-106 rotary tablet press (Korsch, Germany). Gullatz (1996) observed the lower compaction roller pin of the PH-106, on which its ejection cam has been supported, evading the applied ejection force as soon as a counter pressure of a hydraulic piston fell short of a certain value.

Due to the huge oscillations of the entire ejection force signals obtained by the original instrumentation of the Presster, representing a resonance frequency of about 170 Hz, the evaluation of these signals has not been possible.

The original calibration function of the ejection force measurement system became invalid by any modification of the tightening of the connection between the frame of the ejection cam and the machine frame of the Presster.

Unfortunately, the adaptation of the calibration function of the ejection force measurement system, as well as those of any other original measurement system of the Presster, has been inaccessible to the user by design of the Presster data acquisition system.

So, the influence of the quality of fixation on the signal quality and the signal to noise ratio could not be evaluated.

Additionally, as the ejection force measurement system has been activated right at the beginning of the entire compaction cycle, the base line noise level of the ejection force signal has been changed for the worse due to machine vibrations caused by the pre- (PC) and main compaction (MC) events prior to the native ejection event.

Due to these results, the ejection force measurement system had to be totally redesigned in order to use the ejection force signal with respect to product development and/or trouble-shooting purposes.

4.3.2 Modification of the Ejection Force Measurement System

As to the unsatisfying quality of the ejection force signals obtained by the original ejection force measurement system, a new system was designed to replace the original one.

A kit of four quartz load cells (Slim Line 9135BA49, Kistler, Germany) has been used to directly instrument the redesigned ejection cam. Therefore the point of measurement has been relocated closer to the point of origin of the ejection forces.

The load cells have been placed on a straight line in between the grinded mounting surfaces of the upper and lower part of the ejection cam (Fig. 4-16), while the distance between the load cells is equal.

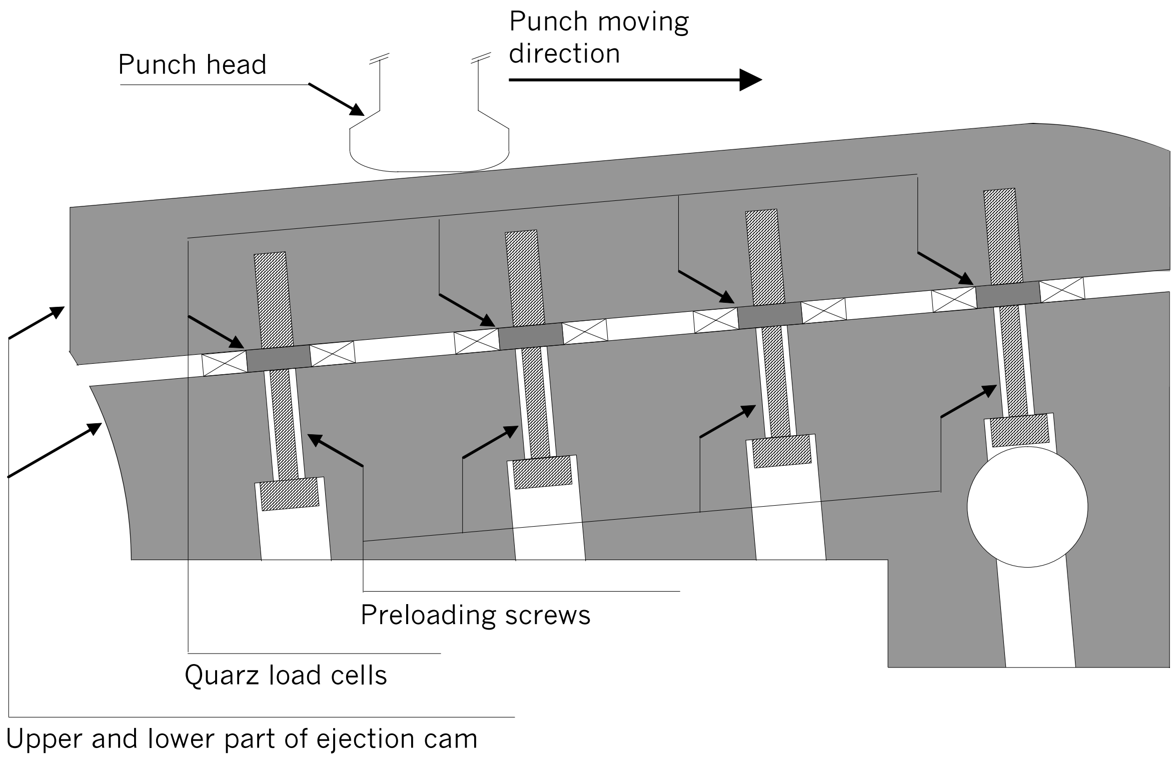


Fig. 4-16 Schematic design of the redesigned instrumented ejection cam

To minimise the unavoidable force shunt, which generally results in a reduction of the sensitivity of the individual sensors, special preloading screws have been used to mount the sensors under preloading into the ejection cam.

By design, the partial forces on each sensor are either summed up to give the total force or measured as specific forces, acting on the individual sensors.

The placement of the sensors inside the cam has been designed to avoid the punch to load the ejection cam outside the outer two of the four sensors. Therefore the bending of the cam over the edge of the outer sensors has been avoided.

Finally, a photoelectric proximity sensor (WT 150-P460, Sick, Germany) has been installed to initialise the data acquisition of signals monitored by the revised ejection force measurement system immediately before the ejection event, and therefore to prevent a time dependant base line drift of the ejection force signals.

4.3.3 Calibration of the Modified Ejection Force Measurement System

The revised ejection force measurement system has been set up to measure the total force applied to the ejection cam. Therefore the sum of the signals of the four load cells has been transferred to the affiliated charge meter (5015A1000, Kistler, Germany).

As the quartz load cells have been supplied uncalibrated, the sensitivity of the new arrangement has to be determined prior to any calibration.

Therefore, each sensor has been individually preloaded up to an uncalibrated force of 2,000 ± 100 N, working with a standard sensitivity for the appropriated load cells of $-3.5\ \mathrm{pCN}^{-1}$, which has been recommended by the supplier.

The preload has been applied to the individual load cells to guarantee a straight vertical force transmission from the punch via the upper part of the ejection cam to the load cells and therefore minimised interfering effects of both bending moment and force shunt.

Too small a preload may lead to falsified ejection force signals due to oblique and inconsistent force transmission over the edge of the sensors.

As with the preload, applied to one load cell mounted in the new ejection cam partly affects the preload of the adjacent load cells, the actual applied partial load on each load cell has to be determined individually by the use of one charge meter per load cell.

Afterwards, the system has been adapted to measure the total force. In the following, the setting of the total sensitivity for the new system has been adjusted until the precision and accuracy of the measured total forces has been found to result in an error smaller than 10 N for the entire measurement range up to 100 kg.

By this method the final used total sensitivity of the new ejection force measurement system was determined to be -3.89 pCN^{-1}.

In the end, each quartz load cell within the redesigned ejection cam has been preloaded again individually between the upper and lower parts of the ejection cam to a still uncalibrated partial force applied on each sensor of 2,000 ± 100 N using the previously specified sensitivity of 3.89 pCN^{-1}.

For calibration as well as for measurements purposes, the measurement range of the charge meter has been set to 250 MUV^{-1} at the recommended operation mode “DC long” ($\tau > 10^5$ s).

A static calibration was performed by the application of different weights up to 100 kg, while 10 kg equals 98.1 N. The ejection cam was therefore levelled horizontally giving a virtual ejection angle of 0° to ensure a straight vertical force transmission to the sensors.

Due to the small dimensions of the ejection cam compared to the one of the weights, a calibration above 100 kg was not possible.

This ejection force measurement system turned out to be linear under preload within an error of ≤ 2 % FSO, the calibration function obtained (Fig. 4-17) was finally extrapolated to larger force values than those of the calibration run. The quality of the calibration function has been shown by the 95 % confidence and prediction intervals, which are both displayed expanded by a factor of ten.

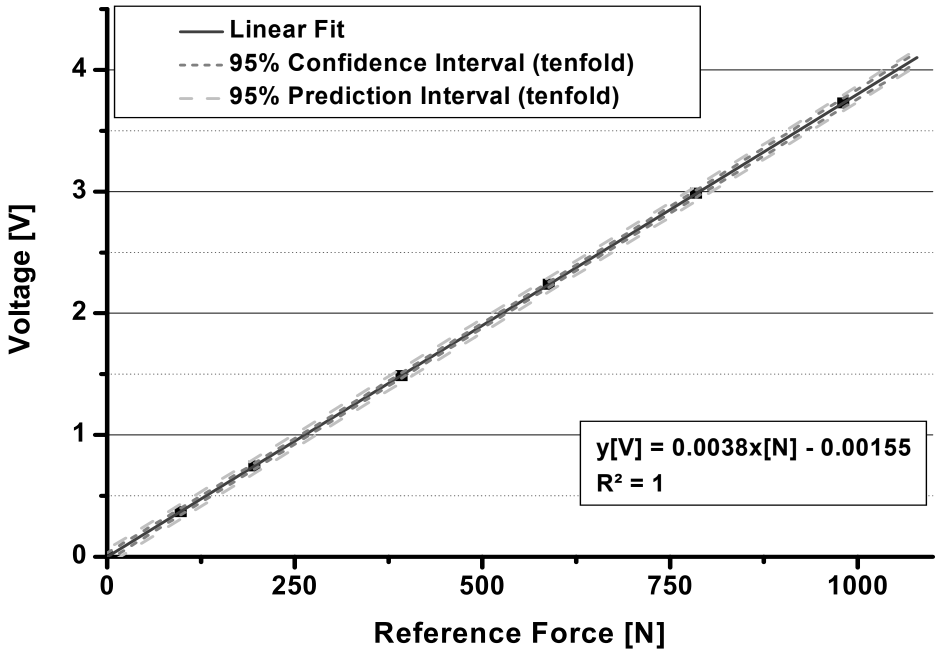


Fig. 4-17 Static calibration of the new designed ejection force measurement system

4.3.4 Evaluation of Measurements Performed by the Modified Ejection Force Measurement System

As the ejection cam has been calibrated while positioned plane horizontally, i.e. a virtual ejection angle of 0°, which is different to any practical ejection angle, the ejection force measurements were corrected according to Eq. 4-3,

$$F = \frac{F'}{\cos \alpha} \qquad \text{Eq. 4-3}$$

F' measured force [N]

F effective force [N]

α ejection angle [°]

as only the vertical force vector of the ejection force will be registered by the sensors of the modified ejection cam (Fig. 4-18).

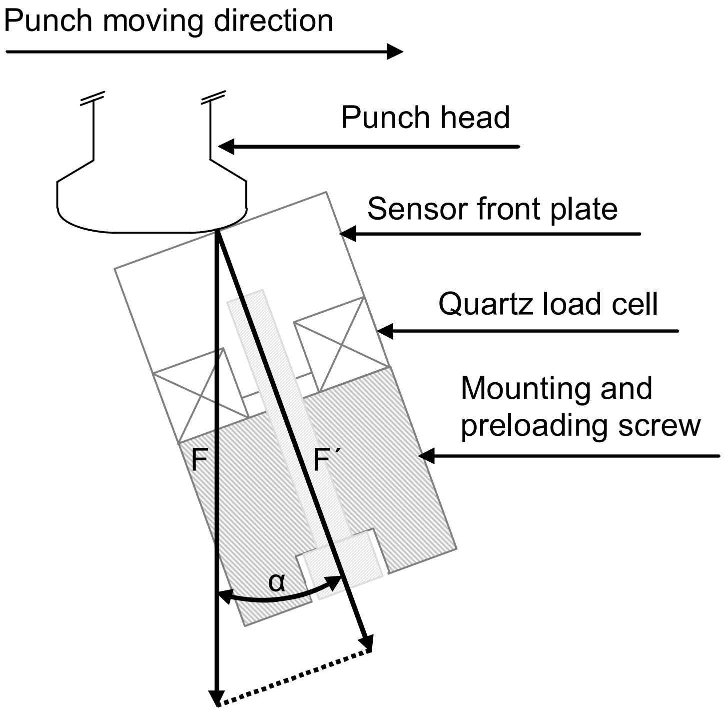


Fig. 4-18 Physical aspects for the correction of any oblique force measurement performed by quartz load cells, exemplary and schematically shown for one quartz load cell

The calibrated ejection force measurement system has now been used to monitor the signal of a blank measurement, performed at a true horizontal speed of the carriage of 0.44 ms^{-1} (Fig. 4-19).

This horizontal speed equals 30 RPM of the turret of the simulated Fette P1200 rotary tablet press. All the ejection force signals presented within the following part of this work have been monitored at this speed and corrected by this blank signal.

The impact of the punch on the ejection cam causes a mean impact peak of about 360 N. As this impact peak is present in any ejection force measurement it can be used as an excellent marker for the temporary alignment of the blank and real ejection force measurement.

In order to simulate the ejection force measurements of a Fette P1200 rotary tablet press, an ejection angle of about 18° would have been necessary on the Presster.

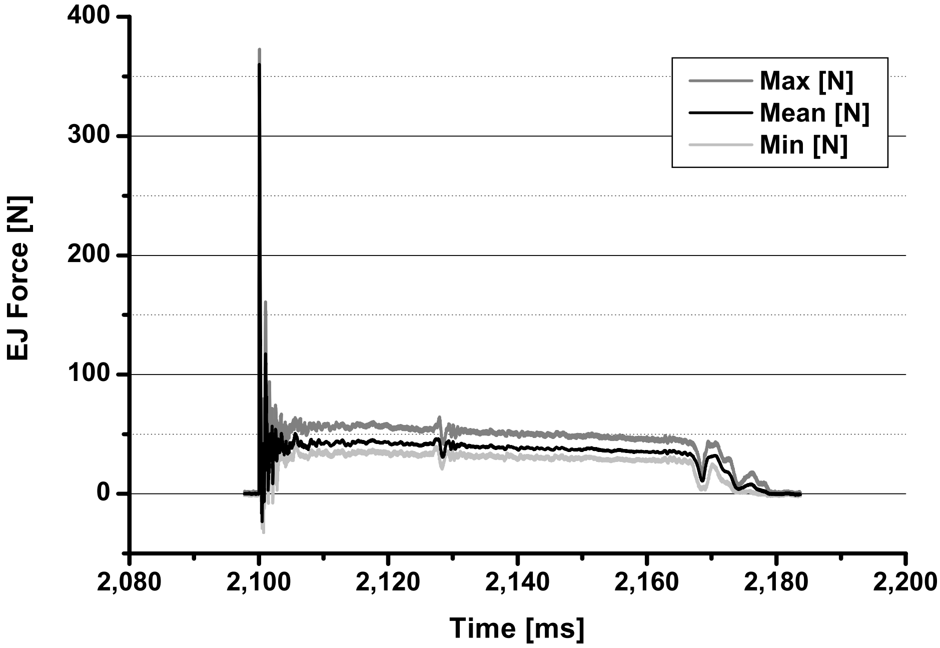


Fig. 4-19 Blanc measurement of ejection force signal (n=10).

As the original system of the Presster used for the adaptation of the ejection angle has also been used for the modified system, it has a maximum feasible theoretical ejection angle of 15.6°, which ultimately turned out to match only 14.5 ± 0.5°. This is as close as practically possible.

A sample rate of 1,800 Hz has been used to monitor these signals on both presses, which equals the sample rate of the Fette P1200.

Nevertheless, some differences between the measurements of the modified ejection force measurement system of the Presster and the measurements performed by the Fette P1200 were expected and verified, presumably due to the slight difference in ejection angle.

While the maximum ejection forces, observed by both systems, matched quite well (Fig. 4-20 and 4-21), an obvious difference in the ejection time, attributed to the variance in the ejection angle, has been observed between both signals.

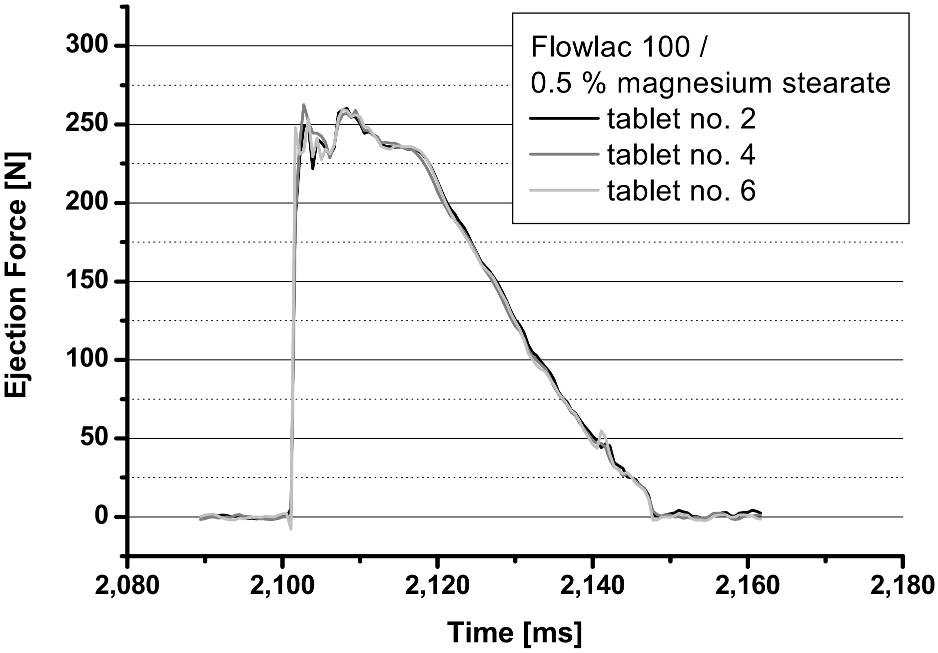


Fig. 4-20 Ejection force measurements obtained on the optimised ejection force measurement system of the Presster at 1,800 Hz

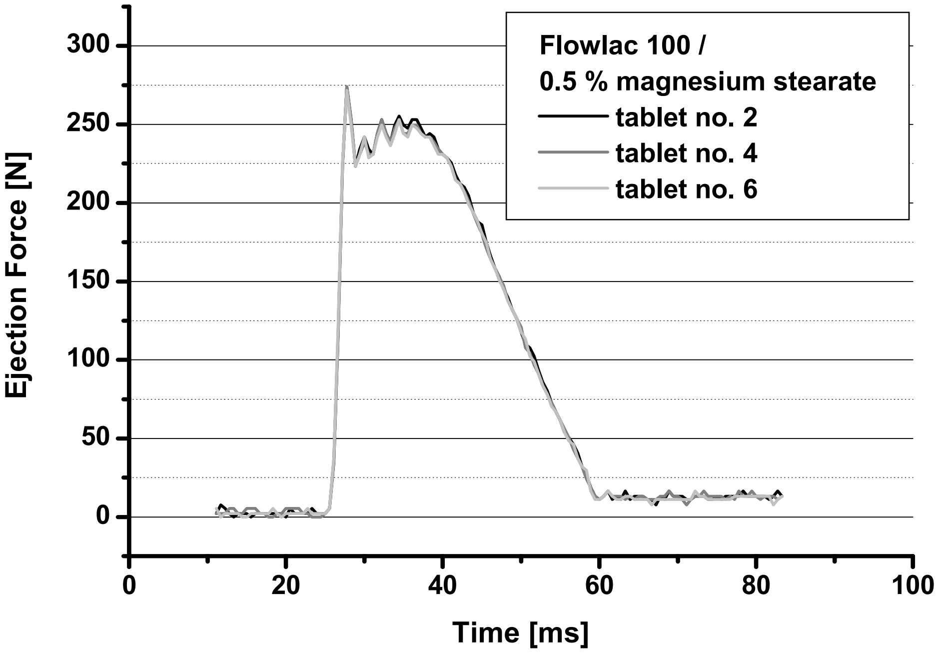


Fig. 4-21 Ejection force measurements obtained on the Fette P1200 rotary tablet press at 1,800 Hz

To avoid any influence of the duration of the ejection force measurements ascribed to differences in the vertical positions of the lower punches in relation to the top level of the die, the settings of both presses have been kept constant during these comparative investigations. Therefore, in case of matching ejection angles between the ejection cam of the modified system of the Presster and the settings of the ejection cam of the simulated Fette P1200, the resulting time period over which the punch would have been in contact with the ejection cam and consequently the duration of the ejection force signals would have been identical.

Aside from the missing temporally compliance due to varying ejection angles, a good consistency of ejection force signals of both presses has been obtained by the modified ejection force measurement system.

To further investigate the quality and validity of ejection force signals obtained by the statically calibrated modified ejection force measurement system, a comparison of the ejection force measurements obtained by the calibrated instrumented punch DigiPunch (PST, Rheinbach, Germany) was performed at different speed settings of the carriage at an effective ejection angle of 10°.

It is obvious from Fig. 4-22 and 4-23, where the results are shown for the slowest and the fastest achievable horizontal speed setting of the Presster (0.4 and 2.0 ms^{-1} respectively), that the impact of the punch on the ejection cam causes a speed dependant resonance frequency, which in the beginning superimposes on the ejection force signals. This impact has not been registered by the DigiPunch, as it measured the forces with its instrumented punch tip, which was not affected by any impact or consecutive vibrations.

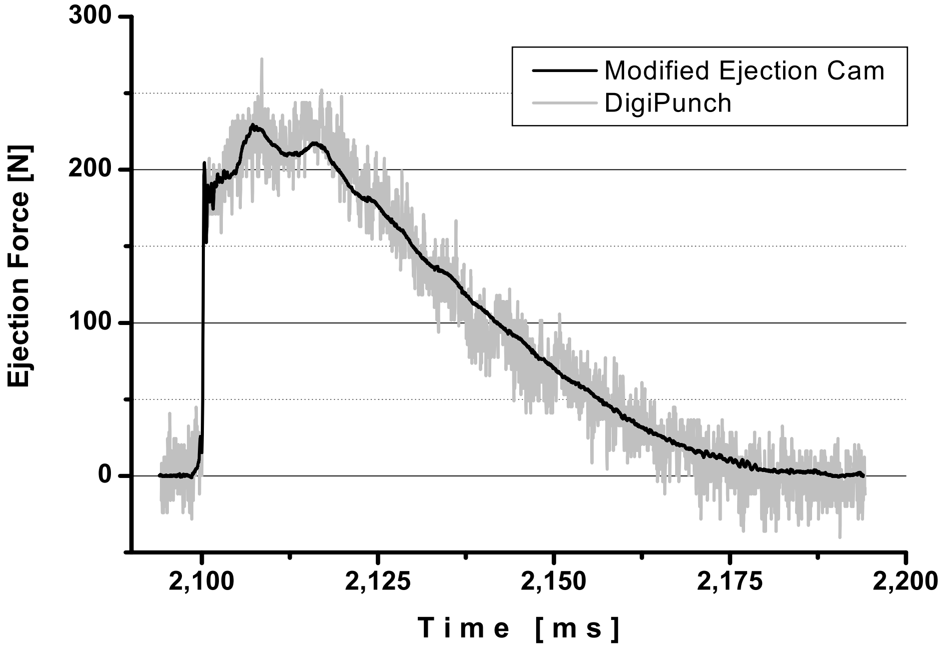


Fig. 4-22 Comparison of the ejection force measurements performed by the modified ejection force measurement system and the DigiPunch at a horizontal speed of 0.4 ms^{-1}.

While the amplitude of these oscillations increases with increasing impact speed, the duration of these oscillations is kept more or less constant at about 3 ms. Thereafter, the measurements obtained by the revised ejection cam matched those obtained by the DigiPunch well (Fig. 4-23).

However, due to the oscillations, an automatic detection of the maximum of the ejection force signal by simply using a maximum value memory, was more or less impossible for the modified ejection force measurement system.

The implementation of a sigmoidal fit, in order to detect the maximum ejection force value, was found to qualify the effective ejection force well enough for practical purposes.

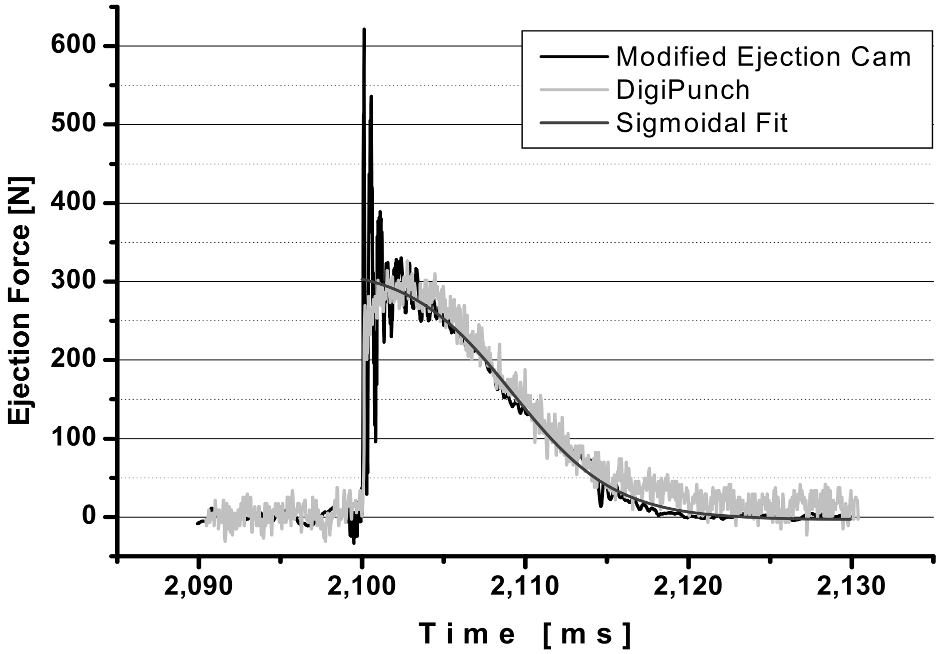


Fig. 4-23 Comparison of the ejection force measurements performed by the modified ejection force measurement system and the DigiPunch at a horizontal speed of 2.0 ms^{-1}

In the following, ejection force measurements have been performed at the settings given by Tab. 4-5.

The punches and die were polished and cleaned prior to the investigation of one particular blend using a polishing paste and isopropanol to ensure identical conditions for all measurements.

Different extents of lubrication have been examined. Ejection force signals have been monitored by the DAQ4 system at a sample rate of 50 kHz.

As far as possible, 6 tablets have been made of different excipients. The results of the investigations into adequate lubrication are presented for Flowlac 100, Emcompress and Neosorb P60W, in order to demonstrate the characteristics of the obtained ejection force signals.

Tab. 4-5 Settings of the Presster for the ejection force measurements

Aspect	**Setting**
Compaction Zone	2 mm
Tablet Band Height	3 mm
Simulated Tablet Press	Fette P1200; 24 Stations
Simulated Speed of the Turret	30 RPM
Ejection Speed	123 mms^{-1} (± 5 mms^{-1})
Ejection Angle	14.5° ± 0.5°
Tooling	EU 19; 10 mm; flat faced
Main Compaction Pressure	127.3 MPa (± 6.3 MPa)
Precompaction Pressure	6.3 MPa (± 1.5 MPa)
Die Feeding	Manually
Sample Rate	50 kHz
Depth of Fill	Variable

Lactose is probably the most widely used and at the same time one of the best known pharmaceutical excipients (Hersey, 1973; Vromans, 1985; Ketolainen, 1995). With respect to the ejection force it holds a central position compared to other fillers (Bolhuis, 1973).

Therefore the ejection force signals of Flowlac 100, a spray-dried α-lactose monohydrate, have been investigated.

Fig. 4-24 gives the ejection force signals of Flowlac 100 compressed without any lubrication.

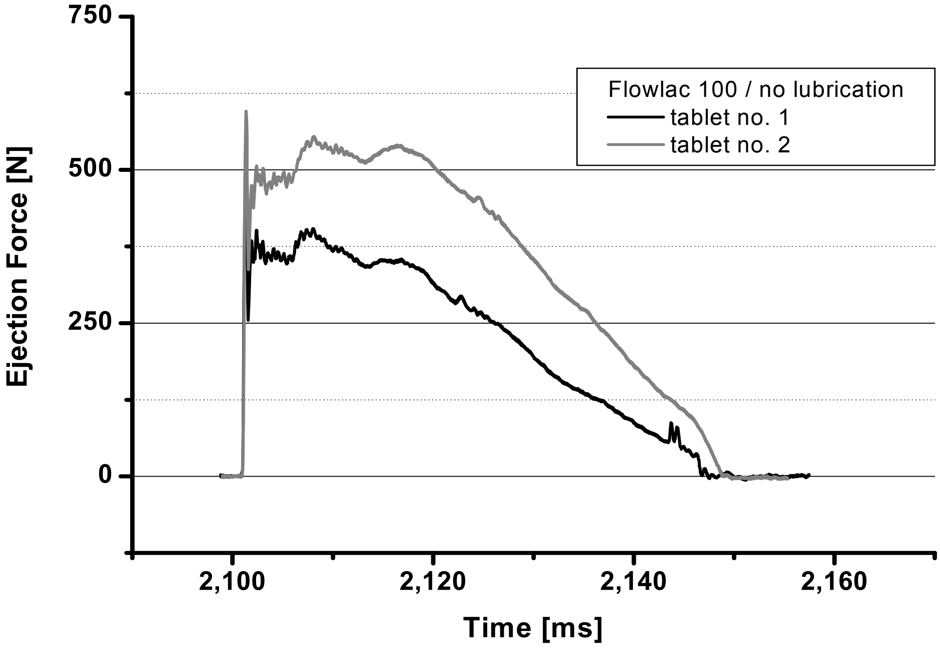


Fig. 4-24 Ejection force measurements of Flowlac 100 without any lubrication

Already the ejection force of the first tablet exceeded the maximum ejection force of about 300N, found to be the maximum for the lubricated blend of Flowlac 100 (Fig. 4-25).

As the ejection force of the second tablet has been obviously larger than the first one and the ejection was accompanied by an immense and atypical noise level, the compaction of any further tablets made from unlubricated Flowlac 100 was stopped. The increase in the ejection force from tablet one to two is explainable by the sticking of material at the surface of the die, causing an obstruction to the action of the lower punch inside the die. This was further verified by the striations in the band of the second tablet.

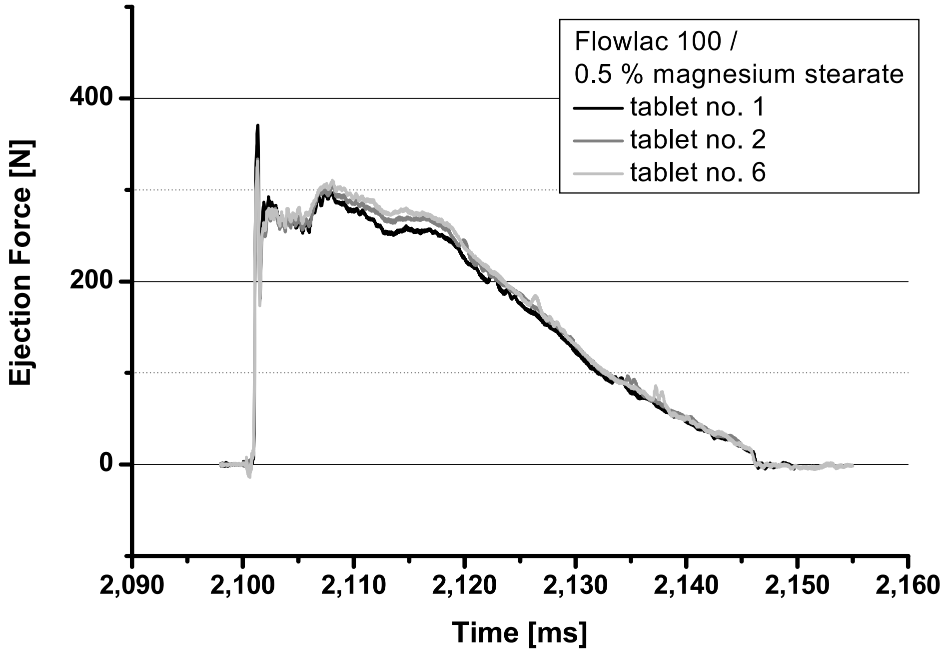


Fig. 4-25 Ejection force measurements of a blend of Flowlac 100 and 0.5 % magnesium stearate

Two blends of Flowlac 100, comprising 0.5 % (Fig. 4-25) and 1.0 % magnesium stearate respectively, were then compressed. Both blends showed almost the same ejection forces of about 300 N.

While the ejection forces of the blend containing 0.5 % lubrication remained at this level the ejection forces of the 1.0 % blend trended to decrease with an increasing number of tablets. This might be due to the creation of a persisting lubrication film covering the surface of the die.

While the initial peak at about 2,100 ms refers to vibrations of the ejection cam, caused by the impact of the lower punch on the ejection cam, a slip-stick effect, caused by a periodic change of sliding and adhering of the tablet inside the die after the first break loose, can be seen for all lubrication grades of Flowlac 100, before the ejection force finally decreases more or less linear. Slip-stick effects have already been described by Hersey (1973).

Calcium phosphates, like Emcompress, used as fillers for tableting, are amongst the cheapest pharmaceutical excipients. An overview on calcium phosphates for direct compaction purposes as well as their compaction behaviour has been given by Herzog (1991) and Doldan (1995). The ejection force signals of Emcompress without any lubrication are shown by Fig. 4-26.

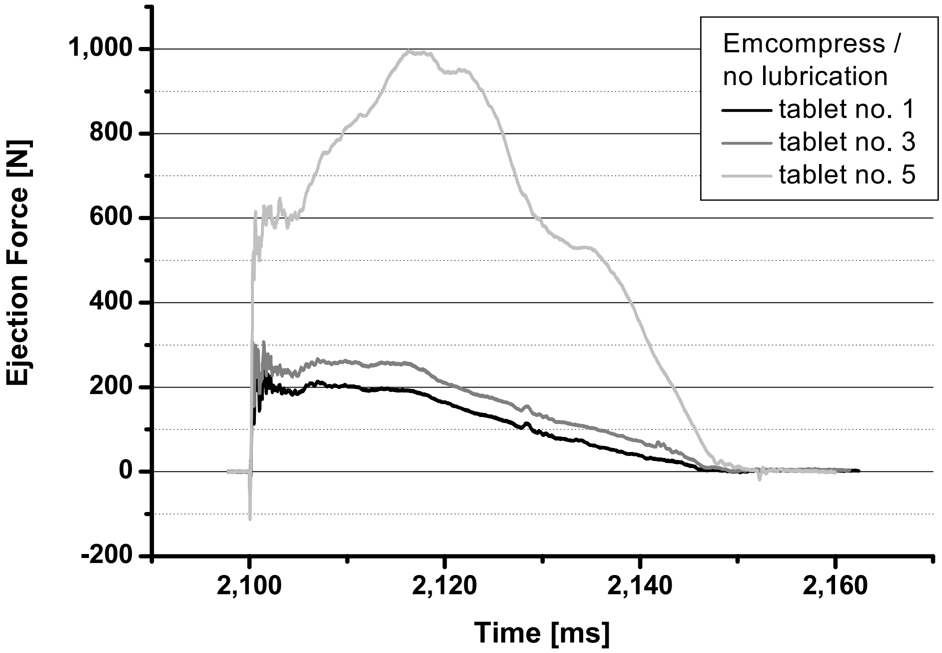


Fig. 4-26 Ejection force measurements of Emcompress without any lubrication

Comparable to the behaviour of unlubricated Flowlac 100 the ejection forces of unlubricated Emcompress increased significantly with the number of pressings to about the quadruple the force, accompanied with increasing noise of the Presster, indicating for insufficient lubrication (Schmidt, 1989). The temporary relocation of the maximum of the ejection force signal further indicates for material sticking at the inner surface of the die. After removing the tooling from the die, Emcompress has been found to stick also on the outer surface of the crown of the punch.

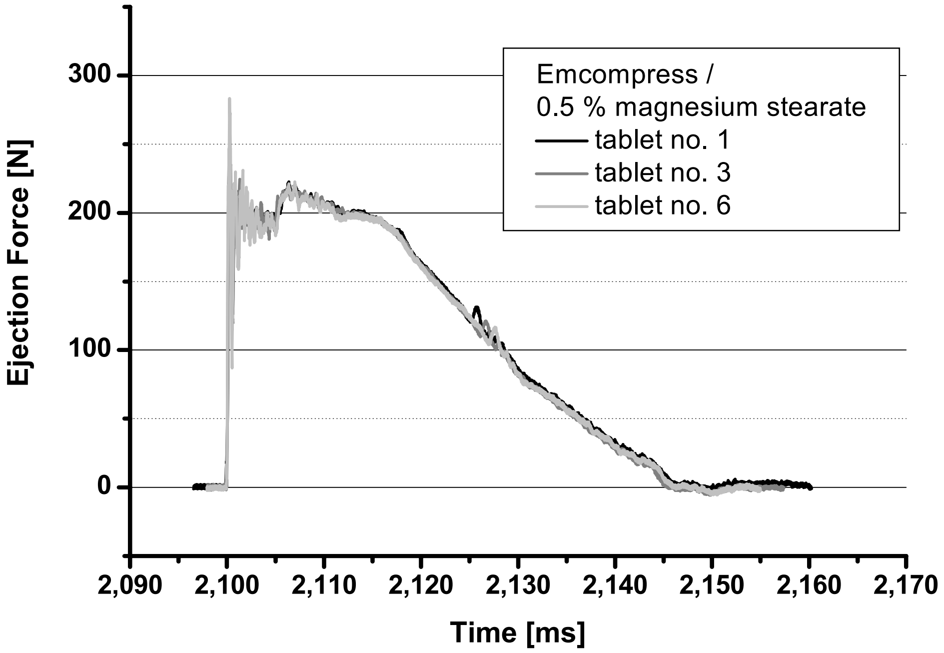


Fig. 4-27 Ejection force measurement of a blend of Emcompress and 0.5 % magnesium stearate

Comparable to the behaviour of Flowlac 100 the blend of Emcompress containing 0.5 % magnesium stearate showed acceptable and reproducible ejection forces (Fig. 4-27). Slip-stick effects, if present at all, are less distinctive.

Finally, the same investigations have been made for Neosorb P60W, as sorbitol, is known as an excipient showing a distinctive sticking tendency.
Without any lubrication, Neosorb P60W shows the most pronounced sticking problems of these three excipients.
A very loud noise occurred at the ejection event indicating for severe sticking problems (Fig. 4-28). As the lower punch was no longer able to move unrestricted inside the die, the production of the remaining tablets was halted to avoid machine damage.

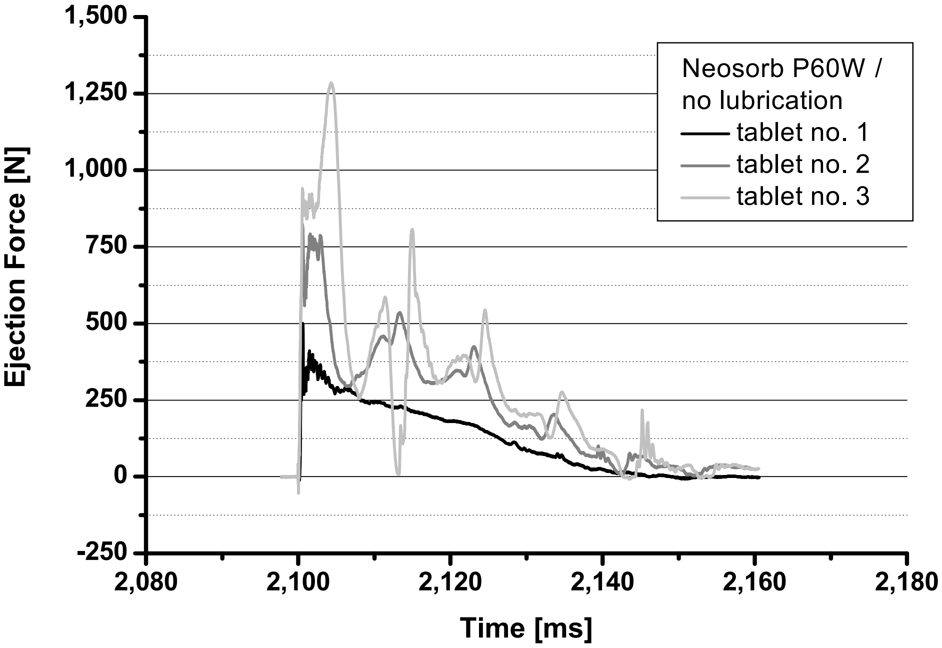


Fig. 4-28 Ejection force measurement of Neosorb P60W without any lubrication

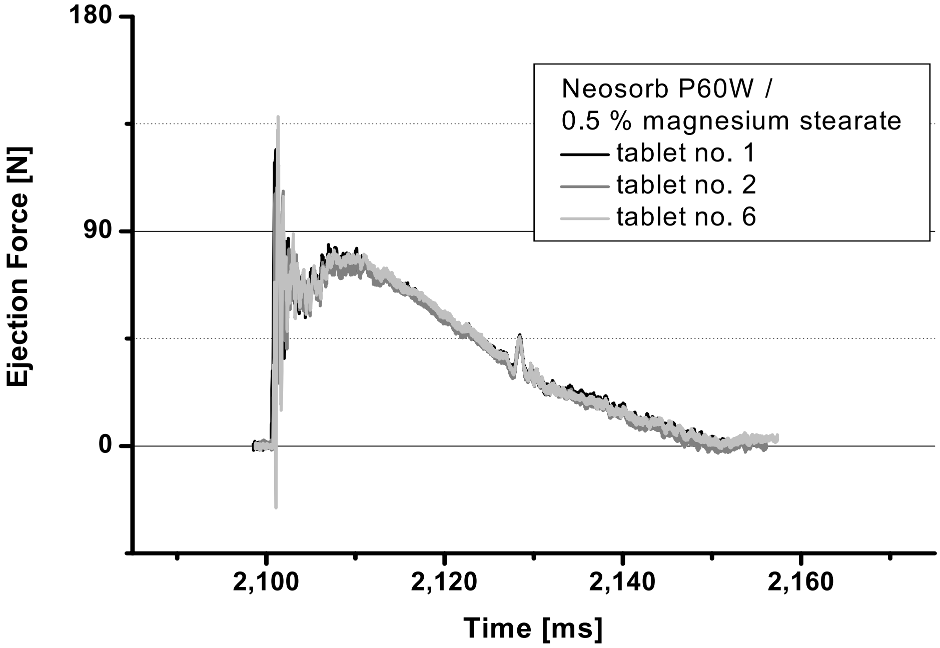


Fig. 4-29 Ejection force measurement of a blend of Neosorb P60W and 0.5 % magnesium stearate

The blend of Neosorb P60W and 0.5 % of magnesium stearate (Fig. 4-29) did not show any detectable issues and had smallest ejection forces of these three excipients.
Therefore, the sticking tendency of all the three excipients has been reduced by the use of only small amounts of magnesium stearate, which verifies the anti-sticking properties of the lubricant magnesium stearate (Lerk, 1988).

Finally, compared to the quality of ejection force signals obtained by the original ejection force measurement system of the Presster, the investigated ejection force measurements demonstrated the improved quality and validity of ejection force measurements performed with the revised ejection force measurement system.
Therefore, the new system might be used to basically investigate the adequate extent of lubrication required in a certain blend during very early stages of development, as the amount of material necessary to perform these investigations under the conditions of rotary tablet presses is comparably small.
The ultimate determination of lubrication, whether there might be any process time dependent sticking problem for a particular formulation definitively requires a larger amount of material and is therefore not going to be investigated on this system, but in full scale production.

4.3.5 Summary

The quality of ejection force measurements, obtained by the original ejection force measurement system of the Presster, was found to be unsuitable to perform reliable ejection force measurements.

The loose supporting of the frame of the original ejection cam within the Presster, based on disk springs, caused interference between other compaction cycle events. Machine vibrations, caused by the compaction events, have been transferred to and monitored by the original ejection force measurement system. Furthermore, as the vibrations have been speed and force dependent, the base line of the original ejection force measurement system has been impinged by variable fluctuations.

Too small sample rate in combination with the missing option for the adaptation of the actual valid calibration function, made the system unable to reliably investigate the ejection behaviour of pharmaceutical excipients or blends.

The entire ejection force measurement system was modified. As quartz load cells have been found to be superior for the measurement of ejection forces compared to strain gauge instrumentations, a kit of 4 quartz load cells was installed in a newly designed ejection cam. The new system was fixed directly and securely to the frame of the Presster, while the data acquisition of the ejection forces has been additionally initialised just a few milliseconds prior to the ejection event using a photoelectric proximity sensor, in order to prevent any time dependant base line drift.

The higher sample rate, provided by the DAQ4, guarantees the proper monitoring of ejection forces even at higher speed settings of the carriage. Unfortunately, the impact of the punch onto the ejection cam caused an overlaying oscillation, but a satisfying correlation between the oscillation carrying signal of the revised ejection cam and the oscillation-free measurement performed by the instrumented punch DigiPunch has been shown using a sigmoidal fit.

A modification of the original system for the adaptation of the ejection angle was not possible due to the missing access to the control unit of the Presster. Therefore, this system had to be used as well for setting the ejection angle of the new designed ejection cam. A limitation of the range of the ejection angle in between 5 and 14.5 ± 0.5°, impeding a most accurate simulation of the ejection process of the Fette P1200, therefore had to be accepted, being a serious drawback of a compaction simulator.

Fortunately, the restriction in the ejection angle showed only small effect on the maximum ejection force observed, as proven by the simulation of the ejection force measurements of the Fette P1200.

The total duration of the ejection force measurement, which is mainly affected by the different ejection angle, is of secondary interest and significance with respect to the evaluation of lubrication levels, as long as the maximum force level will be consistently determined.

Nevertheless, the limitations in the simulation of the proper ejection conditions have to be kept in mind as a potential reason for any observed difference in tablet properties.

Finally, the quality and validity of ejection force signals obtained by the revised ejection force measurement system present a distinctive improvement compared to the original ejection force measurement system of the Presster and therefore facilitates its application for development and trouble-shooting purposes.

Sticking problems and consequently increasing ejection forces do often not occur until a larger number of tablets have been made. So whether a certain extent of lubrication is adequate to avoid those problems during long term production runs on rotary tablet presses, can not be categorically derived from the results obtained by this system.

4.4 Take-Off Force Measurement System

Sticking of tablets to the surfaces of the punches is a substantial hindrance to the process of tablet production and often observed as a consequence of engravings present on the punch surface.

Usually the powder sticks to the lateral symbols first and finally covers the whole surface of the punch tip.

As the identification of tablets produced in the following is missing, these tablets have to be rejected. Increasing take-off forces might indicate the emerging of these sticking problems.

While the sticking tendency itself can not be influenced by monitoring the take-off forces, at least the waste production of tablets can be limited. Therefore, the investigation of take-off forces during early stages of formulation development helps to identify and ultimately minimise the risk of sticking problems later on during production.

At least three cases of sticking problems are possible: first sticking of tablets only to the upper punches, second only to the lower punches and finally to the surfaces of both punches.

If tablets stick to the upper punches they might be compacted twice, as the take-off bar will not take the tablets away from the upper punch. Damage to tooling or other machine parts can occur, as the additional amount of powder inside the die multiplies the force during the subsequent compaction cycle.

When tablets adhere to the surface of the lower punches this often leads to damaged tablets due to the shear stress applied to the tablets during the take-off event.

The measurement of forces required to take-off tablets, sticking to the surface of the lower punch only, will be discussed within this work.

Tablets sticking to the surfaces of both punches might cause a mixture of the above mentioned symptoms. As tablets will be split into fractions, both increasing compaction pressure levels and increasing take-off forces will be observed.

4.4.1 Different Techniques for Take-Off Force Measurements

On most rotary tablet presses, the measurement of take-off forces, if provided at all, takes place by a strain gauge instrumented take-off bar. Schmidt (1983a) already described the signals obtained by those types of instrumented take-off bars as absorbed oscillations and concluded, that the sensitivity of this type of instrumentation is not sufficient for the detection of rather small take-off forces of quite well lubricated tableting blends (Ritter, 1978).

The instrumentation of a take-off bar using a small quartz load cell improved the sensitivity and allowed the measurement of adhesion forces below 1 N (Schmidt, 1983a).

The precision and accuracy of measurements performed by this quartz load cell instrumented take-off bar predominated the quality of measurements of a strain gauge instrumented take-off bar and have been proved to be sufficient to detect sticking problems.

The influence of the presence and the shape of engravings on the punch surfaces with respect to the occurrence of sticking problems as well as the dependency between sticking problems and the applied compaction force and finally the compression behaviour of the excipients have already been investigated by Waimer (1999a, 1999b), using an instrumented upper punch.

4.4.2 Investigation of the Original Presster Take-Off Force Measurement System

The original take-off bar instrumentation of the Presster has been designed as a strain gauge instrumented bar supported unilateral within a mounting, which has been fixed to the machine frame (Fig. 4-30).

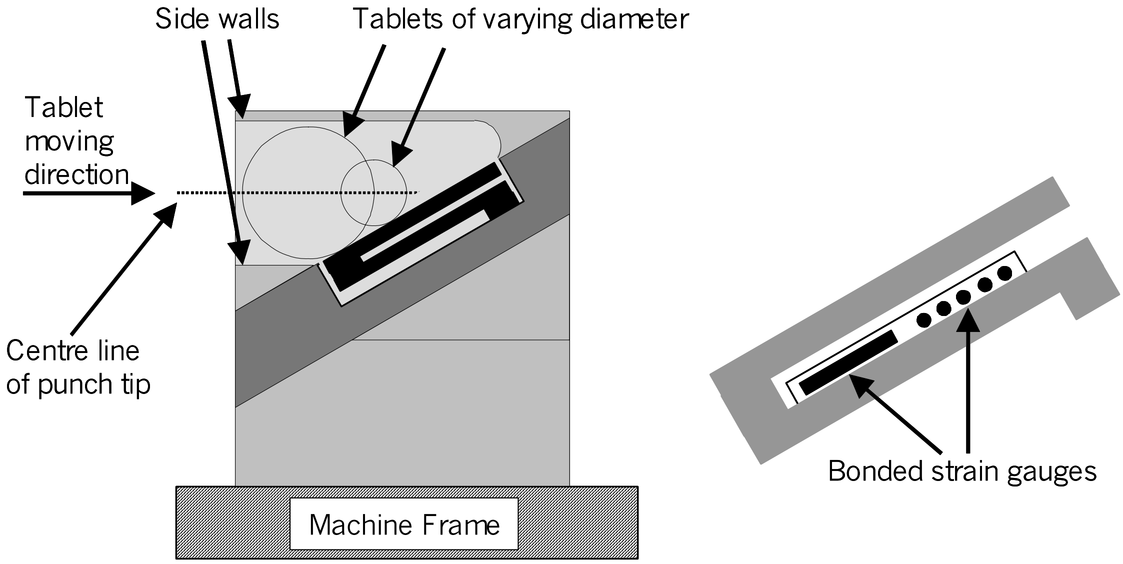


Fig. 4-30 Overview (left) and detailed scheme (right) of the original take-off bar of the Presster within its mounting (top view)

Presumably, the side walls of the mounting, shaping a cavity in front of the take-off bar, have been designed to prevent the tablets from spilling around inside the Presster and to guarantee the collection of tablets in a small container, which has been attached to the rear end of the die table.

As soon as the die table has passed underneath the take-off bar by its entire length, the tablet falls out of the cavity in front of the take-off bar and is collected within the tablet collection container.

Due to the fixation of tablets inside this cavity, tablets are not been taken away directly after the first collision with the take-off bar.

Therefore, as the tablets have still been placed upon the die table, which by itself was still passing underneath the take-off bar, the tablets hit the take-off bar repeatedly.

Take-off force signals obtained by the original Presster instrumentation (Fig. 4-31) were found to be quite similar to those described in literature, being observed using comparable instrumentations (Mitrevej, 1980; Schmidt, 1983a), and similar to sine waves produced by tuning forks.

Lately, the oscillations monitored by the original take-off force instrumentation have been ascribed to both the multiple contacts between the tablet and take-off bar and the too small Eigen-frequency of the system, which turned out to be about 440 Hz.

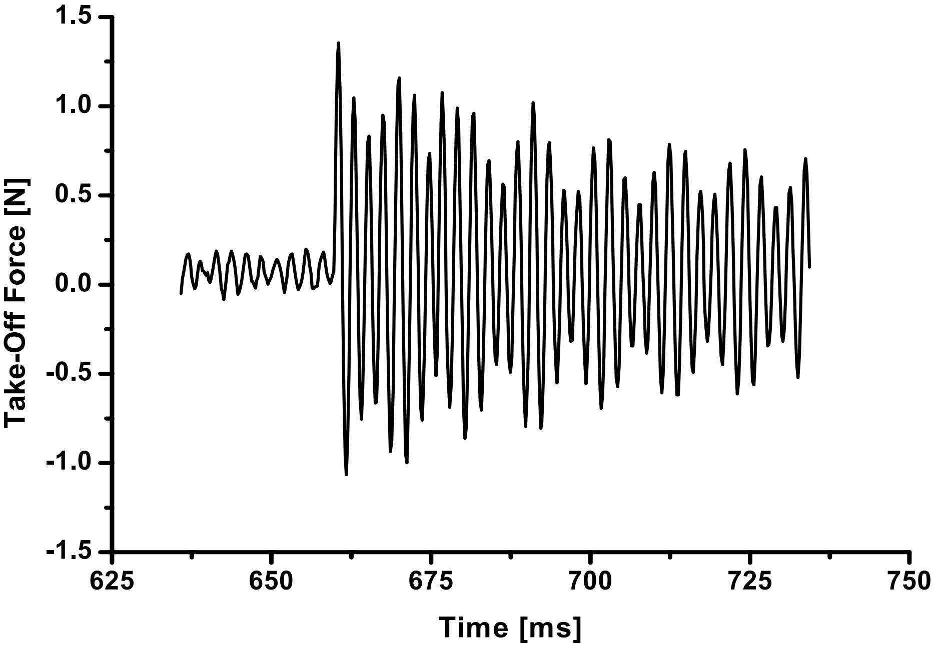


Fig. 4-31 Take-off force signal obtained by the original Presster take-off force instrumentation.

Additionally, as obvious from Fig. 4-30, tablets hit the take off-bar at varying positions depending on the tablet diameter and shape.

Unfortunately, the bending moment of this one-sided supported bar, caused by a certain force, mainly depends on the point of action of this force. Differences in the finally measured take-off force would were expected, although the applied force would have been the same.

A calibration, generally valid for different tablet shapes and diameters, was almost impossible. A recalibration would have been necessary after any change of tooling size and shape, but has been impeded from the user by design of the original data acquisition system.

Furthermore, the amplifier (DSCA38-05, Dataforth, USA) used within the original take-off force measurement system has been found to be identical with those of the compaction force measurement system.

As already mentioned above, the bandwidth of this type of amplifier has been confirmed to be about 3 kHz.

Therefore, the acquisition of take-off force signals without any signal amplitude distortion would only be possible up to a frequency of about 1.5 kHz (equals 50 % of the cut-off frequency of the DSCA38-05 amplifier). Hence, this type of amplifier is not suitable for the investigation of the take-off force signals, as their frequencies, even if the measurements have been performed at rather low speed settings of rotary tablet presses, have already been described in literature to be about 4.5 kHz (Schmidt, 1983a).

Therefore, evaluations of take-off force signals, monitored by the original take-off force measurement system of the Presster, are not possible with this system.

4.4.3 Modification of the Take-Off Force Measurement System

Due to the unsatisfying results obtained by the original take-off force instrumentation of the Presster a new take-off force measurement system was designed (Fig. 4-32).

As, due to its rather high linear speed conditions, peak times of the take-off force measurements performed on the Presster have been expected to be even shorter as those described in literature for rotary tablet presses, and therefore the resulting signal frequencies have been expected to be even higher.

Therefore a quartz load cell (9301B, Kistler, Germany) has been used for the instrumentation of the new designed take-off force system, providing a pre-calibrated measurement range up to 2.5 kN at an Eigen-frequency of the blank sensor of about 90 kHz.
The quartz load cell has been mounted to a beam inside the Presster, realizing a fixed take-off angle of 35° in relation to the horizontal direction of movement of the tablets.

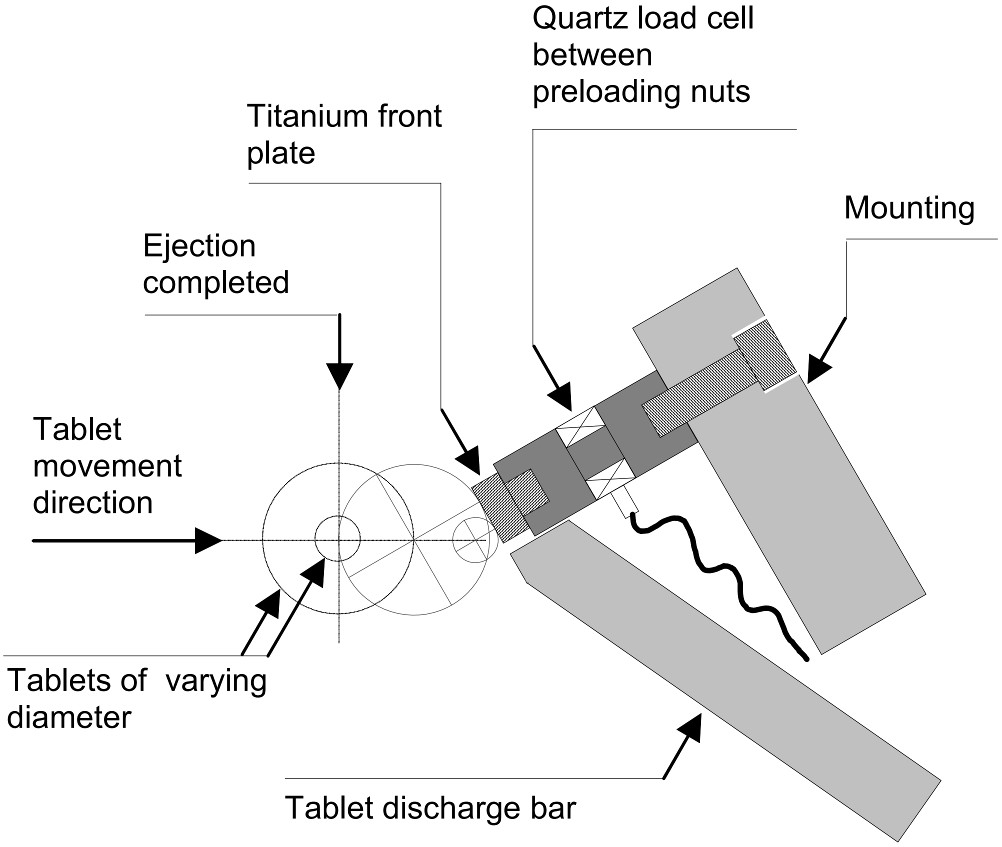


Fig. 4-32 Scheme of the redesigned take-off force measurement system

In order to make sure that tablets strike the sensor independently of their outer diameter, a titanium plate has been fixed in front of the sensor. Titanium has been selected because of its small weight and high rigidity minimising the influence of the mass of the plate with respect to the remaining frequency response range of the take-off force measurement system.

4.4.4 Calibration of the Modified Take-Off Force Measurement System

The quartz load cell instrumented take-off bar has been calibrated statically. Nine different weights over the range of 0.01 kg to 5.0 kg (equalizing 0.0981 N to 49.05 N) have been applied successively on the titanium front plate of the plane horizontally positioned quartz load cell. The coverage of a larger force range has not been possible due to the increasing size of the weights compared to the small size of the quartz load cell. As the proof of linearity of the quartz load cell has been confirmed previously by the manufacturer's calibration, the actual calibration has just been performed to adapt the calibration function to the actual conditions of the quartz load cell, mounted on the supporting beam.

The resulting voltage outputs of the connected charge meter (5015A1000, Kistler, Germany) have been recorded by the DAQ4 system. The sensitivity of the charge meter has been set to -3.129 pCN^{-1}, as certified for the quartz load cell.

For calibration as well as for measurement purposes, the measurement range of the charge meter has been set to 250 MUV^{-1} at the recommended operation mode "DC long" ($\tau > 10^5$ s).

Fig. 4-33 gives the resulting calibration function of the modified take-off force measurement system, while the 95 % confidence and prediction limits have both been displayed expanded by a factor of ten. The quality of the calibration function of the new take-off force measurement system is shown by the residuals shown in Fig. 4-34.

The precise measurement of take-off forces is therefore guaranteed with an accuracy of 0.1N.

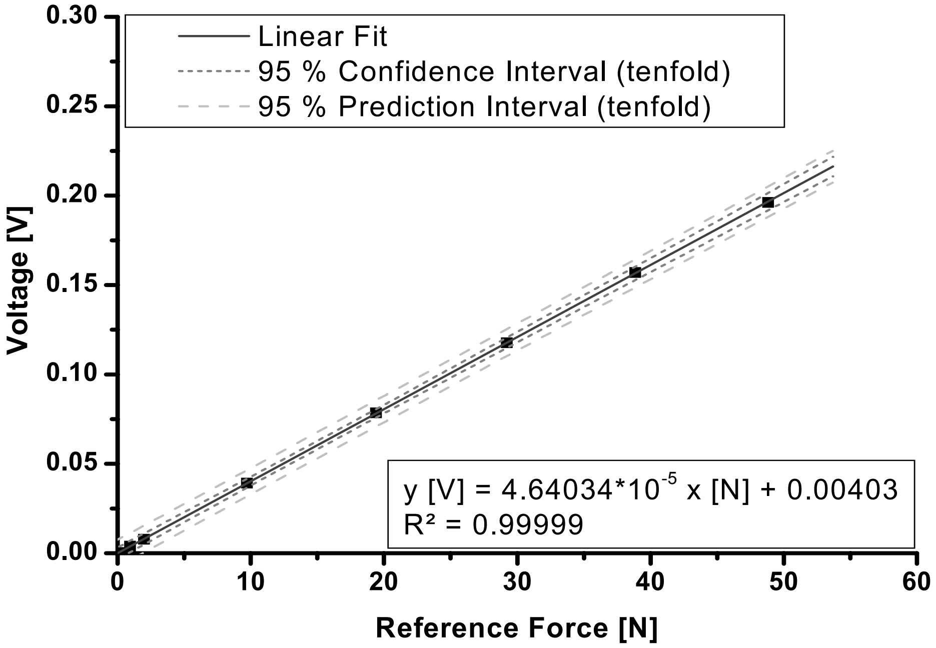


Fig. 4-33 Calibration function of the modified take-off force measurement system

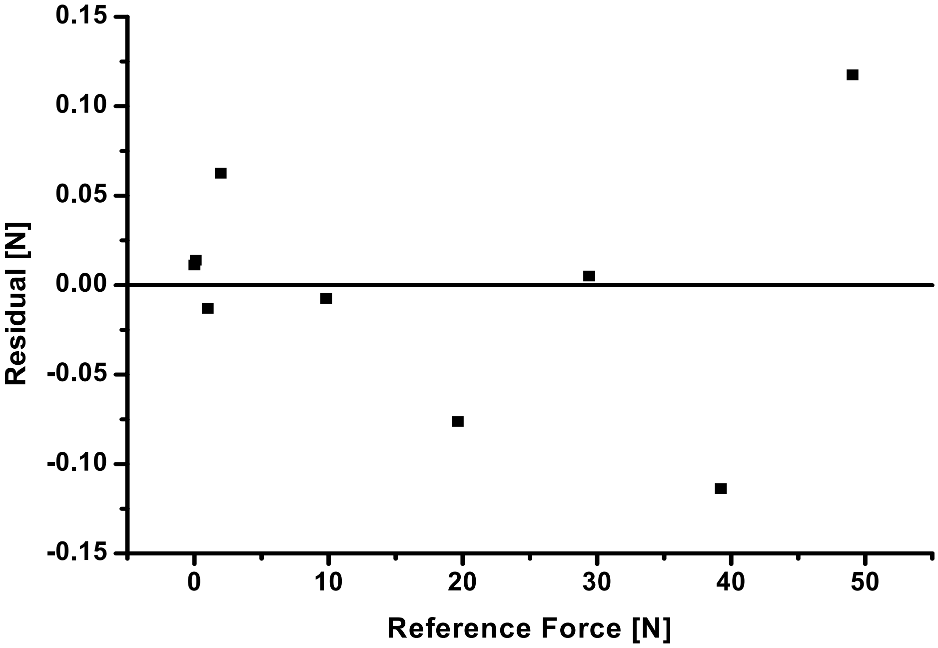


Fig. 4-34 Residuals of the calibration function of the modified take-off force measurement system

Due to the take-off angle of 35°, designed in order to prevent multiple take-off force peaks, the take-off event equals an oblique impact similar to the situation found for the redesigned ejection force measurement system. Therefore, the signal of the take-off force measurement system had to be corrected as well according to Eq. 4-3.

The take-off angle has been set by design to a fixed value of 35°, the constant correction factor of cos 35° equalizing 1.22077 has been implemented to the DAQ4 system.

All take-off forces, monitored by the modified take-off force measurement system, have therefore been automatically corrected by this factor, in order to record the true take-off forces by the DAQ4 system.

4.4.5 Evaluation of Measurements Performed by the Modified Take-Off Force Measurement System

A correction for the momentum of the tablet mass, which causes a virtual take-off force signal but which is not related to the adhesion between the compact and the lower punch, is necessary for take-off force measurements (Walz, 1988).

Due to the known mass and horizontal speed of the tablet, the momentum of the compact is calculated by Eq. 4-4.

$$p = m \cdot v \qquad \text{Eq. 4-4}$$

p	momentum [Ns]
m	tablet mass [kg]
v	horizontal speed of the compact [ms^{-1}]

If the friction between the compact and the punch is neglected, the momentum of the compact before and after the take-off event would be equal.

The change in the momentum during deceleration and acceleration of the compact during the take-off event has been registered as the impulse, which is the product of force and peak time and equals the sum of the momentum from before and after the impact.

As the force is not constant over the entire impact time, the impulse can be determined as the integral of the take-off force over the impact time, and therefore as the area under the take-off-force-time-plot (Eq. 4-5).

$$\mathrm{I} = \Delta p = \int F dt = 2 \cdot m \cdot v \cdot \cos\alpha \qquad \text{Eq. 4-5}$$

I	impulse [Ns]
Δp	change in the momentum [Ns]
F	Take-off force [N]
m	tablet mass [kg]
v	speed of the carriage [ms^{-1}]
α	take-off angle [°]

By the calculation of the momentum as the product of the tablet mass, the carriage speed and the take-off angle, the monitored impulse can be checked.

The take-off event of sticking tablets leads to an increased impulse.

Physically, the take-off force, measured by the take-off bar, partially describes an inelastic impact of the compact against the take-off bar, while the part of the impulse, which goes beyond the momentum, equals the force required to overcome the adhesion between the compact and the lower punch (Eq. 4-6).

$$\int Fdt_{take-off} = \int Fdt_{momentum} + \int Fdt_{adhesion} \qquad \text{Eq. 4-6}$$

Exactly this part of the registered take-off force, required to overcome the adhesion between the tablet and the punch, is the variable of interest when performing take-off force measurements.

Therefore, the measured take-off force has to be corrected by the momentum induced part of the take-off force signal, according to Eq. 4-7.

$$\int Fdt_{adhesion} = \int Fdt_{take-off} - \int Fdt_{momentum} \qquad \text{Eq. 4-7}$$

Unfortunately, the temporal allocation of the momentum, registered by the take-off force signal, is not only dependent on the speed of the carriage and the weight of the tablet.

It is specifically influenced by the deformation characteristics of the compact, which depend mainly on its strength and elastic behaviour (Fig. 4-35).

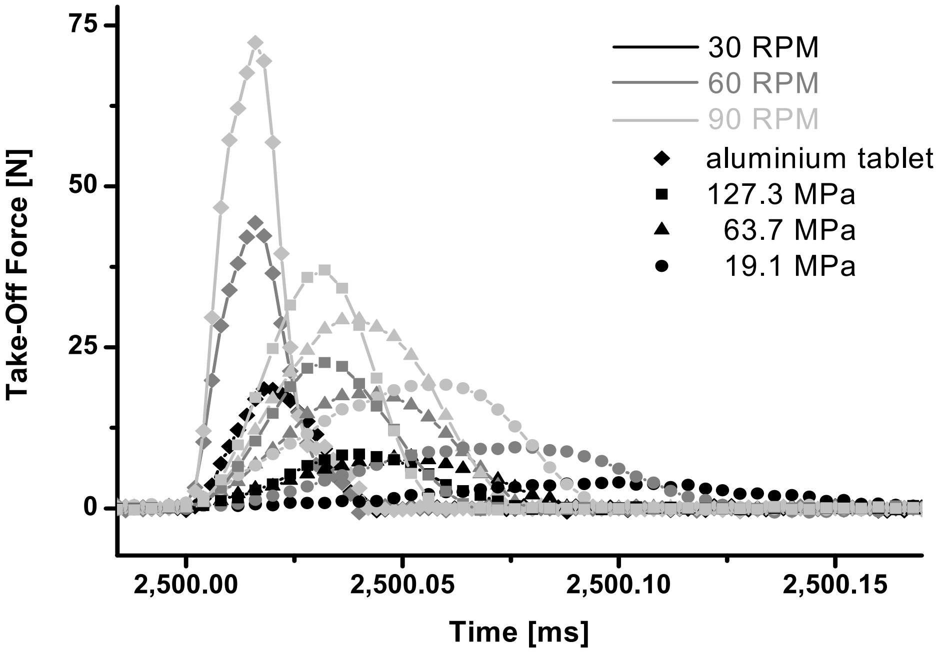


Fig. 4-35 Dependency between the compaction pressure respectively the compact deformation behaviour and the momentum induced take-off force measurement, performed by a non-sticking blend of Neosorb P60W and 0.5 % magnesium stearate (water content 0.5 %) and metal tablets, 500 mg each

Therefore, if the shape and finally the peak maximum of the adhesional part of the take-off force signals are of interest, the correction of the take-off force signal for the momentum of the compact requires a reference measurement, performed by a non-sticking compact of the excipient or blend at the required compaction force and speed of the rotary tablet press.

The correction of take-off force signals, using a non-sticking tablet as a reference of course implies negligible influence of, for example, different moisture contents on compact properties like deformation behaviour.

To verify this method and to investigate the quality of the improved take-off force measurement system, take-off forces of a model formulation of Neosorb P60W and 0.5 % magnesium stearate, conditioned at varying humidities in order to obtain different batches with different sticking tendencies, were monitored.

A first trial, comparing two blends containing 0.1 % (Blend A) and 0.5 % (Blend B) of water, performed to investigate the necessity to dry the blend to a very low water content of 0.1 %, did not show any differences in the observed take-off forces (Fig. 4-36).

Therefore, in the following blend B, containing 0.5 % of water has been used as the non-sticking reference.

A third blend (Blend C) has been conditioned to a water content of about 1.1 % and has been used to show significant sticking tendencies compared to the reference blend.

Tablets have been compressed on the Presster simulating a Fette P1200 rotary tablet press, running at 30, 60 and 90 RPM, using 10 mm flat faced Euro B tooling without any engraving and an untapered die.

Pre- and main compaction pressures were set to 6.4 MPa (± 1.3 MPa) and 133.7 MPa (± 6.4 MPa) respectively, while the Presster was set up to work at a compaction zone of 2 mm.

Take-off force signals have been monitored by the DAQ4 system at a sample rate of 250 kHz.

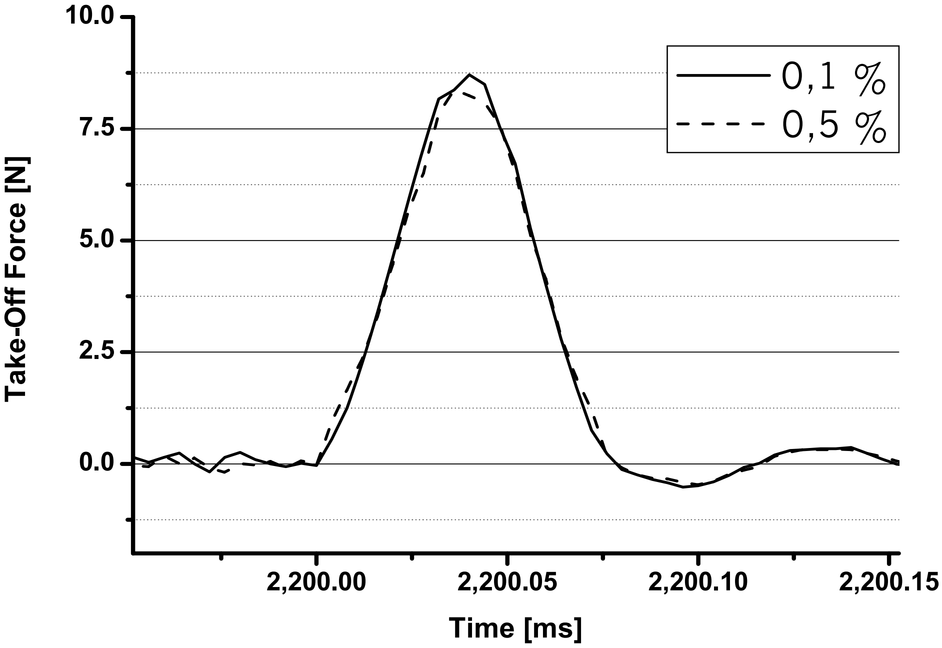


Fig.-4-36 Uncorrected take-off forces of the Neosorb P60W blends containing 0.1 % and 0.5 % of water (n=6), 30 RPM

500 mg (± 2 mg) of the two blends have been weighed using a balance and transferred manually into the die, in order to eliminate any influence of the tablet mass and edge height and therefore the resulting contact area between the tablet and the front plate of the quartz load cell.

The surfaces of the punches and die were polished between individual settings and blends.

The influence of compaction speed and moisture content on the tensile strength of these compacts was evaluated in order to demonstrate the applicability of this method for the determination of the adhesive part of take-off forces.

No essential difference in the tensile strength has been observed for the two blends B and C at one particular speed setting, while the general speed dependency of the tensile strength of sorbitol blends was demonstrated once more (Tab. 4-6).

Tab. 4-6 Properties of compacts of the blend of Neosorb P60W and 0.5 % magnesium stearate at different moisture contents.

Turret Speed [RPM]	**Compaction Pressure [MPa]**	**Sticking observed ?**	**n = ?**	**Moisture content [%]**	**Mean Tensile Strength [MPa]**	**SD**	**Max [MPa]**	**Min [MPa]**	**Median [MPa]**
30	19.1 ± 3.2	no	6	0.5	0.52	0.02	0.55	0.48	0.52
	63.7 ± 6.4	no	6	0.5	2.41	0.06	2.48	2.33	2.41
	127.3 ± 6.4	no	6	0.5	4.81	0.04	4.85	4.78	4.80
	127.3 ± 6.4	yes	20	1.1	4.87	0.09	5.09	4.71	4.84
60	19.1 ± 3.2	no	6	0.5	0.47	0.02	0.49	0.44	0.47
	63.7 ± 6.4	no	6	0.5	2.22	0.04	2.27	2.15	2.22
	127.3 ± 6.4	no	6	0.5	4.61	0.06	4.70	4.56	4.61
	127.3 ± 6.4	yes	20	1.1	4.78	0.07	4.92	4.65	4.78
90	19.1 ± 3.2	no	6	0.5	0.46	0.02	0.48	0.43	0.46
	63.7 ± 6.4	no	6	0.5	2.14	0.05	2.20	2.06	2.13
	127.3 ± 6.4	no	6	0.5	4.49	0.05	4.55	4.44	4.49
	127.3 ± 6.4	yes	20	1.1	4.57	0.17	4.94	4.27	4.55

Therefore the effect of the varying moisture content of the two blends B and C on the compact tensile strength and deformation characteristics during take-off has been neglected with respect to the consecutively performed determination of the adhesive part of the take-off forces of compacts of both blend B and C, produced at 127.3 ± 6.4 MPa.

The unprocessed results of the take-off force measurements of both blend B and C are given by Fig. 4-37.

Maximum take-off forces as well as peak times observed for blend B have been smaller and shorter for all of the three speed settings investigated.

All examined parameters, as the peak area, the temporal allocation of the peak maximum, the peak width and the maximum take-off force were all increased most distinctively for the 30 RPM setting compared to the 60 and 90 RPM settings (Tab. 4-7).

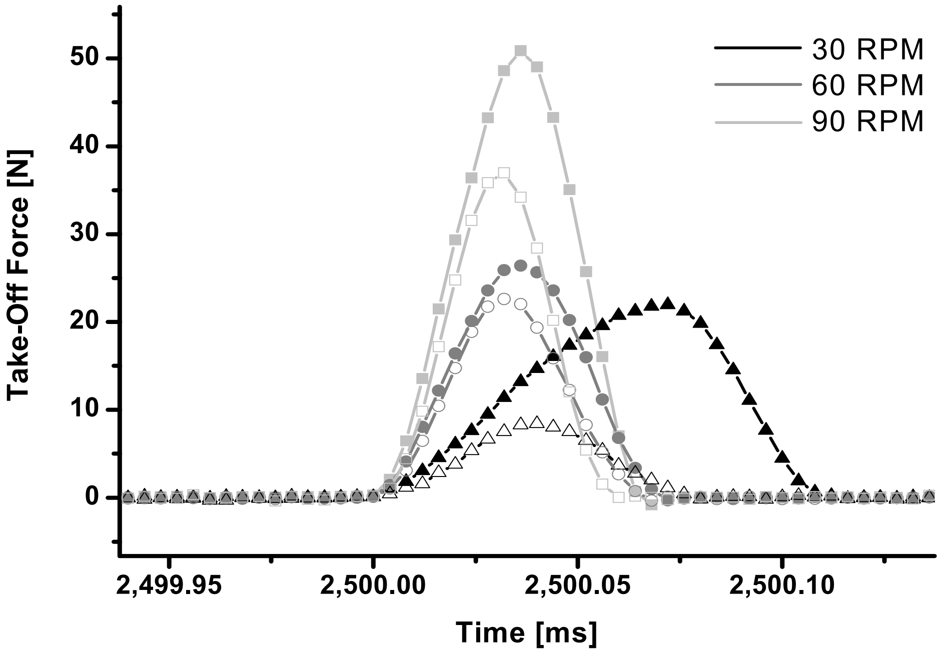


Fig. 4-37 Change in the take-off force peaks due to the sticking of the compact to the lower punch (filled symbols = blend C (n=20), open symbols = blend B (n=6))

Tab. 4-7 Change in take-off forces by the presence of sticking dependent on the speed of the turret

Turret Speed [RPM]	Sticking observed ?	Peak Area [mm^2]	Change [%]	Peak Max. [ms]	Change [%]	Peak Width [ms]	Change [%]	Take-Off Force [N]	Change [%]
30	no	0.332	**297.06**	2,500,040	**0.0013**	0.036	**77.78**	8.425	**160.44**
	yes	1.318		2,500.072		0.064		21.942	
60	no	0.738	32.96	2,500.032	0.0002	0.032	12.50	22.614	16.74
	yes	0.981		2,500.036		0.036		26.400	
90	no	1.052	63.69	2,500.032	0.0002	0.028	28.57	36.984	37.56
	yes	1.721		2,500.036		0.036		50.873	

Finally, the determined take-off forces of blend C have been corrected by those of blend B in order to obtain the adhesive part of the take-off force measurements performed for blend C.

The adhesive forces of blend C turned out to be speed dependent, as the smallest peak maximum has been found for the medium speed of 60 RPM, while the maximum adhesive forces of both the slower and higher speed settings have been found to be about three times larger (Fig. 4-38).

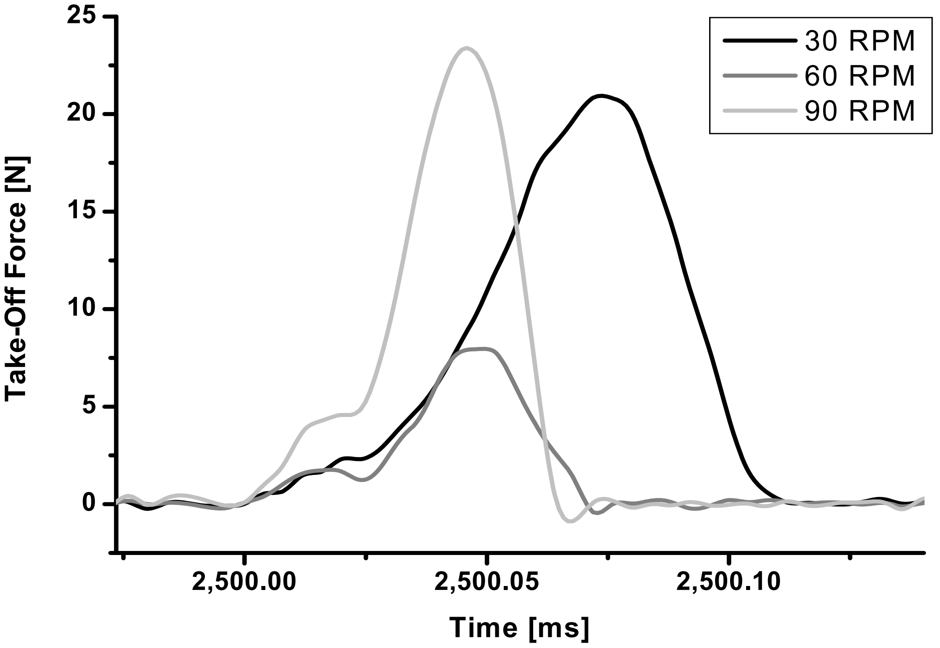


Fig. 4-38 Adhesive part of take-off-forces of blend C

The evaluation of the peak area and the impact finally indicates the most adverse conditions at 30 RPM, even if the peak maximum at 90 RPM is somewhat higher.

If only the maximum peak forces of the original take-off force signals (Fig. 5-4-8) were taken into consideration the predominance of the 60 RPM setting would have not been that obvious.

Moreover, all the signals showed a homogeneous peak shoulder of about 25 µs duration at a force level smaller than 5 N, which have been attributed to the compact deformation as a consequence of the impact of the compact on the front plate of the take-off bar.

While the impact for the 30 and 60 RPM settings have been found to be more or less comparable, a most distinctive increase has been observed for the 90 RPM setting, which has been ascribed to a change in the compact deformation behaviour beyond a certain critical speed setting.

4.4.6 Summary

Take-off force signals obtained by the original take-off force instrumentation turned out to be alike the absorbed oscillations already described during the 1980´s by Schmidt (1983a).

By the design of the original take-off bar, tablets have been kept in front of the take-off bar resulting in multi-peak signals due to repeated contacts between tablet and take-off bar.

Additionally, tablets hit the take-off bar at varying positions depending on their diameter and shape.

As the bending moment of the take-off bar, caused by a certain force, is expected to vary depending on its point of application, a general valid calibration of the original take-off bar has not been possible.

Moreover, due to the too low sample rate of the original data acquisition system of the Presster as well as the too low cut-off frequency of the amplifier, a reliable investigation of high frequency take-off forces was not possible using the original take-off force measurement system.

Hence, a new take-off force measurement system was designed and installed on the Presster.

This new system has been instrumented using a quartz load cell in combination with a new amplifier, providing an Eigen-frequency of the blank sensor of 90 kHz and a cut-off frequency of the amplifier of 200 kHz respectively.

In conjunction with the DAQ4 data acquisition system this new measurement system covers the requirements to reliably investigate high frequency take-off force signals with sufficient precision and accuracy.

By design, the new system multi-peak signals, caused by multiple contacts between tablet and take-off bar, have been ruled out. Beyond that, the validity of the calibration function has been guaranteed to be independent of the tablet diameter and shape.

The investigation of different blends of Neosorb P60W and

0.5 % magnesium stearate at varying moisture contents approved the possibility to discriminate between sticking and non-sticking blends or compacts respectively.

The correction of the total take-off force by its momentum induced part, the parameter of interest, being the adhesive component of the total take-off force, has been accessible and examined.

Therefore, the most advantageous machine settings and formulations, in order to avoid or even minimise sticking tendencies between the compact and the punches, are now easily and clearly detectable using the revised take-off force measurement system.

Furthermore, this optimised take-off force measurement system can be easily used for e.g. the optimisation of the orientation of both engravings on punch tips as well as the one of non-round punches itself with respect to the moving direction of the turret.

4.5 Punch Displacement Measurement System

Powder densification and compaction behaviour have a profound impact on the composition of new drug entities. Compaction pressure vs. in-die-tablet height plots, as already discussed in chapter 2.1.3, are often performed to gather information about the compaction behaviour of new pharmaceutical excipients or blends.

Due to a missing instrumentation for precise displacement measurements on many tablet presses the theoretical vertical punch movement of rotary tablet presses has often been calculated by Eq. 4-8 (Rippie, 1981):

$$z = \left[(r_1 + r_2)^2 - (r_3 \sin \omega t - x_2)^2 \right]^{1/2} \qquad \text{Eq. 4-8}$$

z	vertical punch displacement at time t [mm]
r_1	radius of compression roller [mm]
r_2	radius of the vertical curvature of the punch head rim [mm]
t	time [s]
r_3	pitch circle diameter [mm]
ω	turret angular velocity [rads^{-1}]
x_2	radius of the flat portion of the punch head [mm]

However, this equation does neither take the deformation of punches or other machine parts (Ruegger, 1996) nor the tilting of punches into consideration. Additionally, it is not applicable for any vertical punch movement during the dwell time, occurring as a result of relaxation phenomena of the powder bed.

Special densification behaviour of various materials due to rearrangement and fracture as well as elastic and plastic deformation of particles as a consequence of the applied pressure to the powder bed in a die, resulting in a (time-dependent) reduction of the powder bed volume and thus causing vertical punch movement, would not be registered by Eq. 4-8.

As all these aspects have major influence on the accuracy and reliability of investigations of powder compaction behaviour, a precise and accurate measurement in place of calculation of vertical punch displacement is essential.

In order to measure the individual punch positions of the upper and lower punch, especially during the dwell time period, over which the contact between the flat portion of the punch head and the compaction roller theoretically implies the absence of any vertical punch movement, both punches have to be instrumented independently from each other.

4.5.1 Technologies for Punch Displacement Measurements

Some of the most important technologies used to perform punch displacement measurements are shown in Tab. 4-8.

Tab. 4-8 Different technologies for displacement measurements

Capacitive sensors	Inductive sensors (LVDT)
Digital gauges	Laser sensors
Digital magnetic scale	Linear potentiometers
Digital rulers	Magentostrictive sensors
Draw wire sensors	Optical sensors
Eddy current sensors	Ultrasonic sensors

The choice for the one or the other measurement system or technology depends on various factors like for example accuracy, linearity, densification speed, measurement range or sensor dimension.

A general valid recommendation to prefer the one or the other system for the punch displacement measurement on either rotary or eccentric tablet presses is therefore hardly possible.

The probably most commonly used technology is the one of inductive displacement transducers.

4.5.2 Correction for Deformation of Machine Parts and Punches

Any tablet press as well as the punches deform elastically due to the applied load during compaction as shown in Fig. 4-39, where σ represents the applied pressure while ε equals the percentage ratio of the length variation under pressure over the original length. Within the area of Hook from 0 to A the deformation is purely elastic, while A gives the limit of proportionality. By further increasing the pressure, no elastic but plastic deformation takes place before the material starts to pinch off and finally fractures.

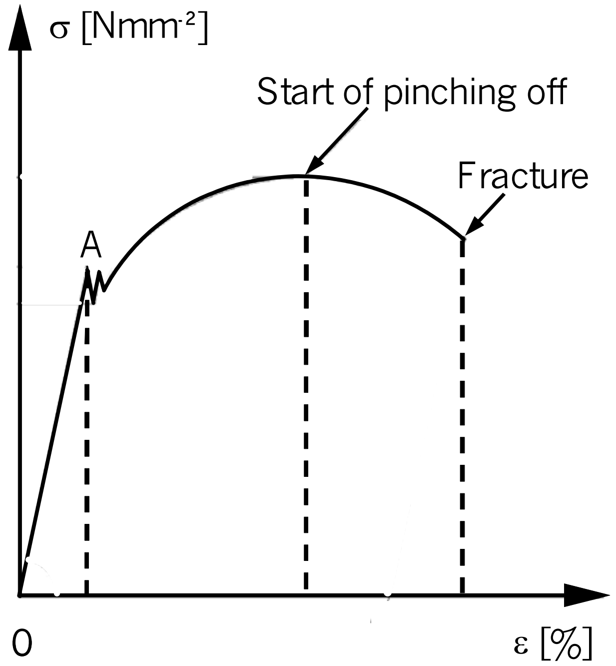


Fig. 4-39 Material deformation under pressure

To ensure accurate and precise punch displacement measurements it is necessary to take any deformation of machine parts and punches into consideration (Alderborn, 1996).

The press manufacturers know the deformation behaviour of punches and their machines during compaction as well as the vertical distance between the upper and lower compaction rollers of the pre- and main compaction stations without any applied load. Therefore, the estimation of the in-die tablet thickness, based on the settings of the compaction rollers at a certain pressure level, might be possible.

However, this method does neither compensate for slightly different lengths of punches nor different deformation behaviours of punches of different size, shape and material (Lloyd, 1991).

Therefore, the precision and accuracy of this method does not sufficiently fulfil the requirements for the investigations of powder compaction behaviour.

As a small error in the determination of punch displacement has a major effect on the reliability of displacement measurements and the subsequent estimation of powder compaction behaviour (Lammens, 1980; Muñoz-Ruiz 1995), the minimisation of this error, by correcting for any deformation as precisely as possible, is essential.

Depending on the mounting position of the displacement transducers on a given tablet press, a correction for the deformation of machine parts and punches or just for the latter is necessary to obtain reliable and accurate punch displacement measurements.

In case of mounting the displacement sensors directly onto the punches the only deformation to be corrected for is the one of the punch sections in between the tip of the punch and the mounting position of the transducer on the punch barrel.

All other deformations, like e.g. of further punch sections up to the punch head or deformations of other machine parts, only need to be taken into account while either the displacement transducers are mounted not directly to the punches but to other machine parts e.g. the machine frame, or the reference position is different from the top level of the die or the die table respectively.

Different methods for the determination of the deformation are conceivable, mainly depending on the mounting position of the sensors.

In case the sensors are not directly mounted to the punches, a punch to punch pressing in connection with a coincident measurement of the theoretical punch movements, monitored by the displacement transducers, might lead to sufficiently precise results and might therefore be the method of choice, as the calculation of the deformation of machine parts might be quite difficult due to their rather complex geometry.

However, this method is limited to the use of flat faced punches as any varying punch tip will be irretrievably damaged by this method.

Whenever the displacement transducers have been mounted directly to the punches the deformation of punches or individual punch sections can be calculated according to Hook´s law.

Different methods of mounting displacement transducers on an instrumented tablet machine result in varying errors in the determination of the in-die tablet height (Ho, 1979). The smallest error was obtained by mounting the displacement transducer directly to the punches and as close to the punch tips as possible. This is due to the fact that no machine part deformation except for the punch deformation affects the displacement measurement, and, as shown in chapter 4.5.3., the precision and accuracy of punch displacement measurements turns out to be less influenced by tilting punches compared to other methods, as the distance between punches and displacement sensors would be considerably larger.

Within this work, the calculation of the punch deformation has been performed according to Hook´s law. Therefore, the punch sections of interest in between the tip of the punch and the overall mounting position of the clamp of the displacement sensors have been divided into several cylindrical segments (Fig. 4-40), of which the dimensions, determined by a sliding calliper (Mitutoyo, Neuss, Germany) are given by Tab. 4-9.

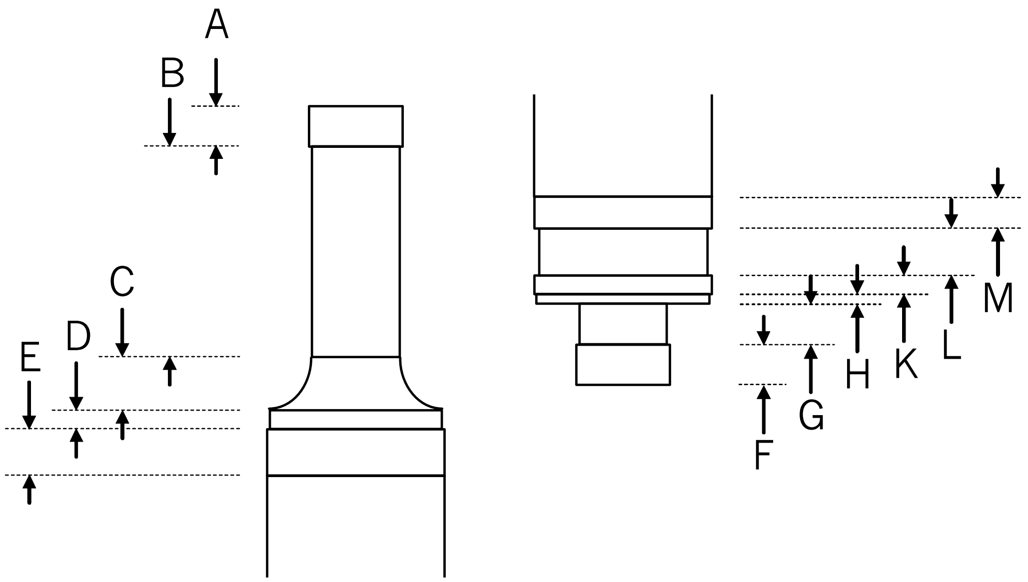


Fig. 4-40 Sections of upper (right) and lower (left) punch being deformed during compaction

Tab. 4-9 Dimensions of punch sections, necessary for calculation of punch deformation (Euro B pair of punches, 10 mm, round, flat faced; Notter, Germany)

Punch	Punch Section	Height of Punch Section h [mm]	Cross-Sectional Area A [mm²]
Lower Punch	A	4.3	78.54
	B	22.4	69.4
	C	5.4	122.72
	D	2.0	265.90
	E	4.9	283.53
Upper Punch	F	4.3	78.54
	G	4.3	67.93
	H	1.0	268.53
	K	2.0	283.53
	L	5.0	254.47
	M	3.4	283.53

The deformation of any individual punch section A to M has been calculated afterwards according to Eq. 4-9,

$$\varepsilon = \frac{\Delta l}{h} \qquad \text{Eq. 4-9}$$

where ε gives the compressive strain as the ratio of the relative change in length (Δl) to the original length (h). In combination with the following Equations 4-10 and 4-11, where σ represents the normal stress, F the applied force and A the cross-sectional area of the individual punch section, the relative change in length can be alternatively calculated following Eq. 4-12, while E represents the modulus of elasticity of the material of the punch.

$$\sigma = \frac{F}{A} \qquad \text{Eq. 4-10}$$

$$\sigma = \varepsilon \cdot E \qquad \text{Eq. 4-11}$$

$$\Delta l = \frac{F \cdot h}{E \cdot A} \qquad \text{Eq. 4-12}$$

Finally, by the conversion of units and the insertion of the modulus of elasticity E, which, according to the specifications of the punch manufacturer (Notter, Ölbronn-Dürrn, Germany), has been set to 210,000 Nmm^{-2}, the relative change in length of the individual punch sections can be calculated by Eq. 4-13.

$$\Delta l \left[\mu mkN^{-1}\right] = \frac{1{,}000 \cdot 1{,}000\ N \cdot h}{210{,}000\ Nmm^{-2} \cdot A} \qquad \text{Eq. 4-13}$$

The addition of all the strains of the individual punch sections resulted in a final compression strain of the upper and lower punch (10 mm round, flat EU19) of 0.707 μmkN^{-1} and 2.125 μmkN^{-1}, respectively. For any further punch displacement measurement within this work, the original measurement data has been corrected using these factors.

4.5.3 Correction for Punch Tilting

In order to allow free movement of punches within the punch bushing and to provide adequate room for lubrication between punch barrel and punch bushing, turret guideways for punches are a bit larger as the punch barrels outer diameter.

Unfortunately, the resulting clearance allows the punches to tilt within the bushing. This tilting represents a second source of error in the determination of punch displacement next to the already discussed deformation of punches under load.

Tilting appears, as the orientation of the compaction force vectors has been found to be not strictly straight vertical on both eccentric and rotary tablet presses, as the participating machine parts of the force transmission are not continuously positioned on a straight vertical line during the entire compaction event (Schmidt, 1986).

Only during the dwell time period the orientation of the force vector is expected to be straight vertical, which theoretically inhibits any punch tilting.

The investigation of the compactibility of excipients, e.g. in terms of compaction pressure vs. in-die tablet height plots or even Heckel-plots, requires a precise and accurate determination of the positions of the tips of the punches with respect to each other or a certain reference position as e.g. the top level of the die, in order to minimise the error in the calculation of the compacts in-die thickness and its volume, respectively.

The investigation of the positions of the tips of the punches, using just one displacement transducer per punch, impedes the observation and investigation of any punch tilting during the compaction cycle.

Hence, two displacement transducers, mounted on a straight line with the punch, one on each side of the punch, are necessary to detect and correct for any punch tilting and therefore being able to improve the precision and accuracy of displacement measurements (Matz, 1999) on any type of tablet press.

The punch tilting angle α, shown in Fig. 4-41, can be calculated according to Eq. 4-14 by the ratio of B over A, where B gives the difference between the results of the punch displacement measurements of the two sensors of a certain punch, while A represents the fixed horizontal distance between those two displacement sensors.

$$\tan\alpha = \frac{B}{A} \qquad \text{Eq. 4-14}$$

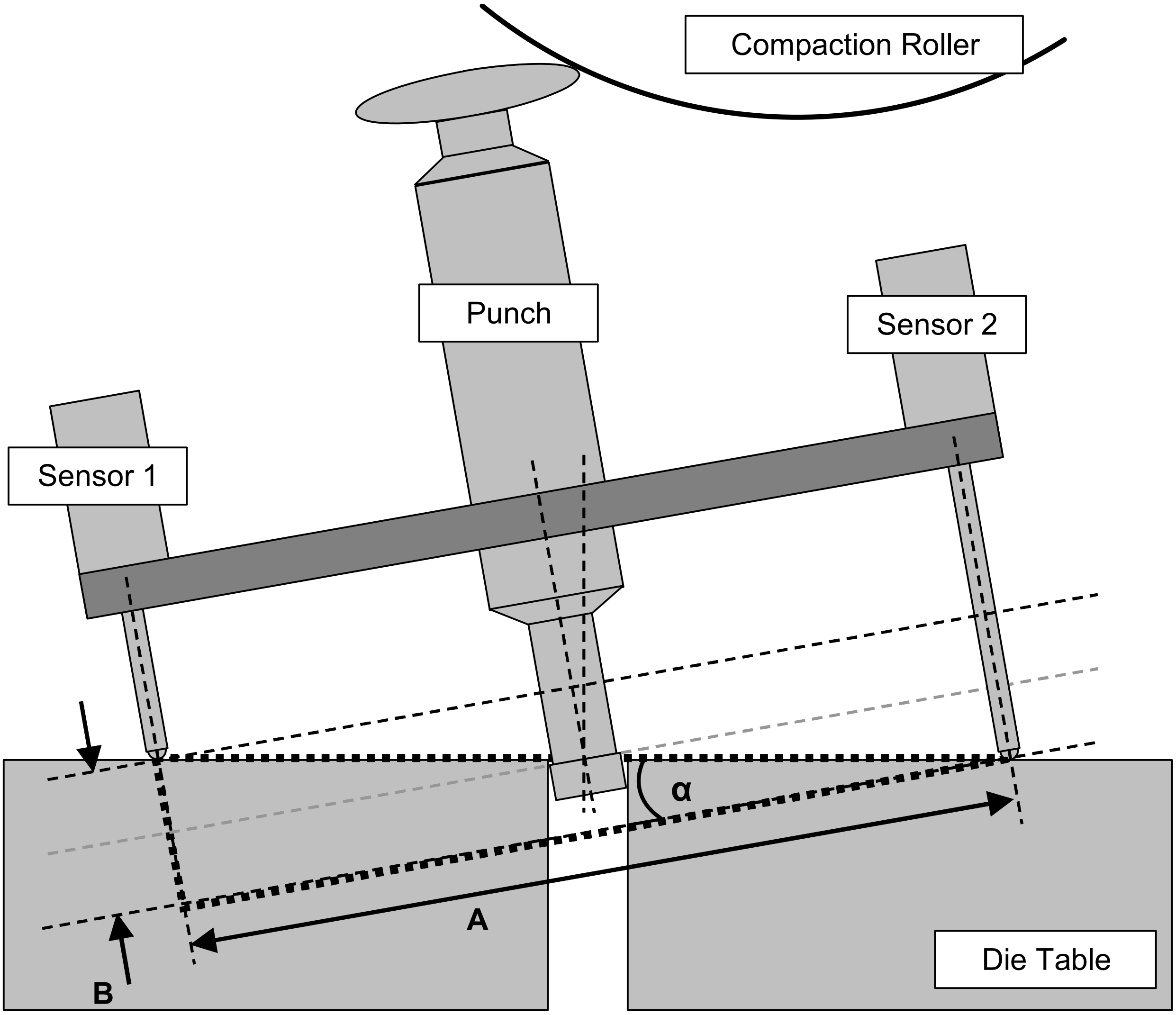


Fig. 4-41 Punch tilting during compaction (exaggerated scheme)

The basic requirement for this calculation is, firstly, the mounting of the two sensors on a straight line with the punch, one on each side of the punch while both have the same vertical and horizontal distance to the tip of the punch. And secondly, the absence of any deformation or deflection of the mounting of the displacement sensors and the sensors itself under pressure. By the knowledge of the tilting angle α of the investigated punch, the theoretical error in the determination of the position of the tip of this punch, in case of using just one displacement transducer per punch, can be calculated by Eq. 4-15.

$$\pm\, err_{tilt} = \tan\alpha \cdot r_{die} \cdot 1000 \qquad \text{Eq. 4-15}$$

err_{tilt} error in the measurement of the position of the tip of the punch caused by punch tilting [µm]

α punch tilting angle [°]

r_{die} radius of the die cavity [mm]

As the positions of the tips of both the upper and lower punch might be afflicted with a variable error, the tilting angle has to be determined individually for each punch.

By the use of two displacement sensors per punch, err_{tilt} will be eliminated automatically, as all calculations will base on the mean punch displacement of the two displacement sensors of one punch, as performed within this work.

Therefore, two displacement transducers per punch are recommended and ultimately indispensable to perform reliable and convincing punch displacement measurements on any type of tablet press until the evidence of no punch tilting under pressure has been furnished.

Beside the determination and quantification of any potential punch tilting under pressure as well as the estimation of the feasibility of punch displacement measurements using just one displacement transducer per punch, the dimension of the observed punch tilting allows the rating of the mechanical quality of the punch guidance.

Any distinctive punch tilting points to an inadequate clearance between the punch and its bushing, raised by either unacceptable tolerances during production or as a consequence of wear, finally indicating to the need for at least extensive machine inspection and an ongoing preventative maintenance program to minimise the risk of further machine damage.

4.5.4 Investigation of the Original Presster Punch Displacement Measurement System

The original punch displacement measurement system of the Presster consisted of only one linear variable displacement transducer (LVDT; 250MHR, Schaevitz, USA) connected to each punch.

Signal processing has been preformed by Schaevitz (USA) conditioners (LDM 1000) and amplifiers (DSCA49-05), while a moving ribbon cable, which was not protected against any interfering signals, had been used within the system.

Referring to the horizontal moving direction of the carriage, the LVDT´s have been mounted square to the punches as seen in Fig. 4-42.

The moving armature of the LVDT`s has been fixed to the punch by a bracket, while the housing of the transformer windings has been mounted next to the punch bushings inside the carriage. Due to this kind of instrumentation, the reference position for the punch displacement measurement has not been located at the top level of the die but in a rather large distance in the height of the middle of the punch bushing of the upper and lower punch respectively.

Therefore, a punch-to-punch-pressing would have been required to correct for both the punch and machine deformation, which would have affected any punch displacement measurement.

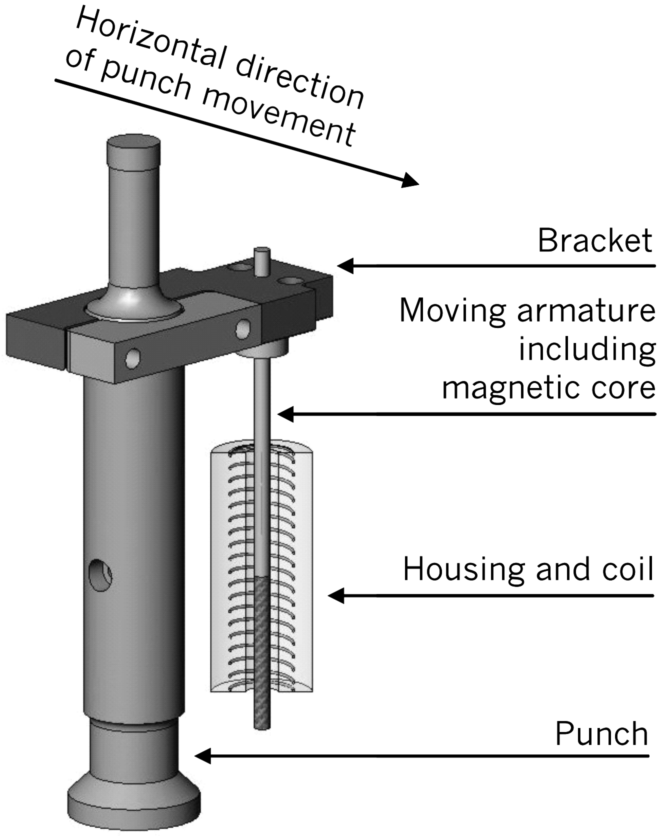


Fig. 4-42 Scheme of the original displacement measurement system

However, the consideration of either punch or machine deformation has not been intended by the original punch displacement measurement system of the Presster. Furthermore, any adaptation of the set calibration function to the original system, as e.g. the implementation of sprain functions of individual punches, has not been possible for the operator. Hence, a subsequent correction of all punch displacement measurements would have been required.

Additionally, due to the unguided armature of this special type of LVDT used on the Presster with its magnetic core installed at the end of the moving armature, and able to randomly touch the transducers body, resulting in pronounced signal variability which was not related to any variation in the present displacement.

Any out of the centre movement of the unguided core, e.g. caused by machine vibrations and inertial forces during the acceleration of the carriage, revealed the insufficient accuracy and design of the punch displacement measurement system (Fig. 4-43).

Furthermore, the investigation of any punch tilting has not been possible due to the presence of only one displacement transducer per punch.

The imperative necessity of taking the tilting of punches into consideration is obvious, as the punch bushings of the original Presster carriage, in particular the one of the upper punch, have been designed to provide a rather large clearance between itself and the punch barrels surface.

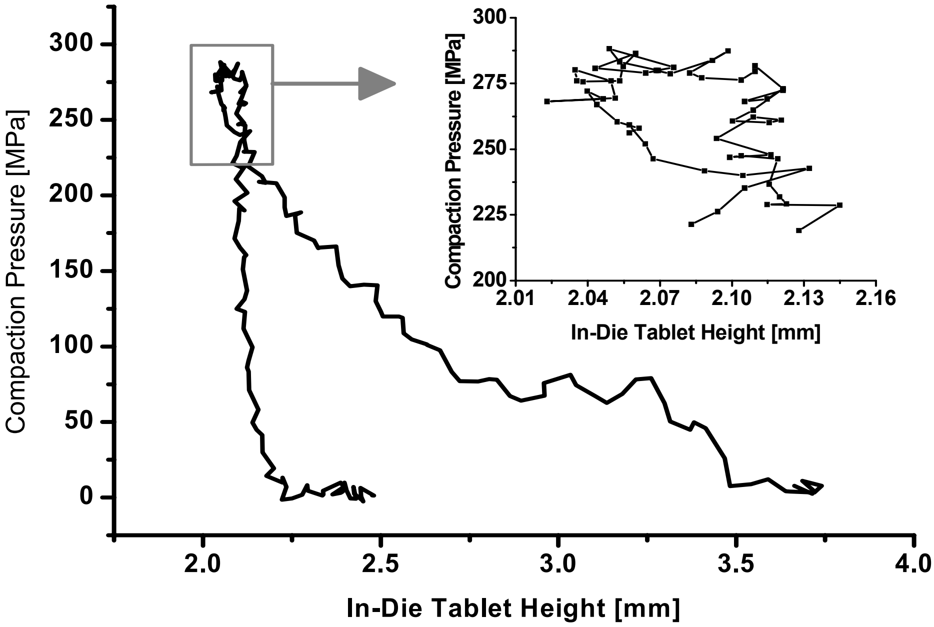


Fig. 4-43 Compaction Pressure vs. In-Die-Tablet Height Plot of Vivapur 102, obtained by the original punch displacement measurement system of the Presster (external lubrication)

The consecutive resulting misalignment of the upper punch and the die, already present during the deceleration of the upper punch, finally hindered the upper punch to enter the die centrally, but even to go foul of the edge of the die.

Hence, especially the edges of non-flat punch tips have been deformed over and over.

The big clearance between the upper punch and the comparably soft original punch bushing might have been also a result of the lateral stress applied to the punch bushings as a consequence of the impact of the punch head to the compaction rollers. This scenario might have been supported by the shorter length of the punch bushing of the upper punch, providing less lateral stability.

As a consequence of all the above mentioned shortcomings of the original punch displacement measurement system of the Presster a new system has been designed and finally used for all further punch displacement measurements performed within this work.

4.5.5 Modification of the Punch Displacement Measurement System

As a result of the previously described shortcomings of the punch displacement measurement system and the misalignment of punches and die present on the original carriage, the modifications of the punch displacement measurement system have not been restricted to the optimisation of the displacement sensors itself, but included a revision of the entire carriage.

Revised punch bushings have been used on the new carriage, providing less clearance between the punch barrels surface and the punch bushing itself, while the upper bushing has been additionally prolonged up to the maximum possible length of 49 mm. Additionally both bushings have been made out of steel and have been hardened up to 58 HRC to avoid any further deflection and punch damage.

The lack in precision of the original displacement measurement system also required the redraft of a modified punch displacement measurement system.

Based on a precision of compaction force measurement systems providing an error less than ± 2 MPa, the requirements to the precision and accuracy of displacement measurement systems, used for the reliable determination of the height of the powder bed inside the die, have been defined to exceed

± 5 µm for the compression and ± 2 µm for the decompression phase (Lammens, 1980; Krumme, 2000).

Beside the given consideration for the deformation of punches under load by the implementation of the function of the calculated punch deformation to the from now on used alternative data acquisition system DAQ4, the tilting of punches had to be taken into account.

Although, for the original mounting position of the displacement transducers of the Presster extensive tilting, if present at all, was not expected to have a large influence on the precision of punch displacement measurements, no experimental proof has ever been given. Therefore, alternative displacement transducers have been attached on a straight line directly to the punches, one on each side of each punch (Fig. 4-44), promising the most accurate method for the investigation of punch displacement (Ho, 1979; Matz, 1999).

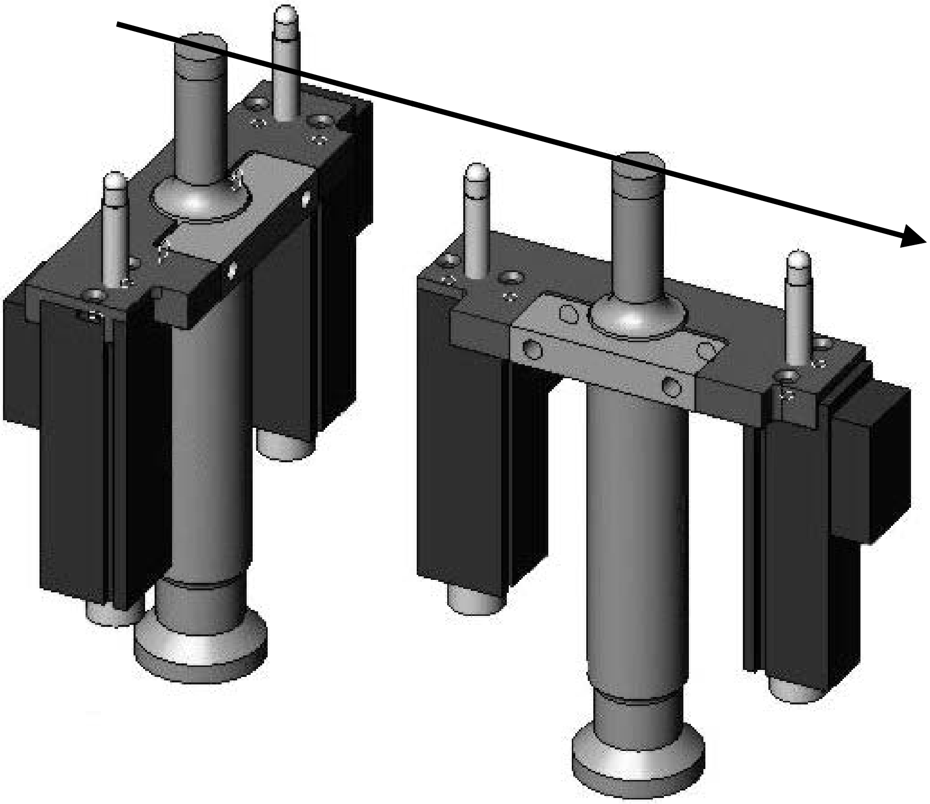


Fig. 4-44 Two displacement transducers mounted on a straight line around the lower punch to investigate punch tilting in the axes A (left) and B (right); the arrow indicates the horizontal direction of punch movement.

By design of the new carriage, the mounting position of the displacement transducers has been provided to be modifiable in steps of 90 degrees around the punch (Fig. 4-44). Therefore, the investigation of punch tilting under pressure, in the two main tilting axes, according to Fig. 4-45, has now been accessible by this modified system.

Furthermore, the reference position for all displacement measurements has been moved from somewhere far away inside the carriage, to the well defined position of the top level of the die and therefore as close as possible to the point of interest.

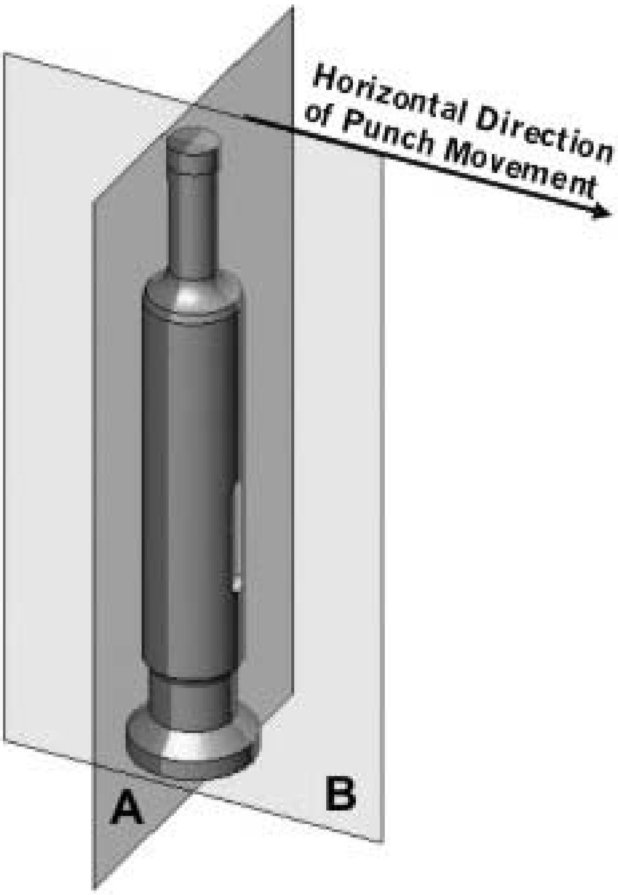


Fig. 4-45 The two main tilting axes A and B during compaction on rotary tablet presses

Due to the linear working principle of the Presster, the alignment of the displacement measurement system and the punch tilting axes stays unaffected over the entire compaction cycle.

Hence, as the determination of punch tilting is not going to be affected by any change in the vectorial direction of the axial force transmission from the compaction roller to the punch, as it would be the case on any rotary tablet press due to the circular pathway of the punch during its passage of the compaction roller, this modified system provides high validity for the investigation of punch displacement and punch tilting under pressure. Slight differences to the conditions present on rotary tablet presses are indisputable due to the design of the Presster.

Due to the very small space available on the Presster, the installation of large dimensioned displacement transducers has not been possible, as it might be a problem on almost any rotary tablet press.

Incremental displacement transducers would be the sensor type of choice for the modified system, as they have been found to be predominant compared to linear variable displacement transducers (Dressler, 2001) for this application.

Ultimately, as no incremental displacement transducer available on the market matched the totality of defined specifications and requirements, position sensors employing conductive-plastic resistance and collector tracks (plastic film potentiometers) have been used (Tab. 4-10) in connection with appropriate amplifiers (MU841, IBS Hühne, Germany).

Tab. 4-10 Plastic film potentiometers used for punch displacement measurements.

Punch	Displacement Transducer	Range [mm]	Amplifier
Upper Punch	TR 10 (original) Novotechnik (Ostfildern, Germany)	10	MU841 IBS Hühne (Rheinstetten, Germany)
Lower Punch	TR 25 (modified) Novotechnik (Ostfildern, Germany)	15	MU841 IBS Hühne (Rheinstetten, Germany)

The previously discussed requirements for the precision and accuracy of displacement measurements were not achievable using these plastic film potentiometers, as their independent linearity was not within the desired specification.
But, due to the provided accuracy in repeatability of +/- 2 µm, they represented the most promising alternative with the background of the necessity for the improvement to the punch displacement measurement system.

As a result of the plastic bearings on both ends of the shaft and the elastomer-damped multi finger wiper these sensors have been quite insensitive to shock and vibration.
Due to the different measurement ranges being of interest for the upper and lower punch, different types of these sensors have been installed. As the TR 25 sensors, used at the lower punch, did not fit in properly, the length of their actuating shaft has been modified to finally match the space restraints of the new carriage.

4.5.6 Calibration of the Modified Punch Displacement Measurement System

For the individual calibration of the plastic film potentiometers TR 10 and TR 25 (Novotechnik, Germany) outside of the carriage, a digital micrometer screw (164-151, Mitutoyo, Japan), providing an accuracy of 0.003 mm, has been used to relocate the shaft of the potentiometer with respect to its housing. The shaft has been displaced in steps of 0.1 mm over its entire measurement range of 10 and 15 mm respectively. The output voltage of the total instrumentation has been set to be 0 V at 0 mm (TR 10) or 15 mm (TR 25) and 10 V at 10 mm (TR 10) or 0 mm (TR 25) prior to the calibration run.
In order to avoid any hysteresis of the spindle drive of the micrometer screw, affecting the quality of reference positions, the micrometer screw has been

displaced only in one direction during calibration, equalizing the direction of movement of the shaft of the individual sensor during the compaction phase. The resulting calibration functions of the individual displacement transducers are given by Tab. 4-11.

Tab. 4-11 Results of the calibration of the four displacement transducers

Transducer	DISUP 1 (total)	DISUP 1 (partition)	DISUP 2 (total)	DISUP 2 (partition)	DISLP 1	DISLP 2
Calibrated Range [mm]	10	3.3	10	3.4	15	15
Number of Points	51	34	51	35	151	151
A (constant)	-0.03581	-0.08817	-0.06697	-0.09742	-14.90896	-14.91252
B (linear)	-0.50853	-0.48912	-0.49374	-0.48914	1.49097	1.49149
C (quadratic)	0.00134	-2.45E-04	–	–	–	–
Error of A	0.00381	0.00628	0.00467	0.00203	0.00208	0.00183
Error of B	0.00179	0.00232	8.10E-04	3.45E-04	3.61E-04	3.18E-04
Error of C	1.74E-04	1.96E-04	–	–	–	–
COD (R^2)	0.99996	0.99998	0.99987	0.99998	0.99999	0.99999
SD	0.00974	0.00407	0.01725	0.00421	0.01295	0.01143
Residuals [+/- µm]	35.8	9.1	67.0	8.8	19.8	23.6

The two displacement transducers of the upper punch (DISUP 1 and DISUP 2) showed unsatisfying calibration errors over the entire measurement range. Therefore, smaller sections of the entire range, which have shown the highest linearity during the overall calibration, have been recalibrated separately.

As these smaller measurement ranges, providing an improved independent linearity, still covered the measurement range of interest, these ranges have been used for the displacement measurements of the investigations described in the following.

The displacement of the lower punch has been of interest for both the compaction and the ejection event. Hence, a restriction of the measurement range of the lower punch displacement transducers has not been possible to avoid any restriction with respect to lower punch displacement measurements during ejection. Therefore the rather large residuals of the two displacement measurement systems of the lower punch (DISLP 1 and DISLP 2) had to be accepted.

After calibration, two transducers have been fixed within one linkage, which has been mounted securely to the punch barrel.

The mounting position of the linkage on the punch has been chosen to prevent any limitation of the vertical punch movement as well as to guarantee the operation of the transducers within their calibrated measurement range.

Prior to any investigation, all individual channels of the modified punch displacement measurement system have been readjusted by implementing the final physical offset of any individual displacement transducer into the DAQ4 data acquisition system.

In order to take any unevenness within the top levels of the die table and die into consideration, the readjustment of the measurement systems of both punches has been carried out in relation to their individual reference positions, being the top level of the die table for the systems of the upper punch as well as the top level of the die for the measurement systems of the lower punch.

4.5.7 Evaluation of Measurements Performed by the Modified Punch Displacement Measurement System

Despite the partially unsatisfactory independent linearity of the modified punch displacement measurements systems, different investigations have been performed in order to finally evaluate their ultimate quality under working conditions.

4.5.7.1 Punch Tilting

As already mentioned above, tilting of punches during compaction might have a major influence on the reliability of punch displacement measurements and has therefore to be taken into account for the investigation of the compressibility and compactibility of (pharmaceutical) excipients.

Tilting, if present, has been found to occur both at the beginning and at the end of the contact time as well as shortly after the peak maximum of the compaction force (Matz, 1999).

Any potential punch tilting on rotary tablet presses might be attributed to several factors, as e.g. the extent of clearance between the punch bushing and the barrel of the punch or the densification rate and speed.

Due to the straight linear working principle of the Presster the two main tilting axes A and B are conceivable (Fig. 4-45).

For the investigation of punch tilting in either axis the two pairs of displacement sensors have to be mounted to the punches along one of these axes A or B, according to Fig. 4-44.

While tilting in axis B might occur mainly by the high speed collision between the horizontally moving punch head and the fixed, not rotating compaction roller, the one along axis A might result due to the deflection of the only one-sided mounted compaction rollers during compaction.

The investigation of the presence and extent of any punch tilting during compaction along both axes A and B has been performed at two different speed settings, simulating a Fette P1200 rotary tablet press at 30 and

90 RPM and a theoretical compaction zone of 2 mm.

To observe most distinctive punch tilting, if present at all, Emcompress has been used for these investigations due to its brittle deformation behaviour and its comparably large mean yield pressure.

All investigations have been performed using a 10 mm flat Euro B pair of punches in combination with an untapered die. Data acquisition has taken place using the DAQ4 system at a sample rate of 50 kHz per channel.

Punch tilting in axis A, observed at 90 RPM, is exemplarily shown for both the upper (Fig. 4-46) and lower punch (Fig. 4-47).

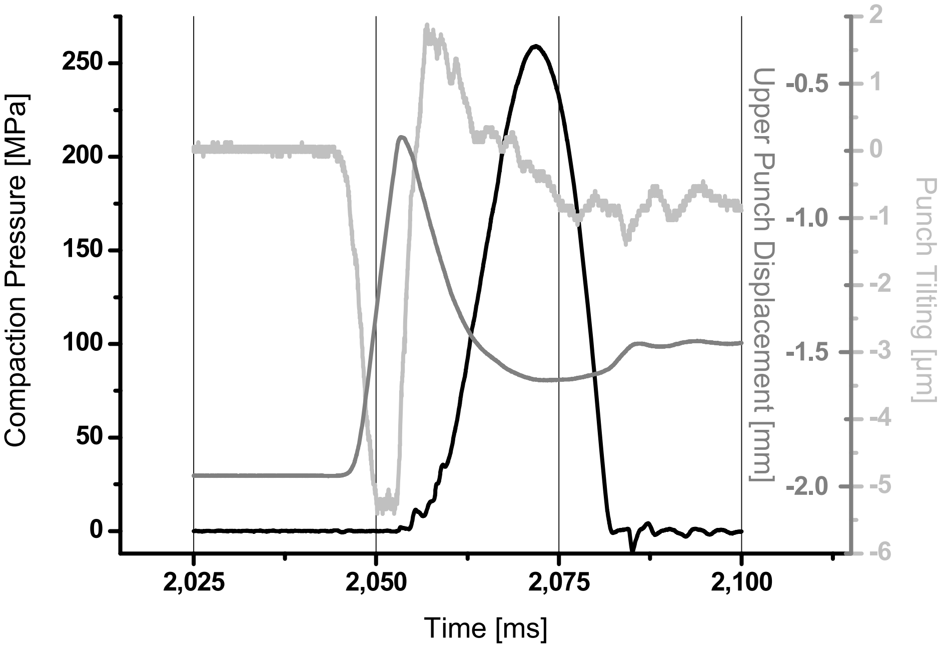


Fig. 4-46 Compaction pressure, punch displacement and punch tilting of the upper punch during compaction of Emcompress at 90 RPM (Fette P1200) axis A

The pronounced tilting of the upper punch (Fig. 5-5-14) at about 2,050 ms has not been caused by any compaction event, but describes an interaction between the displacement of the upper and lower punch.

The upwards moving lower punch shifts the powder bed inside the die upwards and consecutively the upper punch, which has been positioned on top of the powder bed, upwards as well. This upward shift of both powder bed and upper punch takes place until the upper punch contacts with the upper compaction roller, characterising the beginning of the contact time.

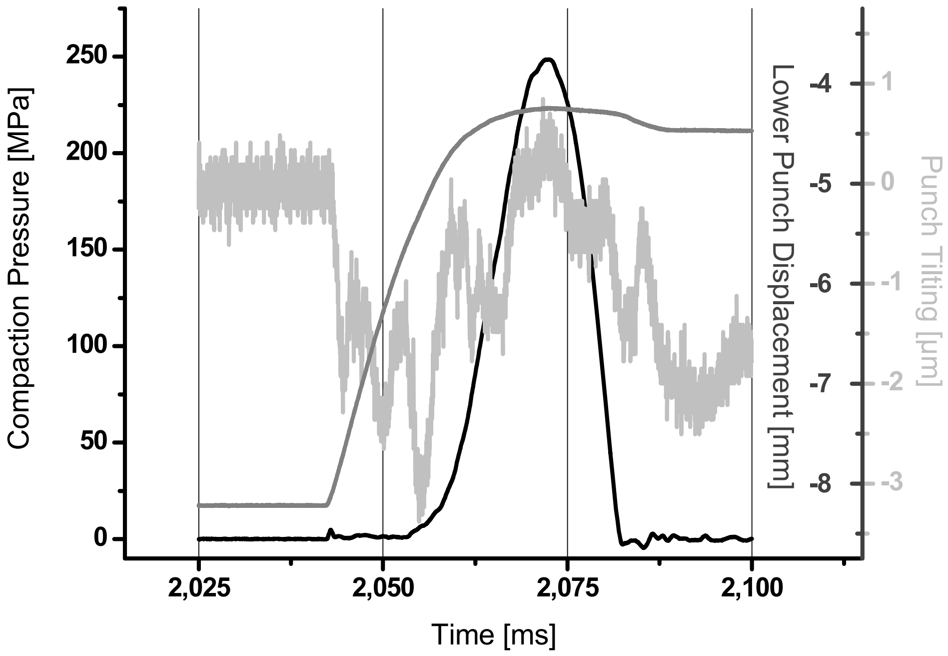


Fig. 4-47 Compaction pressure, punch displacement and punch tilting of the lower punch during compaction of Emcompress at 90 RPM (Fette P1200) axis A

Neither the upwards movement of the upper punch nor the resulting tilting of the upper punch would have been observed if a holding ledge would have been installed in-between the upper pre- and main compaction roller, as it is the case on most rotary tablet presses.

These punch movements and therefore the resulting punch tilting, being not part of the compaction period required to calculate compressibility profiles, have not been considered for the estimation of any punch tilting.

Rather, the final evaluation of any punch tilting has been performed for the period over which the compaction pressure level has been found to be larger than 5 MPa. The results of the investigations of punch tilting during the compaction of Emcompress at the two speed levels of 30 and 90 RPM, simulating a Fette P1200 rotary tablet press, are given by Tab. 4-12 and 4-13 for both tilting axes A and B respectively.

As both punches might tilt in both, a positive and negative direction, a tilting orientation had to be defined. For both punches the punch tilting has been described in terms of action of the individual punch head along one certain tilting axis.

Therefore, referring to the horizontal moving direction of the punches, the punch head tilts to the left or right for tilting axis A, for tilting axis B the punch head might tilt to the front or back.

The overall punch tilting gives the tilting of one punch observed in both directions during one defined compaction event. A punch head tilting to one direction implicates the tip of the same punch tilting to the opposite direction.

The most distinctive punch tilting, if at all, would have been expected to appear for the upper punch, as its punch bushing had to be designed shorter compared to the one of the lower punch, due to the cramped conditions.

Therefore the guidance of the upper punch would have been expected to be of lower quality compared to the one of the lower punch.

Furthermore, punch tilting would have been expected to increase by increasing speed settings of the turret.

The results tend to confirm the speed dependency for both tilting axes, but showed the contrary to that expected for the magnitude of tilting for the upper and lower punch, as the more pronounced tilting has been found for the latter. No major difference has been observed for the tilting of punches along the two tilting axes A and B.

The most distinctive absolute punch tilting, observed for both the upper and lower punch and both tilting axes A and B, has been found to be smaller than 4.4 μm.

The small extent of punch tilting is ascribed to the rather small clearance between the barrels of the punches and the new punch bushings, which have been redesigned in combination with the new designed carriage, in order to prevent or at least minimise any potential punch tilting.

Tab. 4-12 Punch tilting during one compaction cycle of Emcompress observed in tilting axis A

Punch		**Lower Punch**				**Upper Punch**			
Speed [RPM]		**30**		**90**		**30**		**90**	
Tilting Dimension		**[µm]**	**[°]**	**[µm]**	**[°]**	**[µm]**	**[°]**	**[µm]**	**[°]**
Punch head tilts to the back	**Mean**	-3.4	-0.039	-3.3	-0.038	0.7	0.008	1.8	0.021
	SD	0.3	0.004	0.3	0.003	0.1	0.002	0.2	0.002
	max	-3.0	-0.035	-2.9	-0.033	0.9	0.010	2.1	0.024
	min	-3.9	-0.045	-3.7	-0.042	0.5	0.006	1.5	0.017
Punch head tilts to the front	**Mean**	0.8	0.010	0.8	0.010	-1.0	-0.012	-1.0	-0.012
	SD	0.3	0.004	0.3	0.003	0.1	0.001	0.2	0.002
	max	1.1	0.013	1.2	0.014	-0.9	-0.010	-0.7	-0.008
	min	0.3	0.003	0.4	0.005	-1.1	-0.013	-1.2	-0.014
Absolute punch tilting	**Mean**	4.2	0.048	4.2	0.048	1.7	0.019	2.8	0.032
	SD	0.1	0.002	0.1	0.001	0.1	0.001	0.2	0.003
	max	4.4	0.050	4.2	0.048	1.9	0.022	3.1	0.035
	min	4.0	0.046	4.1	0.047	1.5	0.018	2.6	0.029

Tab. 4-13 Punch tilting during one compaction cycle of Emcompress observed in tilting axis B

Punch		**Lower Punch**				**Upper Punch**			
Speed [RPM]		**30**		**90**		**30**		**90**	
Tilting Dimension		**[µm]**	**[°]**	**[µm]**	**[°]**	**[µm]**	**[°]**	**[µm]**	**[°]**
Punch head tilts to the left	**Mean**	-0.7	-0.008	-2.1	-0.024	1.4	0.016	1.8	0.021
	SD	0.3	0.003	0.6	0.007	0.2	0.002	0.3	0.003
	max	-0.4	-0.005	-1.3	-0.015	1.6	0.019	2.1	0.024
	min	-1.1	-0.013	-2.9	-0.033	1.2	0.014	1.5	0.017
Punch head tilts to the right	**Mean**	2.6	0.029	1.9	0.022	-1.0	-0.012	-1.5	-0.017
	SD	0.2	0.003	0.5	0.006	0.2	0.002	0.2	0.002
	max	2.8	0.032	2.5	0.029	-0.9	-0.010	-1.2	-0.014
	min	2.1	0.024	1.3	0.015	-1.3	-0.015	-1.8	-0.021
Absolute punch tilting	**Mean**	3.3	0.037	4.0	0.046	2.5	0.028	3.4	0.039
	SD	0.1	0.001	0.1	0.002	0.1	0.001	0.3	0.004
	max	3.4	0.039	4.2	0.048	2.6	0.030	3.9	0.045
	min	3.2	0.037	3.8	0.043	2.3	0.026	3.1	0.035

As the observed tilting has been found to be smaller than the independent precision of each of the four displacement transducers used by the modified punch displacement measurement system, a final and reliable determination of the magnitude of punch tilting has not been possible.

Therefore, as long as no punch tilting larger than the residuals of the calibrations of the displacement sensors has been observed, the tilting of punches might be negligible for any punch displacement measurement performed by this modified system.

Therefore, in case of staying with this system, the use of just one displacement transducer per punch might be sufficient for the determination of the height of the compact during the compaction cycle, as long as the quality of clearance between the punch barrels and bushings stays the same.

However, all punch displacement measurements discussed within the following investigations of punch displacements with respect to the determinations of compaction pressure vs. in-die tablet height plots or even Heckel-plots have been processed using two displacement transducers per punch.

Therefore, all further calculations of tablet heights within this work have been based on displacement values, which have been corrected for the observed punch titling.

4.5.7.2 Compaction Pressure vs. In-Die Tablet Height Plot

In order to verify the improved quality of the modified punch displacement measurement system compared to the original system of the Presster, compaction pressure vs. in-die tablet height plots of various materials have been investigated.

The obtained plots, exemplarily shown for Starch 1500 (Fig. 4-48) and Emcompress (Fig. 4-49), have been found to be free of major vibrations, while variations in the slopes of the plots have been obvious.

The necessity for the correction of punch and/or machine deformation in order to avoid major errors in the determination of the in-die tablet height has been clearly observable.

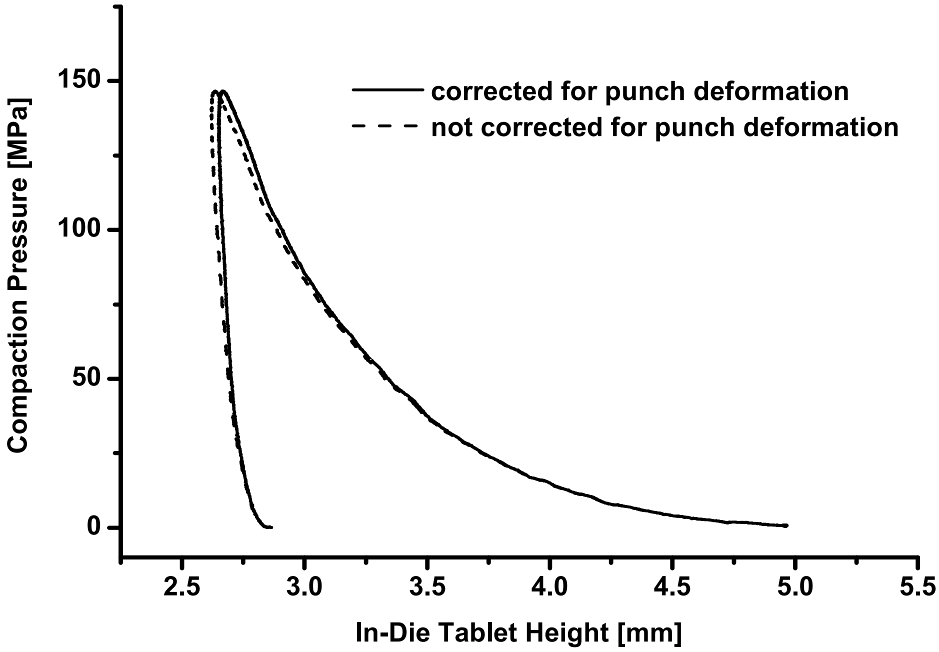


Fig. 4-48 Compaction pressure vs. in-die tablet height plot of Starch 1500

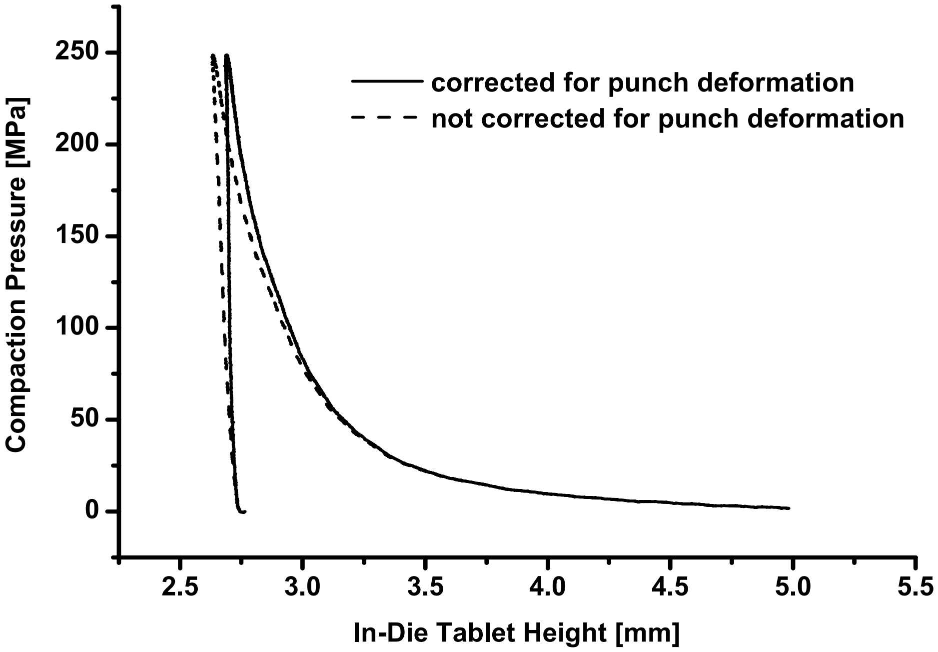


Fig. 4-49 Compaction pressure vs. in-die tablet height plot of Emcompress

As a result of the modifications of the punch displacement measurement system, the compaction pressure vs. in-die-tablet-height plot represents a useful tool to finally illustrate the decrease in powder bed height due to the applied compaction pressure.

Therefore, the quality of signals obtained by this optimised system finally facilitates the investigation of materials in terms of compressibility profiles.

Furthermore, it provides some important information about the in-die elastic recovery of the compact, which might indicate for capping tendencies of certain formulations, without the need for further data processing.

Furthermore, due to the feasibility to illustrate this plot in real time, these compaction pressure vs. in-die-tablet-height plot might be used as a valuable in-process control tool.

Presuming constant compaction conditions, any change in the slope of these plots indicates a change in the materials compressibility, which has to be ascribed to any change in the properties of the material itself.

Therefore, compared to the quality of compaction pressure vs. in-die-tablet-height plot (Fig. 4-43) and the overall performance of the original punch displacement measurement system, the modified punch displacement measurement system has been found to be better.

Hence, by the use of this modified system, further investigations with respect to compressibility profiles or Heckel-plots of individual excipients and/or active ingredients as well as binary or ternary blends can now be performed with adequate precision.

4.5.7.3 Heckel-Plot

To further prove the improved quality of the modified punch displacement measurement system, Heckel-plots of five excipients, representing the three main deformation mechanisms (brittle fracture, plastic and viscoelastic flow) of pharmaceutical excipients, have been investigated, based on the determination of the in-die compact height, as already mentioned above.

Each of the five excipients has been compressed at two different speed settings equivalent to 30 and 90 RPM of the simulated Fette P1200 rotary tablet press, in order to evaluate the feasibility to detect any speed dependency in materials compressibility.

External lubrication has been used to minimise the lubricant affected modification of the materials compressibility profiles, which has been shown by Dressler (2002). Therefore, magnesium stearate used as the lubricant has been applied to the punches and die before each compaction cycle using a small brush, while excess lubricant has been exhausted using a vacuum cleaner. All the excipients have been weighed out on a balance before being transferred to the die manually.

To detect the most linear span of the compaction slope of the Heckel-plot a set of 50 data points, separated in steps of 1 MPa, has been selected out of a pressure interval of 50 MPa. A pressure interval of 50 MPa has been selected as it firstly contains a sufficient number of data points and secondly to limit the interval to a maximum of about 30% of the investigated compaction pressure range. A linear regression has been applied to this data set. Parameters as the slope of the linear regression, the intercept with the ordinate and the coefficient of determination, have been stored.

Afterwards, the data point, showing the smallest pressure level within the 50 MPa interval, has been displaced by a new data point, showing a by 1 MPa larger pressure level than the data point with the largest pressure level so far, followed by another linear regression and storage of the parameters as before (stepwise linear regression).

This procedure has been continued over the entire compaction slope of the Heckel-plot, while all parameters have been calculated for each setting.

Finally the 50 MPa pressure interval showing the largest coefficient of determination has consecutively been selected to be the most linear span of the compaction slope of the Heckel-plot.

The reciprocal of the slope of the linear regression has been set as the mean yield pressure of the particular excipient investigated, referring to the resistance of the material against persisting deformation.

The minimum edge height of the compact during a compaction cycle has not been necessarily obtained at the point of maximum pressure. Usually, the edge height of the compact rather decreases due to relaxation even though the maximum pressure level has already been achieved.

Depending on the investigated material, a varying pressure relaxation Rx [%] between the edge height at maximum pressure level of the compaction cycle and the minimum edge height have been observed and evaluated by Eq. 4-16.

$$Rx\,[\%] = \frac{(h_{P\max} - h_{\min}) \cdot 100}{h_{\min}} \qquad \text{Eq. 4-16}$$

where $h_{P\max}$ has been set as the tablet edge height at maximum pressure, while $h_{\min}$ gives the minimum edge height observed.

Furthermore, a variable elastic recovery ER [%] has been observed during the decompression phase. The calculation of ER has been carried out according to Armstrong (1974), while the elastic recovery has been calculated for the range between the minimum edge height of the compact and the edge height at a residual force level of 5 MPa. To be able to compare the elastic recovery of compacts of varying edge heights, a relative ER, referring to the minimum edge height, has been calculated by Eq. 4-17:

$$ER\,[\%] = \frac{(h_{5MPa} - h_{\min}) \cdot 100}{h_{\min}} \qquad \text{Eq. 4-17}$$

where $h_{5\,MPa}$ gives the edge height of the compact at a residual force level of 5 MPa, while the minimum edge height of the compact is represented by h_{min}.

Resulting parameters of the Heckel-plots of the five investigated excipients have been summarised in Tab. 4-14, showing the average values of 6 individual plots.

Fragmenting materials, in some cases also called brittle substances, e.g. Emcompress (Fig. 4-50) and Flowlac 100 (Fig. 4-51), show significant deviations from linearity at smaller pressure levels.

By increasing pressure levels, the yield pressure increases while the primary particle size is reduced. From a certain particle size, the energy required to further reduce the particle size increases dramatically. The deformation mechanism switches over to plastic flow, identifiable by the approximate linearity of the compaction slope at higher pressure levels.

Furthermore, the constant linearity at high pressure levels indicates to very low viscoelastic behaviour.

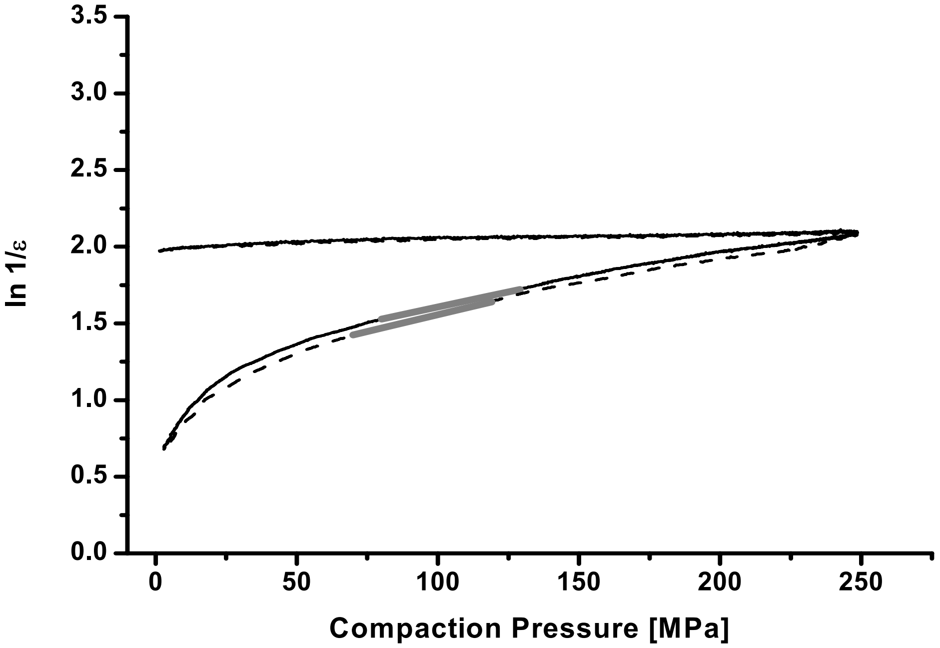


Fig. 4-50 Heckel-plot of Emcompress investigated at 30 RPM (solid) and 90 RPM (dashed) including the associated Linear Fits (grey)

The highly linear Heckel-plots of Emcompress even at highest pressure levels, and therefore in the region of small changes of the vertical punch velocity, indicates for very low strain-rate sensitivity and confirms the findings of Roberts (1985).

The apparent yield pressures of Emcompress, obtained at the two speed settings investigated, have been more or less identical, reflecting its speed insensitive compaction behaviour, which has been also visible by the very low pressure relaxation. The slope of the post-compaction phase of the Heckel-plots, especially the one of Emcompress, is rather small, indicating for only very low elastic recovery.

In contrast, compressibility of Flowlac 100 turned out to be slightly time dependent for the covered punch velocity range, while its pressure relaxation has been more pronounced (Fig. 4-51).

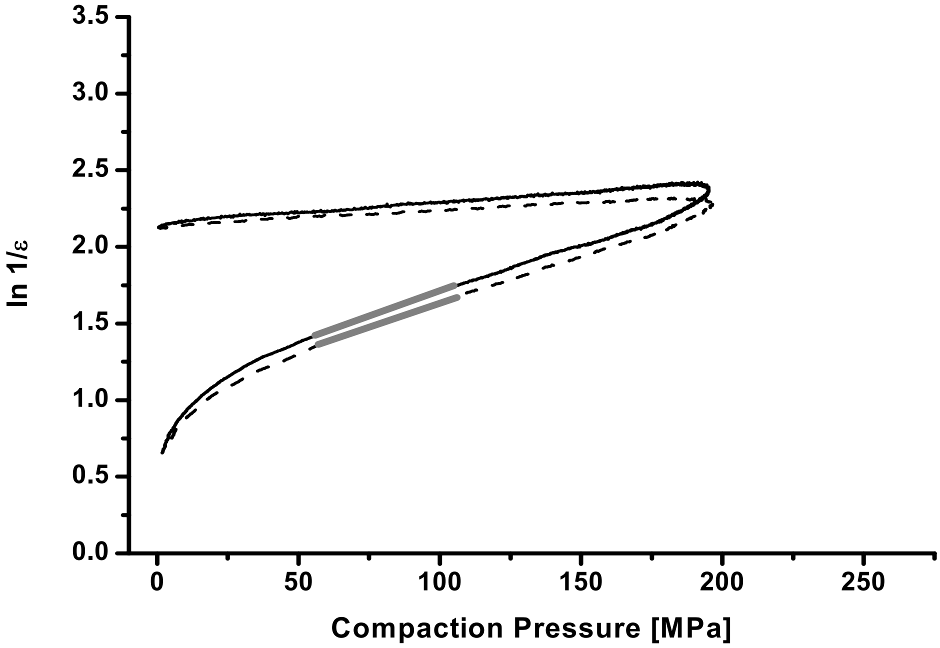


Fig. 4-51 Heckel-plot of Flowlac 100 investigated 30 RPM (solid) and 90 RPM (dashed) including the associated Linear Fits (grey)

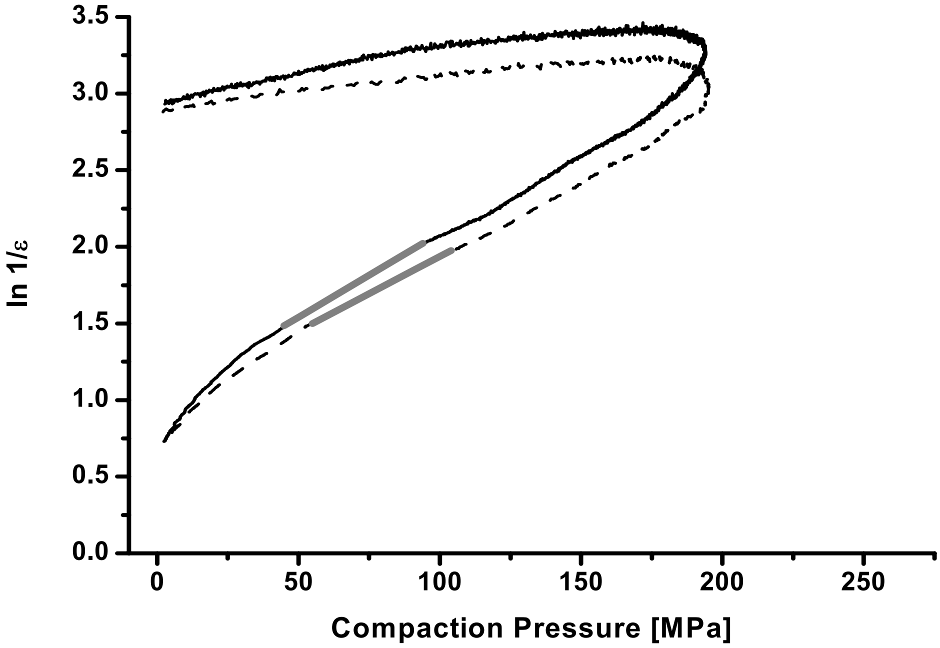


Fig. 4-52 Heckel-plot of Neosorb P60W investigated 30 RPM (solid) and 90 RPM (dashed) including the associated Linear Fit (grey)

Neosorb P60W (Fig. 4-52) and Vivapur 102 (Fig. 4-53) represent mainly plastically deforming materials.

The slope of their Heckel-plots showed distinctive linearity during the compaction phase. Some fragmentation during compaction is obvious for Neosorb P60W at lower pressure levels up to about 30 MPa, while Vivapur 102 has been found to be almost free of any fragmentation.

Compared to the situation found for the brittle deforming materials discussed above, the energy required to compact these plastic deforming materials is much smaller, as apparent by the smaller yield pressures found for Neosorb P60W and Vivapur 102.

Non-linear sections at high pressure levels present in the slopes of the Heckel-plots of both materials indicate to small viscoelastic components during compaction.

Neosorb P60W shows very low elastic recovery while its pressure relaxation is comparably high and increases by increasing speed settings, indicating to distinctive time dependent deformation behaviour.

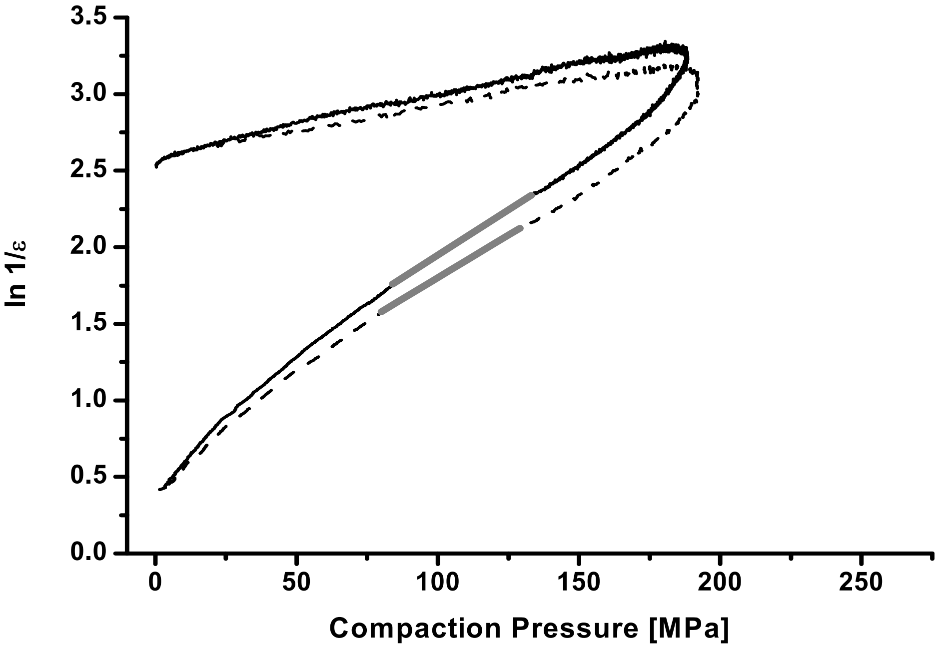


Fig. 4-53 Heckel-plot of Vivapur 102 investigated 30 RPM (solid) and 90 RPM (dashed) including the associated Linear Fit (grey)

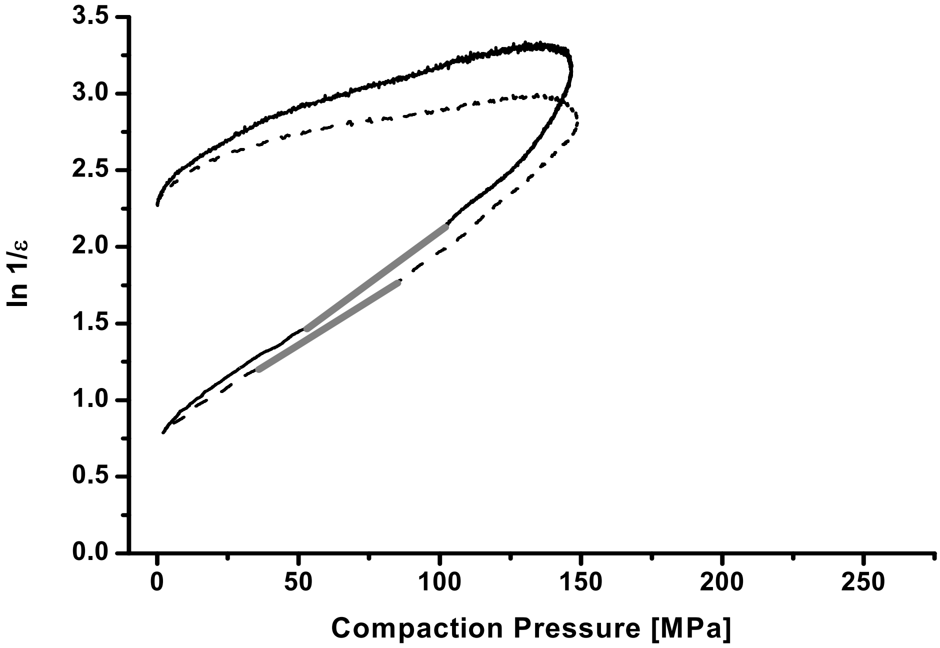


Fig. 4-54 Heckel-plot of Starch 1500 investigated 30 RPM (solid) and 90 RPM (dashed) including the associated Linear Fit (grey)

A comparably large elastic recovery has been found for Vivapur 102.

Starch 1500 (Fig. 4-54), being a viscoelastic material, has been found to deform within the particles (Paronen, 1983), while individual particles remain as individuals. Therefore Starch 1500, as most other starch qualities, works as a system free of any fragmentation. The slope of the Heckel-plot, which has been found to be almost linear in the lower pressure sections, changes to non-linearity at medium pressure levels. The increasing steepness at high pressure levels clearly indicates the viscoelastic behaviour. Compared to the brittle and plastic deforming materials discussed above, Starch 1500 showed the most extensive pressure relaxation, indicating to its distinctive strain rate sensitivity. Finally a high gear curvature due to relaxation referred to a most pronounced elastic recovery.

Tab. 4-14 Comparison of compaction and Heckel parameters (bold) including their SD values (italics) of different excipients (n=6).

Excipient	**Pycnometric Density [g/cm^3]**	**Simulated Speed of the Turret [RPM]**	**Compaction Pressure [MPa]**	**Heckel Slope**	**Axis Intercept**	**Yield Pressure [MPa]**	**Elastic Recovery [%]**	**Pressure Relaxation [%]**
Neosorb P60W	1.4992	30	**194**	**0.011**	**0.994**	**91**	**3.6**	**0.5**
			0.9	*2.0E-05*	*4.8E-03*	*0.1*	*0.09*	*0.1*
		90	**198**	**0.009**	**1.073**	**116**	**3.4**	**0.7**
			1.0	*1.3E-04*	*1.8E-02*	*1.8*	*0.17*	*0.2*
Vivapur 102	1.5863	30	**189**	**0.012**	**0.775**	**85**	**6.1**	**0.5**
			1.1	*5.0E-05*	*8.1E-03*	*0.4*	*0.04*	*0.4*
		90	**193**	**0.012**	**0.587**	**81**	**5.4**	**0.5**
			1.3	*3.9E-04*	*3.4E-02*	*2.6*	*0.10*	*0.1*
Emcompress	2.3221	30	**248**	**0.004**	**1.175**	**230**	**4.0**	**0.2**
			1.1	*6.0E-05*	*1.9E-02*	*3.3*	*0.10*	*0.1*
		90	**249**	**0.004**	**1.120**	**230**	**3.8**	**0.1**
			1.6	*5.0E-05*	*3.2E-03*	*2.5*	*0.07*	*0.3*
Starch 1500	1.5056	30	**147**	**0.014**	**0.744**	**73**	**6.8**	**0.6**
			0.6	*1.1E-04*	*3.8E-03*	*0.6*	*0.05*	*0.1*
		90	**147**	**0.012**	**0.781**	**86**	**5.5**	**0.9**
			0.8	*5.0E-05*	*3.2E-03*	*0.3*	*0.04*	*0.2*
Flowlac 100	1.543	30	**194**	**0.006**	**1.087**	**160**	**4.8**	**0.4**
			1.0	*1.1E-04*	*1.0E-02*	*2.6*	*0.06*	*0.1*
		90	**196**	**0.006**	**0.998**	**158**	**4.0**	**0.5**
			1.3	*8.0E-05*	*8.3E-03*	*1.9*	*0.15*	*0.1*

4.5.8 Summary

The original punch displacement measurement system of the Presster has been investigated with respect to the precision and accuracy as well as the reliability of measurements, in particular in terms of compaction pressure vs. in-die tablet height plots.

These plots contained comparably large noise levels, which have been ascribed to machine vibrations monitored by the LVDT´s due to their unguided core inside their housing.

Furthermore, the quite large clearance between the punch barrel and its bushing, which allowed the punch tip to hit the edge of the die bore while entering the die and finally resulting in damaged tips of upper punches, lead to tilting punches during compaction, increasing the noise level and inaccuracy present in punch displacement measurements.

Finally, neither the deformation of machine parts and punches nor the tilting of punches during compaction has been taken into consideration.

Any implementation of these aspects to the standard data acquisition system of the Presster has been impossible either by restrictions of the system itself or by design of the punch displacement measurement system, using only one displacement transducer per punch.

Hence, a reliable investigation of the compressibility of pharmaceutical excipients was not possible with the original system.

Therefore, a new punch displacement measurement system was designed in order to meet the requirements for punch displacement measurements and hence being able to reliably investigate powder compaction behaviour.

The clearance between punch barrel and its bushing has been minimised on the new designed carriage to avoid any further major shortcoming by tilting punches. Despite the prospect for only minor punch tilting present in punch displacement measurements performed by the redesigned system, two displacement transducers have been used per punch in order to be able to finally correct for the from now on accessible and quantifiable punch tilting. The option to install the two pairs of displacement transducers in steps of

90° around each punch opened the possibility to investigate the tilting of punches in the two main tilting axes.

The new displacement transducers of the redesigned system have been connected directly to the punches while their reference position has been moved to the well defined top level of the die and therefore as close as possible towards the compaction area.

As no machine deformation will furthermore affect the punch displacement measurement it is no longer taken into consideration. The deformation of punches has been calculated according to Hook´s law and taken into account by implementing these correction functions to the new data acquisition system DAQ4.

Using the new punch displacement measurement system the compressibility profiles of five pharmaceutical excipients has finally been investigated in terms of Heckel-plots at two different speed levels simulating a Fette P1200 rotary tablet press.

The compressibility profiles, obtained by the new punch displacement measurement system, matched the well known compressibility data of the individual excipients and therefore demonstrated the improved quality of the redesigned system and the reliability of measurements.

Typical compaction behaviour as brittle fracture, plastic and viscoelastic flow as well as conversions within the deformation behaviour during compression phase has been identified reliably.

Nevertheless, the estimation of the compressibility data had to be carried out carefully, as the accuracy in the determination of the height of the compact performed by the new punch displacement measurement system did not match the above-mentioned requirements of ± 5µm and ± 2µm during compression and relaxation phase respectively.

A further optimization of the accuracy of the punch displacement measurement system by e.g. incremental sensors would therefore be recommended as soon as suitable sensors become available.

4.6 Speed of the Turret and Resulting Dwell Time

Depending on the deformation behaviour of the individual ingredients of a formulation, the speed of the turret and the resulting densification speed and the dwell time have a major influence on tablet properties. This is especially valid for the time depending deformation of plastically deforming excipients.

Therefore, the achieved horizontal speed of the carriage of the Presster has to match the set simulated speed of the turret of a rotary tablet press as close as possible. Hence, the horizontal speed of the carriage of the Presster has been investigated using a digital high speed imaging system (Hisis 2002, KSV Instruments, Finland).

A blend of Flowlac 100 and 1 % of magnesium stearate has been compacted within these trials at a compaction pressure of 127 ± 6 MPa, forming 10 mm round, flat tablets of 300 mg. The achievable linear speed of the Presster, in contrast to its specification of 0.055 and 2.2 ms^{-1}, has been found to be within the range of only 0.4 to 2.0 ms^{-1} (Fig. 4-55).

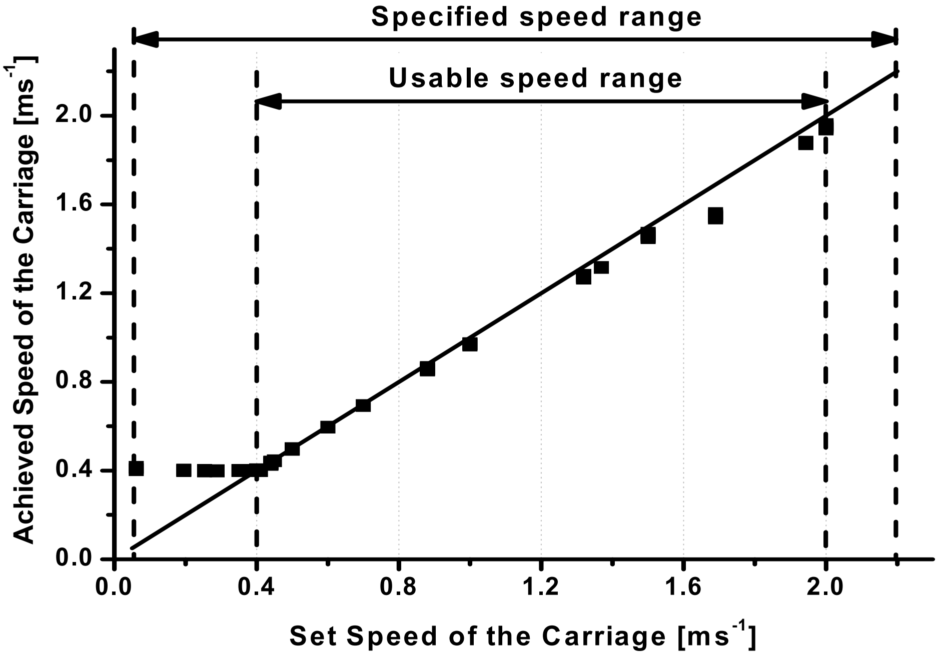


Fig. 4-55 Differences between the set and the achieved horizontal speed of the carriage of the Presster

The carriage of the Presster has been moving at a minimum horizontal speed of 0.4 ms^{-1}, independent of any minor set speed value.

A different situation has been found for the speed range above 2.0 ms^{-1}. As soon as the carriage was obviously moving faster than 2.0 ms^{-1}, none of the compaction cycle related signals has been monitored and recorded properly by the original data acquisition system of the Presster.

Therefore, the missing information about the finally achieved speed value while running at a set speed larger than 2.0 ms^{-1} finally impeded the use of any set speed larger than 2.0 ms^{-1}.

Upon request at the manufacturer, the specifications of the horizontal carriage speed of the Presster have been declared to be valid only as long as no load has been applied to the system.

In case of any applied load, the carriage had to be pulled at least with a linear speed of 0.4 ms^{-1} in order to prevent the carriage from becoming stuck in between the compaction rollers. Recent models of the Presster ought to have a more powerful actuation, therefore slower carriage speeds should be realisable even under applied load.

Unfortunately, the verification of any achievable speed of the carriage smaller than 0.4 ms^{-1} without any applied load finally resulted in an achieved speed of 0.4 ms^{-1} and therefore did not show any difference to the situation found while running the Presster under load.

Furthermore, the achieved linear speed in between the limits of 0.4 to 2.0 ms^{-1} has been found to tend to be slightly smaller compared to the set ones (Fig. 4-55). The largest deviation between both the set and the achieved linear horizontal speed of the carriage has been observed to be 0.15 ms^{-1}, being equal to 10.3 RPM simulating a Fette P1200 rotary tablet press.

Nevertheless, the finally achieved speed of the carriage within the valid limits of 0.4 and 2.0 ms^{-1} has been displayed correctly by the original data acquisition system.

4.6.1 Summary

The investigation of the speed of the carriage of the Presster showed some differences between both the set and the achieved horizontal speed, while the achieved speed has been found to be up to 0.15 ms^{-1} smaller compared to the set one.

Therefore, in order to achieve the desired linear speed of the carriage, finally matching the horizontal speed of the turret of a certain simulated rotary tablet press and hence resulting in similar dwell times, an adequate larger speed value has been chosen for any investigation within this work.

As the adjustment of the speed settings might be accompanied with the need for additional material, which might be rare and therefore expensive during the early development stages, the speed deviation has been declared as a major shortcoming, which would not be accepted in a standard rotary tablet press.

Hence, a more accurate and precise actuation should be installed on all further Presster models to avoid any inconsistency between set and achieved speed of the turret and therefore to simplify the operation of the Presster and to further reduce the amount of material required to match the tableting conditions to be simulated.

4.7 General Aspects

Beside the investigation of the various measurement systems of the Presster, some uninstrumented machine parts and process steps, some of which also having an influence on tablet properties, have been investigated with respect to the most accurate simulation of a Fette P1200 rotary tablet press.

4.7.1 Vertical Adjustment of Compaction Rollers

To change the applied compaction force the vertical position of the lower compaction rollers in relation to the upper compaction rollers is adjusted by computer control.

While the adjustment of the vertical position of the lower pre-compaction roller has been achieved with retention of the vertical alignment of the upper and lower pre-compression rollers, the situation was found to be different for the main compaction station.

The vertical adjustment of the lower main compaction roller takes place according to the method which is still found on older rotary tablet presses, like e.g. Kilian T100 (Kilian, Germany).

Instead of changing the vertical position of the lower main compaction roller on a linear vertical path, as found on for example Fette presses, an eccentric vertical adjustment system has been installed on the Presster.

The vertical alignment of the upper and lower main compaction rollers has been given at a set position of the lower main compaction roller resulting in a distance of the tip of the punches without any applied load (resembling the theoretical band width of the tablet) of about 4.1 mm.

A vertical misalignment of the main compaction rollers appears and increases up to the maximum of 0.75 mm, as soon as the distance between the tips of the punches is either increased up to the maximum of 8.1 mm or decreasing towards its minimum of 0 mm.

This misalignment shifts the lower main compaction roller rightwards and therefore the moment when the lower punch gets into contact with its compaction roller was found to be delayed.

Therefore irregularities known from older Kilian presses have been present on the Presster as well. The most important impact is on standard calculations regarding the dwell time, as they are, dependent on the extent of misalignment, more or less inaccurate.

Based on the definition of the dwell time as the time over which the flat portion of both punch heads has contact with the compaction rollers, the misalignment finally equals a shortening of the dimension of the flat portion of the punch head as obvious from Fig. 4-56.

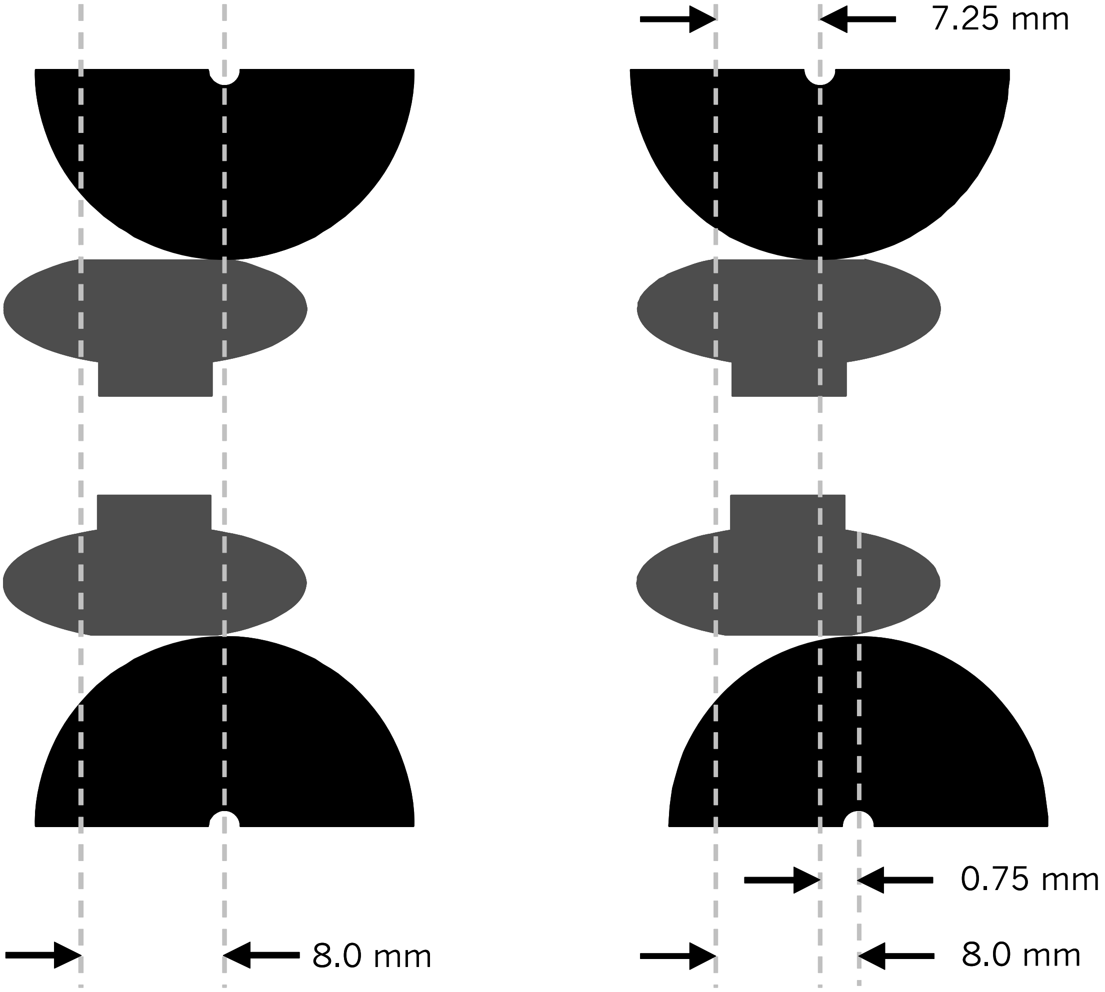


Fig. 4-56 Abridgement of the dwell time due to misalignment of main compaction rollers

Based on the dwell time calculations using a set of punches with a flat portion of the punch head of e.g. 8 mm and a theoretical dwell time of

10 ms, the finally resulting dwell time would be abridged to 9.06 ms (-9.4 %). A similar effect on the dwell time might be observed by a change of the machine speed from 61.1 RPM to 67.5 RPM.

Adaptations in the speed settings of the Presster, which might result in matching dwell times, are finally inappropriate to solve this shortcoming, as the densification speeds and therefore both compressibility and compactibility profiles would be affected as well.

4.7.2 Vertical Punch Movements Unrelated to Any Compaction Event

Beside the simulation of applied forces, the Presster has been designed to mimic vertical punch movements of rotary tablet presses as close as possible.

The path profiles of the punches on the Presster should match exactly the conditions of rotary tablet presses, guaranteed first by the use of punch cams and secondly by compaction rollers in the same dimensions as those of the rotary tablet presses to be simulated.

A closer investigation of vertical punch movements showed some major differences between the Presster and rotary tablet presses, not only affecting tablet properties and the quality and reliability of measurements, but also the condition of machine parts, especially the condition of punches.

In order to avoid any vertical punch movement not related to the compaction cycle, the upper and lower punches of the Fette P1200 as well as of other rotary tablet presses are guided closely. Furthermore, holding ledges keep the punches in contact with the compact, in particular in between the pre- and main compaction station.

The situation on the Presster has been somewhat different, as holding ledges have been missing. Furthermore, the punch cams present on the Presster have been found to be inappropriate by design to sufficiently control the action of the punches.

Only the vertical movements of the lower punch have been restricted by an attached punch break. This break has been designed as a plastic pin which has been pushed against the punch barrel's surface by a screw.

The effectiveness of the break depends on the tightening torque of the screw. This way of limitation of the vertical punch movements of the lower punch was working satisfactorily for the whole compaction process.

However, as the vertical movements of the upper punch have not been restricted, it has been found to simply sit on top of the compact due to its own mass.

Therefore, accidental upper punch movements, caused by e.g. machine vibrations, have been observed.

Hence, in combination with the redesigned carriage, which has been already described in chapter 4.5.5, punch breaks, similar in design to the original one, have been installed for both the upper and lower punch, to ensure that both punches stay in contact with the powder bed during the compaction cycle and therefore to improve the reliability of punch displacement measurements.

The tightening torque of the screws, with which the punch brake has been pushed against the punch barrel's surface has been standardised by tightening the screws to a predefined position. Therefore, user-dependant influences of the punch break with respect to compaction or ejection forces have been foreclosed.

The influences of these breaks on compaction and ejection force measurements have been eliminated by taking these effects into consideration during the calibration of the affected measurement systems.

Furthermore, the missing restrictions for the vertical movement of the upper punch caused some additional friction to the powder column inside the die.

As the lower punch gets into contact with its main compaction roller prior to the upper punch, both the powder inside the die as well as the upper punch have been lifted by the upwards moving lower punch.

In rare cases of either rather large settings for the depth of fill, e.g. due to a small bulk density of the powder, or as a result of rather small compaction zones, the upper punch has been lifted even above the top level of the die, only snatches before the position of the upper punch has been lowered due to its in the meantime obtained contact with the upper main compaction roller.

This situation has been most distinctive when no pre-compaction has been applied and therefore the lower punch has been still positioned at the depth of fill, hence getting into contact with its main compaction roller quite early.

As a result, powder spilled out of the die and thus the resulting tablets did not match the weight specifications.

Even if the upper punch has not been totally pushed out of the die, the additional frictional work applied to the (pre-compacted) powder bed, might have some influence on the properties of the final compact, especially in case of some very sensitive tablet formulations, provoking some significant and vital differences between simulation and reality.

Also working with tapered dies, the compaction zone might be shifted into the tapered region of the die, which might yield to varying tablet properties.

These shortcomings should be avoided by either working at a deeper compaction zone or by simply installing holding ledges between the pre- and main compaction station, impeding the upper punch to be lifted far above the top level of the compaction zone.

4.7.3 Lag Time between Pre- and Main Compaction Station

Beside the need for consistent punch movements between Presster and simulated rotary tablet presses during the time period between pre- and main compaction station, the duration of this period at a certain horizontal speed has to be kept in mind. To simulate rotary tablet presses as close as possible, this lag time between both compaction stations should be adopted to the conditions present on the particular rotary tablet press to be simulated. As the positions of the pre- and main compaction station of the Presster have been fixed with respect to each other at a distance of about 0.56 m, an adaptation of the lag time to the conditions of any particular rotary tablet press, about 0.31 m for the Fette P1200, has not been possible.

Therefore, variations in the time available for some intermediate elastic recovery, which might take place between pre- and main compaction event, might be responsible for slight differences in the properties of compacts produced on both the Presster and the Fette P1200.

4.7.4 Die Feeding Process

Regarding the die feeding process of the Presster, the main difference obvious to the system of rotary tablet presses has been the gravity feeding unit compared to enforced feeding systems of rotary tablet presses.

The design of the feeder of the Presster has been closer to the ones of eccentric presses than to those of rotary tablet presses.

Even the impeller, present on many gravity feeding systems of eccentric tablet presses to guarantee a more constant die fill and a destruction of powder bridges inside the feeder is missing.

Due to less powder densification by the gravity feeding unit of the Presster in comparison to the enforced feeding system of the Fette P1200, variable larger settings for the depth of fill had to be realised for any material on the Presster, to finally produce tablets having the same final edge height than those produced on the Fette P1200 at comparable pressure level.

The advantage of the pure gravity feeding, applying less stress to the powder was more than offset by some disadvantages which will be described as follows.

The feeder, connected to the carriage, has been designed to wipe several times over the die right at the beginning of each compaction cycle. After the die feeding has been finished, the feeder has been positioned at one side of the die table in order not to interfere with the upper punch during the compaction event. But, in contrast to any rotary tablet press, where the feeder has been fixed at a certain position on the press, the feeder of the Presster, as it has been fixed to the carriage, had to follow the carriage during the entire compaction cycle. Therefore, all the machine vibrations have been transferred to the material placed inside the feeder.

As a consequence, with an increasing number of compaction cycles, the bulk density and finally the tablet mass increased, although the machine settings have not been changed. An adaptation of machine settings had to be performed to guarantee comparable tablet properties.

Similar to rotary tablet presses, the lower punch has been pulled down as soon as the feeder covered the die, in order to support the die feeding by some “powder suction” caused by the descending lower punch.

By design, the lower punch of the Presster has always been pulled down to the maximum depth of fill of 17.4 mm, an therefore different to the situation of most rotary tablet presses, where the extent of die overfill has been related to the set depth of fill.

As the lower punch passed the dosing cam a varying part of the material previously fed into the die had to be pushed back into the feeder, depending on the set depth of fill.

For some materials and extents of die overfill, the volume of powder, which had to be pushed back has been just too large. The feeder has not been able to handle this volume. As a consequence the feeder has been lifted by the pushed back material. This caused a gap between the feeder and the die table, by which powder spilled out onto the die table.

This malfunction has rarely been observed on rotary tablet presses, for example if the number of revolutions of the feed shoe impellers has been set too high in comparison to the speed of the turret.

Furthermore, as the profile of the gravity feeder showed a cross-section reduction in combination with a just too small inner diameter (Fig. 5-7-2), the feeder has not been working properly for materials showing poor flowability, e.g. native starch qualities. The oscillating movement of the feeder over the die might have been designed to prevent this feeding problems but showed only small effect.

Moreover, as the original feeder has been made out of plastic it has been observed that fine or even micronised ingredients tended to stick to the walls of the feeder causing a segregation of blends.

A modified feeder (Fig. 4-57) made of bronze, providing a uniform cross-section over its entire length, ensured a more reliable die feeding than the original one.

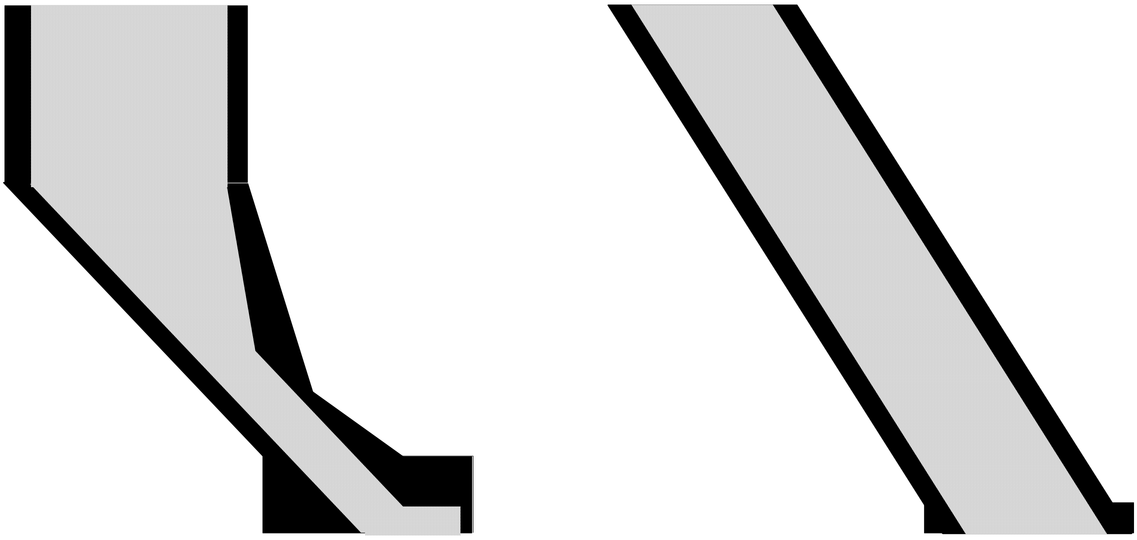


Fig. 4-57 Schematical side view of the original feeder of the Presster (left) and a modified version (right)

Over and above that, the acceleration of the carriage at the beginning of each compaction cycle, in order to speed up the carriage to the previously set speed to be simulated, has been taken place prior to the sealing of the die bore by the upper punch.

Therefore, due to the inertia of its mass, powder has been discharged out of the unclosed die (Fig. 4-58). This shortcoming of powder loss has been supported by the fact, that, in contrast to current rotary tablet presses, the position of the lower punch has not been slightly lowered after the die feeding process.

Hence, additional powder has been spilled out of the die as soon as the upper punch touched the powder at the top level of the die.

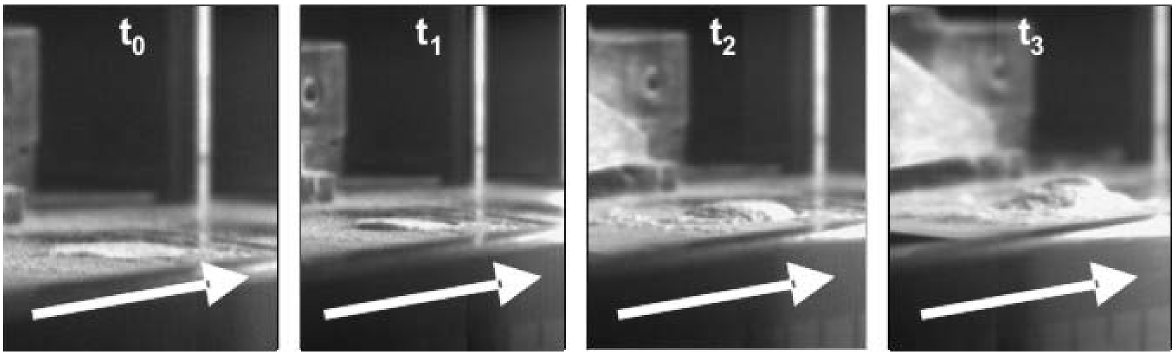


Fig. 4-58 High speed images of powder discharge out of the unsealed die during carriage acceleration at time t_0-t_3 (the arrow indicates the direction of movement of the carriage).

As the amount of powder discharge has been found to be dependent on the extent of acceleration of the carriage, the weight of tablets made at a certain depth of fill abated with increasing speed of the carriage (Fig. 4-59).

Due to limited availability of material during early stages of development, this discharge is unacceptable. Therefore, by revision of first the upper punch push-down cam the upper punch is now lowered sooner. Second, by modification of the lower punch cam and the feeding cam the lower punch has been additionally descended after the die feeding, according to the principle of rotary tablet presses, and thus preventing any powder being blown out of the die as the upper punch enters the die bore.

Hence, the powder filled die has been sealed by the upper punch prior to the acceleration of the carriage. Hereby the discharge of powder has been eliminated totally (Fig. 4-59), thus preventing variations in tablet weight by changes in the carriage speed.

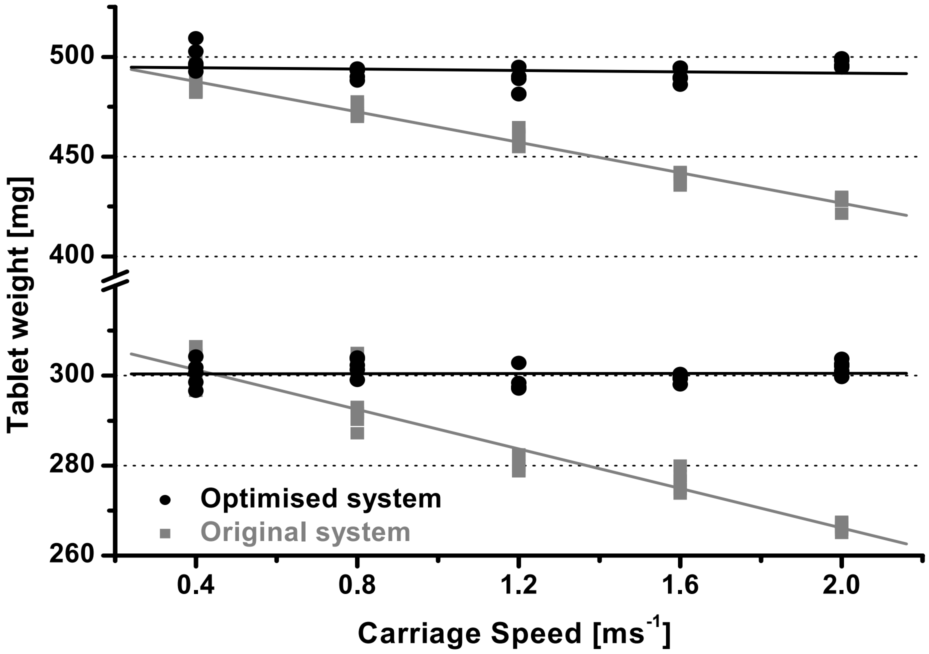


Fig. 4-59 Comparison of discharged powder out of the die during carriage acceleration between the original and the optimised system

The immersion of the upper punch at comparably low horizontal speed values of the carriage has been a beneficial side-effect of the modification of the earlier lowering upper punch. Therefore, the upper punch entered the die more easily, which prolongs the punches working life.

Unfortunately, the change of the upper punch cam led to an interaction between the upper punch and the feeder, impeding any further use of the die feeding system.

Nevertheless, during early stages of development the prevention of powder loss predominates the loss of the functionality of the die feeding system.

Thus, balanced quantities of material, required for one tablet, have been henceforth transferred manually into the die prior to each compaction cycle.

4.7.5 Centrifugal and Inertial Forces

Centrifugal forces are especially present on rotary tablet presses working at high speed conditions. The Comprima (IMA, Italy) rotary tablet press even feeds its dies using centrifugal forces.

Initially, the powder inside the die is filled in quite loosely and therefore might to tend to move towards the outer wall of the die.

Therefore, in some special cases, the height of the powder bed inside the die might not be uniform over the diameter of the die. In relation to the die wall next to the centre of the turret it might be somewhat higher at the die wall furthermost to the centre of the turret.

The powder inside die of the Presster shows similar behaviour. But, as the carriage of the Presster works on a straight line instead on a circle path the powder moves not to the die wall comparable to the furthermost to the centre of the turret on rotary tablet presses, but rather moves in the opposite direction compared to the moving direction of the die itself as a consequence of inertial forces. This of course is the reason for the powder discharge out of the unclosed die mentioned in chapter 4.7.4.

With respect to the instant when the dies on both machines passes the compaction rollers the following situations, shown in Fig. 4-60, might be distinguished.

It is obvious from Fig. 4-60, that the influence of oblique powder beds on tablet properties, present on rotary tablet presses working at high speed conditions, can not be simulated exactly by the Presster due to their slightly different working conditions.

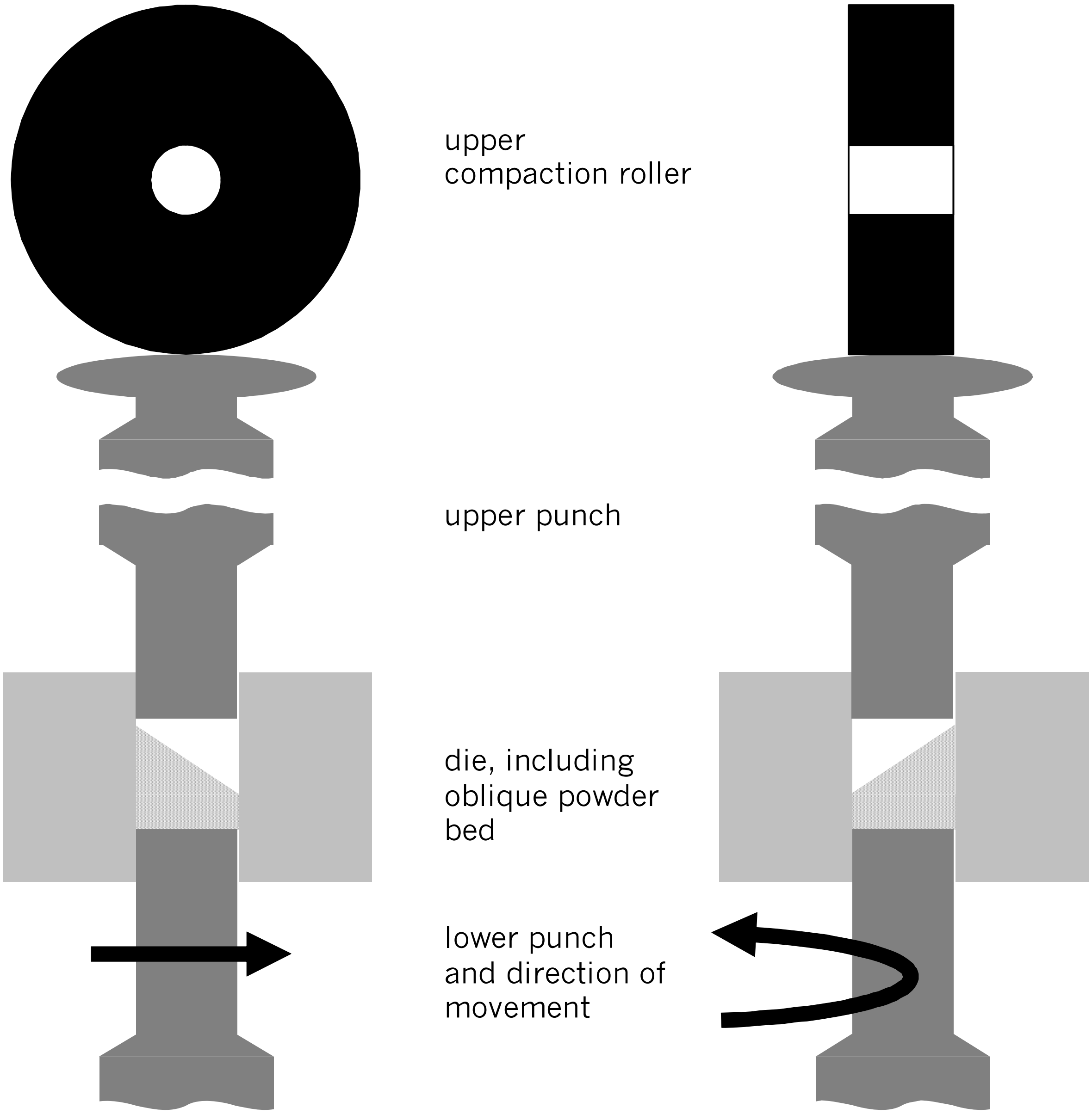


Fig. 4-60 Oblique powder bed on the Presster (left) compared to the situation on rotary tablet presses (right)

The effect of these oblique powder beds on tablet properties, if present at all, might be observable by compacting powders at high speed conditions, which deform mainly by brittle fragmentation.

Powders deforming mainly plastically have not been used for this investigation, as the flow of these materials under pressure have been expected to harmonise the powder distribution inside the die.

Finally 10 mm round, flat faced tablets of Emcompress, target weight 500 ± 5 mg, have been produced at different main compaction pressure levels and horizontal speed settings of the carriage, while no pre-compaction pressure has been applied.

External lubrication of the punches and die, using magnesium stearate, has been applied to avoid any internal lubrication. The orientation of the tablet inside the die during the compaction event has been determined, as a marker, attached to the lower punch prior to each compaction cycle, has been transferred to the tablet during compaction.

After a storage time of 1 day at room conditions, the hardness distribution over the diameter of the tablets has been investigated using a tablet drill. Differences in the hardness distribution over the diameter of the tablet might refer to variations in the density distribution, caused by oblique powder beds. The method in general has been described in detail by Busies (2006).

The hardness of each tablet has been determined at three equidistant points on a straight line, passing the centre of the tablet (Fig. 4-61).

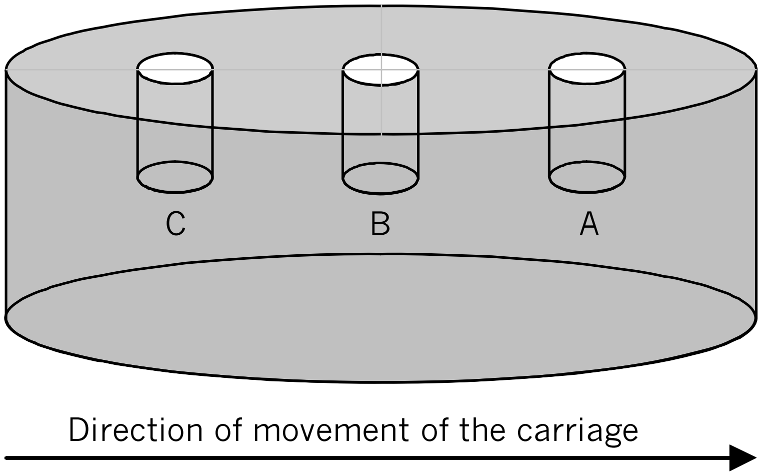


Fig. 4-61 Tablet including drilling holes A, B and C of the investigation of the hardness distribution over the tablets diameter

A flat end cutting drill, having a diameter of 1 mm, has been operated at 500 RPM to drill the compact from the upper plane up to half way of its edge height at a constant feeding motion of 1 mmmin^{-1}.

As no change in the hardness distribution over the diameter of the investigated tablets has been detected (Tab. 4-15), the influence of the oblique powder bed might be just visible for some most challenging formulations and machine settings.

Tab. 4-15 Hardness distribution in terms of drilling force of Emcompress tablets including SD values (italics); (n=10)

Simulated Speed of the Turret [RPM]	**Compaction Pressure [MPa]**	**Tablet Height [mm]**	**Drilling position on Tablet**	**Drilling Force [N]**
30	**65** *1.28*	**3.58** *0.01*	**A**	**8.79** *1.30*
			B	**8.19** *1.21*
			C	**8.02** *1.39*
	129 *0.88*	**3.32** *0.02*	**A**	**15.49** *1.17*
			B	**15.23** *1.12*
			C	**15.46** *1.09*
90	**65** *1.47*	**3,58** *0.01*	**A**	**7.64** *1.43*
			B	**7.4** *1.14*
			C	**7.58** *1.45*
	130 *0.99*	**3.34** *0.01*	**A**	**15.21** *1.13*
			B	**15.21** *1.17*
			C	**14.78** *1.33*

4.7.6 Tablet Handling after the Take-Off Event

Tablets made by the Presster are taken away from the top of the punch after ejection by the take-off bar. Due to the design of the original take-off bar, which has already been characterised in chapter 4.4.2, tablets had to stay on the die table until the entire die table had passed underneath the take-off bar.

Finally tablets dropped from the die table into a tablet collection box, which has been connected to the rear end of the carriage and therefore followed the carriage movements.

Depending on the horizontal speed of the carriage and the extent of acceleration to achieve the set speed, tablets swirled around inside the tablet collection box during the following compaction cycles (Fig. 4-62).

Hence, all tablets had to get through their first inconsistent post-compaction stress, even before they left the Presster.

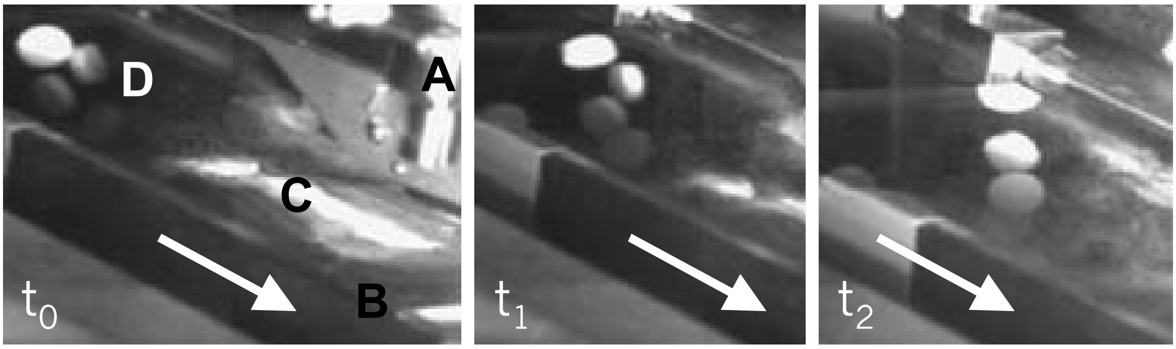


Fig. 4-62 High-speed images of post-compactional stress intake to tablets in tablet collection container of the original version of the Presster at time t_0 – t_2 (A – upper punch; B – die table; C – trace of powder spilled out of unclosed die; D – tablets inside collection container; the arrow indicates the moving direction of the die table)

As this special type of “in-process friability tester” applied the most stress to the first tablet out of a batch while the last stayed almost unaffected, each single tablet has been taken out manually directly after its individual compaction cycle

Of course, this procedure impedes once more the use of the serial mode option of the Presster, but has been necessary to prevent adulteration of compact properties causing misinterpretation.

The installation of the modified take off bar eliminated this problem, as it removed any individual tablet from the die table directly to a small container outside the Presster, like on any rotary tablet press.

4.7.7 Compaction Rollers

Regarding the compaction rollers of the pre- and main compression station of the Presster, a deviation from the ideal round shape up to +/- 55 µm has been observed. Therefore, the precision of these Presster compaction rollers has been more than 10 times greater deviation than found on the Fette P1200 (+/- 5 µm). This shortcoming would not extensively affect tablet properties but will affect the consistency of compaction forces with respect to for example investigations of materials compressibility.

Due to the already discussed large fluctuations in tablet weight due to the gravity die feeding, there has been no given necessity to improve the quality of the roundness of those compaction rollers.

The compaction rollers have rather been adjusted manually to a predefined position to finally minimise influences of the deviation of the rollers on compact properties and the consistency of measurements.

Furthermore, the compression rollers of the Presster don't move until punches actually hit the rollers. Therefore, compared to rotary tablet presses, where the compaction rollers never stop while the machine is running, the stress to and abrasion of both the rollers surface and the punch head is much more extensive on the Presster.

Hereby, especially the integrity of the flat portion of the punch head has been worn out much more extensively compared to punch heads of punches running on rotary tablet presses. Additionally, as the rotation of the punches inside the bushings has been intentionally impeded on the Presster to ensure the alignment of the punch displacement measurement system, the wearing of the punch head takes place in only one spot and is therefore even more pronounced.

As the flat portion of the punch head represents the critical dimension for the calculation of the dwell time it might be recommended to use brand new punches to perform reliable investigations of the influence of dwell time on tablet properties. Due to this evidently higher stress, the compaction rollers and the punches of the Presster have a shortened working life, which might be compensated by the comparably small number of compaction cycles performed by the Presster.

Finally, the punches of the Presster do not get into contact with the centre of the compaction rollers surface, but contact on one side.

4.7.8 Sticking Punches

The consequence of the powder entering the lateral clearance in between the tip of punches, in particular the lower punch, and the die bore are tight moving or even sticking punches.

The force, necessary to move the punches in vertical direction is often measured on rotary tablet presses to avoid any damage to either machine or tooling parts.

As there has been no equivalent instrumentation on the Presster, the information and control of sticking punches has not been directly accessible. As the ejection force might be affected at first by a sticking lower punch, the observation of this signal might be used in place of the missing instrumentation for tight moving punches.

On the other hand, as the ejection forces measured on the Presster might be affected by tight running punches, the unrestricted vertical movement of the lower punch has to be guaranteed with respect to the investigation of ejection force measurements.

4.7.9 Press Chamber Lubrication

In order to minimise the quantity of lubrication required to ensure either a proper lubrication in order to reduce the friction between the compact and tooling during compaction or to minimise the adverse interaction between the lubricant and any other ingredient of a tablet formulation, the press chamber lubrication has been established on rotary tablet presses (Gruber, 1988; Laich, 1997, 1998).

A comparable press chamber lubrication system as e.g. the PKB II system used on Fette rotary tablet presses has not been available for the Presster.

The only way to roughly simulate the press chamber lubrication is to manually apply some dry lubricant on the surface of the tooling using a brush, as it has been performed within this work.

4.7.10 Multilayer and Laminated Tablets

Due to different reasons, as e.g. incompatibility of compounds, modified release options or just unpleasant taste of ingredients, multilayer tablets have been developed more often in recent years.

The production of these special forms of tablets takes place either on special single punch presses as e.g. the pneumo-hydraulic FlexiTab (Roeltgen, Germany) or on multi-station rotary tablet presses.

After the first layer has been only pre-compacted the powder of the second layer is filled into the die on top of the first layer by a second feeder. Followed by an optional second pre-compression event the final main compression event has to take place before the tablet will be ejected.

As there has been only one filling station available on the Presster, the serial and automated production of both multilayer and laminated tablets is not possible. It might only be feasible by the manual preparation of the final tablet layers inside the die prior to the compaction cycle.

Therefore, the production of both multilayer and laminated tablets using the Presster, simulating a rotary tablet press, might be restricted to a rather small number of tablets.

4.7.11 Special Aspects of the Presster

In contrast to any rotary tablet press, the punches of the Presster have to pass also anti-cyclical through all the various compaction cycle related stations on their way back to the start position for the subsequent compaction cycle.

Due to the lack of a pull down cam for the way back to the start position and the manually tightened punch break of the lower punch, present on both the original and the modified carriage of the Presster, the position of the lower punch has not been lowered on its way back to the start position after passing the ejection cam.

Therefore, its tip has been still positioned on the same plane as the top level of the die, when the punches came across the compaction rollers. However, as the upper punch has been pushed down by a cam just before getting into contact with its compaction roller, the upper punch tip went foul of the lower punch ones.

This has been of minor importance for the quality of punch tips of flat faced punches, but provoked the damage of any convex-faced or facetted punch tip.

Therefore the punch break of the lower punch had to be loosened manually prior to any run of the carriage back to the start position of the Presster, in order to allow the lower punch to fall inside the punch bushing by its own weight and finally to follow the path profile of the ejection cam.

This finally prevented the use of the serial mode of the Presster, by which a certain predefined number of compacts would have been produced in several sequent compaction cycles.

4.7.12 Summary

Various general aspects of the Presster have been investigated with respect to the simulation efficacy of rotary tablet presses, in particular a Fette P1200.

The eccentric system of the Presster, used to adjust the vertical position of the lower main compaction roller and consecutively apply the compaction pressure level, resulted in a variable vertical misalignment of the main compaction rollers.

The misalignment of main compactions rollers finally shortens the effective dwell time, similar to an increased machine speed of the simulated rotary tablet press.

A comparison of compactability and compressibility data has therefore to be carried out carefully, in case of dwell time sensitive materials, even while working at ostensible equal conditions.

In comparison, on the Fette P1200 dwell time conditions did not change by any adaptation of the compaction pressure level, as the vertical position of compaction rollers has been adjusted under retention of their vertical alignment.

A further effect on the validity of dwell time calculations has been found by the abrasion of punch heads, which has been observed to be much more distinctive on the Presster compared to rotary tablet presses, due to the collision between the punch head and compaction rollers being static prior to contact.

Vertical punch movements, not related to any compaction event, have been observed in particular for the upper punch and the time in between the pre- and main compaction station.

To ensure both punches to stay in contact with the compact over the entire compaction cycle, an additional punch break for the upper punch has been installed on the revised carriage.

Nevertheless, punch cams present on the Presster did not restrict the vertical liberty of action of the upper punch sufficiently, as holding ledges have been missing. Therefore, in case of rather large settings for the depth off fill (pre-compressed) powder inside the die as well as the upper punch have been lifted as soon as the lower punch got into contact with its compaction roller.

Dependant on the set compaction zone and the edge height of the powder column inside the die immediately before the main compaction event, the upper punch has been lifted upwards, provoking additional friction, shifted compaction zones and occasionally powder loss from the die.

Above that, an adaptation of the horizontal distance between the pre- and main compaction station, to most accurately match the conditions of the simulated Fette P1200 rotary tablet press, has not been possible, as the distance between both stations of the Presster has been fixed by design.

The gravity feeding unit of the Presster has been found to work satisfactorily only for quite well flowing materials. Beyond that, it represents one of the most distinctive differences compared to the force feeding systems of rotary tablet presses.

The consecutive differences in stress intake and the die feeding process impeded the simulation of the influence of the feeder on tablet properties.

The importance of taking this aspect into consideration for any tablet formulation development has been shown by Jahn (2005).

Of course, the simulation of some special designs of rotary tablet presses, including their unique die feeding process using centrifugal forces, as seen on the Comprima (IMA, Italy), will not be possible at all.

Furthermore, dependant on the set horizontal speed of the carriage, powder loss from the unclosed die bore has been observed during the acceleration of the carriage, resulting in speed dependent deviations between the specified and the obtained tablet weight.

Modifications of both the upper and lower punch cam finally eliminated this shortcoming, ensuring a consistent compact weight at a particular machine setting, independent of the extent of acceleration necessary to achieve the set speed of the carriage.

Unfortunately, due to spatial interactions between the upper punch and the feeder, the modifications impeded any further application of the gravity feeding unit of the Presster.

Although, being able to use all the disposable material for investigation purposes takes priority over the imperative necessity of manual die feeing.

Oblique powder beds have been observed inside the die prior to the compaction event as a consequence of the inertia of the powder mass during the acceleration of the carriage. However, a homogenous hardness distribution, referring to a consistent density distribution has been found over the diameter of Emcompress tablets.

The possible impact of oblique powder beds on compact properties as, for example, the density distribution of tablets, must be considered.

On the original version of the Presster, tablets have been collected in a small container attached to the carriage, where they stayed until the end of a particular batch. Due to unrestricted tablet movement inside the container the tablets were subject to unplanned stress.

By modifications of the take-off bar, a consistent removal of tablets out of the Presster, similar to the system of rotary tablet presses, has been ensured.

The roundness of the compaction rollers of the Presster have been found to be less accurate compared to the ones of the Fette P1200. Manual adjustment of the compaction rollers has been carried out to avoid any impact on compact properties and to ensure consistency of measurements.

Non-continuously rotating compaction rollers exacerbates the wear of both the rollers and the punch heads, the latter affects the reliability of investigations based on dwell time calculations.

A dedicated measurement system for the observation of tight moving or even sticking punches, as present on some rotary tablet presses, was not present on the Presster.
Unrestricted vertical movement of especially the lower punch has to be guaranteed in particular to avoid any interference of sticking punches with the investigation of ejection force measurements.
Therefore, the ejection force measurement system might be used as an alternative system to monitor the unrestricted vertical movement of the lower punch.
An equivalent press chamber lubrication system as e.g. the PKB II of the Fette P1200 was not available for the Presster. Lubricating material had to be applied manually to the punches and the die using a brush to simulate these systems and therefore avoiding internal lubrication, which could affect the reliability of compressibility investigations.

The automated production of both multilayer and laminated tablets is not possible using the Presster, as options for repeated and variable die feeding are not present.
The manual preparation of both types of compacts might be possible, but heavily manual and ensuring uniformity would be a challenge.
Therefore, the specification of the Presster, being able to simulate all rotary tablet presses, should be further specified to the simulation of single station rotary tablet presses only.

As the Presster works on a straight line in comparison to the circular path of rotary tablet presses, the carriage including the punches had to pass all the various compaction cycle related stations also in anti-cyclical direction. Due to missing punch cams, the punch break of the lower punch had to be loosened manually prior to any movement of the carriage back to the starting position of the compaction cycle, in order to avoid punch tip deflection of non flat punches.

Therefore, the serial mode of the Presster has been deactivated.

5 Summary and Conclusions

The present work first dealt with investigations of the linear compaction simulator Presster, in particular with respect to its data acquisition system, the various force and displacement measurement systems as well as of general aspects, which might have an influence on compact properties.

Secondly, in order to have an easy to use and powerful tool for reliable and convincing investigations of powder compaction behaviour under the conditions of a Fette P1200 rotary tablet press, feasible optimisations have been realised where necessary.

Finally, the predominant quality and reliability of measurements obtained by the various improved systems have been furnished evidence during exemplary investigations.

The machine speed dependant maximum sample rate of about 7.4 kHz, observed for the original data acquisition system of the Presster, has been found to be too low to reliably monitor high frequency signals, for example take-off forces.

Furthermore, due to their specified cut-off frequency the amplifiers used within the original measurement systems of the Presster, as well as those implemented to provide all signals electrically isolated to an independent external data acquisition system, proved to be appropriate to process only rather low frequency compaction force signals without any signal distortion or phase shift.

In addition to the replacement of amplifiers in connection with the revision of entire measurement systems, the Presster independent data acquisition system DAQ4, providing a user selectable sample rate up to 1.25 MHz superseded the original one.

Investigations of the compaction force measurement systems of the Presster have been performed by simulating a Fette P1200 rotary tablet press.

Differences in the obtained compactibility profiles have been revealed over the entire range of compaction pressures and speed settings, while both machines have been operated at comparable conditions.

Dynamic recalibrations of all the compaction force measurement systems of both the Presster and the Fette P1200 revealed wrong calibrated compression force measurement systems of the Presster only.

After recalibration, compactibility profiles of the blends of Emcompress and Flowlac 100 matched for the two machines, while the ones of Neosorb P60W still showed some inconsistency, in particular at compaction pressure levels larger than 175 MPa.

As the profiles of Emcompress and Flowlac 100 matched even at high pressure levels, a general rejection of compaction data, obtained at high pressure settings, has not been indicated. Data obtained at compaction pressures larger than 175 MPa as well as compacts, having a tensile strength larger than 6 Nmm^{-2}, have to be handled carefully, while the latter might be found quite seldom during normal situations.

Remaining deviations in the compactibility profiles are ascribed to inaccessible and therefore unadjustable general variations in the compaction process of the two machines.

A rather small Eigen-frequency of the ejection force measurement system, in combination with the impact of machine and process vibrations on its base line noise level and signal integrity, initially impeded accurate investigations of ejection force signals.

Therefore, the original ejection force measurement system of the Presster was found to be unsuitable for reliable investigations of the ejection behaviour and forces of pharmaceutical excipients or blends.

Hence, a revised ejection force measurement system has been designed and installed on the Presster. Providing a higher Eigen-frequency and less vibration sensitivity, the reliable monitoring of ejection force signals has been improved.

As a result of both increased data acquisition rate and higher cut-off

frequency of the entire system, impact signals have been found to temporary superimpose the ejection force signals, in particular present while running the Presster at high speed conditions.
Unchangeable constructive limitations of the range of the ejection angle impeded a most accurate simulation of the ejection process of the simulated Fette P1200.
Nevertheless, effective ejection forces have finally been reliably determinable by adequate approximation, clearly demonstrating the improved quality of the revised ejection force measurement system.

Due to its design and its too small Eigen-frequency, the original take-off force measurement system of the Presster turned out to be inapplicable with respect to accurate and reliable investigations of take-off forces.
The previously mentioned too low sample rate of the original data acquisition system, in combination with the too low cut-off frequency of the amplifiers, the measurement was of the absorbed oscillation of the system itself and not of the take-off event.
Therefore, a redesigned take-off force measurement system has been installed on the Presster.
The revised system provided a sufficient Eigen-frequency and has been proved to monitor take-off forces accurately and reliably, even at high speed conditions. Hence, discriminations between the adhesive and the momentum induced part of the total take-off force have been possible. Therefore, the redesigned system has been applicable to investigate the effect of e.g. varying lubrication levels and extents of humidity on the sticking tendencies of formulations.

Punch displacement measurements, performed by the original system of the Presster, contained comparably large noise levels. These were a result of the unguided cores of the displacement transducers as well as machine vibrations and tilting punches. Tilting of punches was not measurable due to the presence of only one displacement transducer per punch. Neither machine nor punch deformations were taken into account by the original system.

Therefore, accurate and reliable punch displacement measurements, with respect to the investigations of powder compression behaviour in terms of compaction pressure vs. in-die tablet height plots, compressibility plots or even Heckel-plots, were not possible using the original punch displacement measurement system of the Presster.

Hence, a new punch displacement measurement system has been designed and installed within a redesigned carriage. By the use of two vibration resistant displacement transducers per punch, the investigation of punch tilting became possible. The absolute punch tilting under pressure observed for the new system for both tilting axes A and B did finally not exceed 4.4 µm, indicating the improved conditions of the revised system.

The deformation of punches, calculated according to Hook´s law, has been taken into account for the new system, while the deformation of the machine itself became negligible, as the new displacement transducers have been mounted directly onto the punches, while their reference position has been the well defined top level of the die.

Compaction pressure vs. in-die tablet height plots as well as Heckel-plots of various excipients, obtained by the new punch displacement measurement system at various speed settings, further demonstrated the improved quality of the redesigned system.

Reliable discriminations between deformation characteristics of various excipients have been feasible within the investigated speed range.

Even while the quality of measurements obtained by the improved punch displacement measurement system of the modified Presster has been proved to enable relevant investigations of powder compression behaviour with sufficient accuracy and reliability, further improvements of the punch displacement measurement, in particular its displacement transducers, would be recommended.

Furthermore, beside the investigation of the various measurement systems of the Presster, general process aspects have been examined with respect to the simulation efficacy of rotary tablet presses, in particular a Fette P1200.

The eccentric system for the adjustment of the vertical position of the lower main compaction roller has been found to cause a vertical misalignment of the main compaction rollers.

Therefore, the validity of dwell time calculations, which has already been impaired due to excessive abrasion of the flat portion of the punch heads, has been additionally affected.

Vertical punch movements in between the pre- and main compaction station, caused by less accurate punch guidances, resulted in additional friction between the material and the die, shifted compaction zones and rarely powder loss out of the die.

Due to a fixed horizontal distance between the pre-and main compaction stations of the Presster, a most accurate adaptation to the conditions of the simulated rotary tablet press has not been possible.

The gravity feeding unit of the Presster was redesigned. Unfortunately, the simulation of any influence of the die feeding process on compact properties was found to be impossible using the Presster.

Speed dependant powder loss has been observed out of the unclosed die prior to the pre-compaction station, resulting in major compact weight variations. Modifications of punch cams finally stopped further powder loss and ensured a constant compact weight, independent of the set speed of the carriage, but impeded any further use of the gravity feeding unit due to spatial interactions.

Oblique powder beds observed on the Presster did not show any distinctive effect on the uniformity of the compact hardness distribution.

Variable stress to tablets collected in a small container, attached to the carriage, has been eliminated in progress of the modifications of the take-off bar.

The roundness of compaction rollers has been found to be less accurate compared to ones of the Fette P1200. Manual positioning of the rollers prevented any effect on the consistency of measurements.

Systems for the observation of tight moving punches as well as for an automatic press chamber lubrication have not been available for the Presster, while the manual application of lubricant material to the die and punches has been used.

The automated production of both multilayer and laminated tablets has not been possible using the Presster, as options for repeated and variable die feeding as well as options for partial compaction cycles are missing.

Anti-cyclical passages of all the compaction cycle related stations finally applied some additional stress and wear to the system, in particular to the punches, impeding any further use of the Presster in serial mode.

Finally, the numerous modifications implemented on the Presster, as a consequence of the results of the entirety of investigations of the original version of the Presster, improved the quality and reliability of measurements taken.

Even while some differences within the compaction process of the Presster and the simulated Fette P1200 were not possible to harmonise, the improved accuracy and reliability of measurements, performed by the modified version of the Presster, allows the investigation of powder compaction and compression behaviour already during very early stages of development.

Therefore, this modified Presster has been proved to be applicable as a valuable tool, going to be used for research and development as well as for trouble-shooting purposes.

6 Materials and Methods

6.1 Presster

Presster; Model PR2002; s/n: 107
Metropolitan Computing Corporation (MCC), New Jersey, USA

6.2 Fette P1200

Fette P1200; s/n: 391
Fette GmbH, Schwarzenbek, Germany

The Fette P1200 rotary tablet press, placed at the University of Bonn, has been fully equipped with 24 sets of punches and dies.

Force measurements on the Fette P1200 have been carried out by standard load cell instrumented mountings of the lower pre- and main compression rollers.

A 9R15 Euro B tooling has been used during investigations of the compactibility of excipients, while die feeding has been performed using the standard Fil-O-Matic feeder.

In contrast, ejection force measurements performed on the Fette P1200 have been carried out using only one pair of 10 mm round, flat faced punches, while the Fette P1200 has been operated in a special galenic mode.

Hereby, the machine stopped automatically after one rotation of the turret, in order to impede any punch damage. This operation mode has been selected to prevent multiple ejection force signals as a result of more than one punch being in contact with the ejection cam simultaneously. Die feeding has been performed manually for this investigation.

6.3 Multicheck Turbo III

Multickeck Turbo III; s/n: 1113326.0518
Erweka, Heusenstamm, Germany

The Multicheck Turbo III is a tablet testing tool used to automatically analyse tablets weight, diameter, height and crushing force.

6.4 Data Acquisition System DAQ4

DAQ4; Version 1.5 rev. 644
Hucke Software, Solingen, Germany

DAQ4 has been designed on a LabView (National Instruments, USA) basis. High-speed multifunction data acquisition boards (NI 6254 and NI 6250, National Instruments, USA) providing a sample rate of up to 1.25 MSs^{-1} and a 16 bit resolution have been used to monitor the various signals.
Exclusively screened cables have been used in between sensors and amplifiers as well as to fed the amplified signals to the DAQ4 system, in order to minimise the impact of external drop ins to the signal quality.

6.5 High Speed Imaging System

Hisis 2002; s/n 2145
KSV Instruments Ltd., Finland

The high speed imaging system has been used in combination with several lenses and the HISIS 2000 software package to monitor particulars of the compaction cycle process, recorded at 2000 frames per second.

6.6 DigiPunch

DigiPunch; s/n: prototype
Pharmaceutical Science Technology (PST), Rheinbach, Germany

The instrumented punch DigiPunch has been developed to measure compression forces on tablet presses as close as possible at their point of origin, particularly inside the die.

A standard EU19 punch has been instrumented at its tapered punch stem by the application of two strain gauges, each working as an active Wheatstone bridge.

The resonance frequency of the electronic module of the DigiPunch, implemented to the hollowed punch barrel, has been about 10 kHz (-3dB).

Therefore, due to the low mass in between its tip and the instrumented punch stem, the frequency response of the entire force measurement system of the DigiPunch has been adequate for force calibration purposes on any type and size of tablet press.

The internal electronic module monitored compression force signals measured by the strain gauges at a pre-selected sample rate of 50 kHz.

As no cable is necessary to connect the DigiPunch with any external amplifier, its running time is restricted by the lifetime of its battery only.

Compression force data, monitored by the DigiPunch, have been afterwards transferred to a standard PC, where they have been compared with those measured and monitored by the compression force measurement systems of the Presster and the DAQ4 system respectively.

A 9 mm flat faced EU19 version of the DigiPunch has been used to review the calibration functions of both pre- and main compression force measurement systems of both the Presster and the Fette P1200 and finally to recalibrate the ones of the Presster dynamically at 30 RPM.

6.7 Pharmaceutical Excipients

The selection of pharmaceutical excipients used in this work went by to cover the following aspects:

· universally used materials for direct compaction purposes
· varying powder compressibility and compactabilty profiles
· well-known powder compaction behaviour during tableting

6.7.1 Lactose

Lactose is probably the most widely used diluent in tablet formulation. Amongst its modifications, α-lactose monohydrate is the most commonly used. Different qualities of α-lactose monohydrate are produced by either sieving, milling, agglomeration or spray-drying. Depending on the production process the portion of amorphous lactose varies, being up to 15 % in spray-dried qualities. Compared to other lactose grades, spray dried α-lactose monohydrate exhibits a higher rate of plastic deformation and a better compactability (Bolhuis, 1996), mainly attributed to its non-crystalline portion. The crystalline portion of the α-lactose monohydrate accounts for the compressibility while the amorphous parts are responsible for its compactability. Spraying lactose suspensions, the amorphous lactose covers the lactose crystals, which are sticking together inside the sprayed droplets. This results in more or less spherical particles showing good flowability. As the amorphous part of spray-dried α-lactose monohydrate crystallises out in time, it is responsible for a known storage instability. Long storage periods of spray dried α-lactose monohydrate may therefore lead to decreasing tensile strength values. Flowlac 100 was especially designed for direct compression purposes. It shows an angle of repose of 28° (Meggle, 2000), unifying excellent flow properties with a quite good compactability.

6.7.1.1 Flowlac 100

Spray dried α-lactose-monohydrate; LOT: L0307 A 4921
Meggle, Wasserburg, Germany

6.7.2 Dibasic calcium phosphate

Derivatives of calcium phosphate, especially dibasic calcium phosphates, are widely used in pharmaceutical applications. This is on the one hand due to its cost and therefore helps to keep down the expenses for new tablet development, but on the other hand mainly due to its product characteristics as to enhance the flowability of blends or simply its functionality as a tablet filler-binder in direct compression (Schmidt, 1993). Di-Cafos consists of small primary particles (crystals) of calcium phosphate. As all the different types of calcium phosphates available at the market also Di-Cafos deforms extensively by brittle fragmentation (Bolhuis, 1996) at relatively low and intermediate compaction pressures (Duberg, 1986). The fracture creates a large number of clean, lubricant-free surfaces. Therefore, lubricants, such as magnesium stearate, have practically no effect on the binding properties of dicalcium phosphate dihydrates. Additionally, these new surfaces show clear bindings sites to produce new interactions, such as van-der-Waals forces.

As previously mentioned for Di-Cafos, also Emcompress deforms mainly by brittle fragmentation. The plastic deformation of Emcompress at higher pressures (Duberg, 1986) accounts for the time difference between the maximum load and the minimum porosity.

6.7.2.1 Di-Cafos

Dibasic calcium phosphate dihydrate; LOT: A15439A
Chemische Werke Budenheim, Budenheim, Germany

6.7.2.2 Emcompress

Dibasic calcium phosphate dihydrate; LOT: C27LX
JRS Pharma, Rosenberg, Germany

6.7.3 Microcrystalline Cellulose

While powdered cellulose is used just as a tablet diluent, microcrystalline cellulose offers properties of a binder as well. It is therefore used in both wet granulation and direct compression blends. Several grades of microcrystalline cellulose are commercially available, which differ in their physical properties, for example, their particle size, flowability or moisture. The larger particle-size grades provide better flowability while the higher density grades improve flowability and weight uniformity (Rowe, 2006). The quality used in this work provides a mean particle size of about 90µm and is frequently used for direct compression.

6.7.3.1 Vivapur 102

Microcrystalline Cellulose; LOT: 5610230605
JRS Pharma, Rosenberg, Germany

6.7.4 Pregelatinised Starch

Pregelatinised starch qualities are processed by mechanical or thermal modifications of native starch qualities. The starch granules show a water take-up during this pregelatination process. The swollen granules burst at higher temperature and the partially dissolved polysaccharides form a gel with the surrounding liquid. This process is described as gelatination (Rein, 1993). Starch 1500 is a partially pregelatinised maize starch consisting of both individual starch grains and aggregates of starch grains bonded to the hydrolysed starch. As part of the hydrogen bonding between amylose and amylopectin are partially ruptured due to the manufacturing process, it contains 15 % free amylopectin, 5 % free amylose and 80 %

native starch (Rowe, 2006). The free amylopectin, which is soluble in cold water, is responsible for the binding properties of Starch 1500, while the rate of free amylose and unmodified starch accounts for its disintegration properties. Compared with other filler/binders, the flowability of Starch 1500 is poor due to the large specific surface of the powder, resulting in cohesion between particles (Bolhuis, 1973). Starch products exhibits plastic deformation during compaction. Changes in contact time have a major effect on tablet properties (Rees, 1978).

The post-compactional elastic recovery of starch compacts is comparably large (Schmidt, 1988). This matches some post-compactional observations of discrete primary particles in the same size as before compaction. Due to this extensive elastic recovery (Sheth, 1980) tensile strength values of starch compacts are low compared to other plastically deforming materials (Bolhuis, 1996). The work of compaction applied to starch granules does not lead to the formation of new bonds but is just stored over a short period of time before being released due to elastic recovery of reversible deformed particles. Pregelatinised starches and Starch 1500 in particular are, due to its plastic behaviour under pressure and the film formation of lubricant around the granules (Bolhuis, 1975), very sensitive to mixing with lubricants. As starch products have lubrication properties on their own (Gullatz, 1996) the amount of additional lubrication (~0.25 % magnesium stearate) necessary for direct compression is rather small (Bolhuis, 1973). Therefore, the residual forces as well as ejection forces of starch compacts are quite small.

6.7.4.1 Starch 1500

Partially pregelatinised maize starch; LOT: IN507820
Colorcon, Dartford, Kent, England

6.7.5 Sorbitol

Sorbitol is a chemical isomer of mannitol. It has become a major industrial sugar alcohol used in the food and pharmaceutical industries, where it is used for direct compression as well as for wet granulation purposes. Sorbitol deforms plastically into very hard compacts. At high pressures sorbitol undergoes a sintering effect leading to glittering tablets (Schmidt, 1983b). The individual particles of a compact, which are visible after compression at low pressures, were completely sintered forming a smooth surface. The very high hygroscopicity of Sorbitol and its tendency to stick to the surface of the punches are appreciable disadvantages of Sorbitol and limit its use for direct compression. Furthermore, tablets of sorbitol can become harder during storage due to dissolution and recrystallisation during aging (Bauer, 1997). Neosorb P60W, produced by crystallization, is a representative of the χ-modification of Sorbitol providing the least hygroscopicity and the best compactability of all the Sorbitol modifications (Bolhuis, 1996). It has a mean particle diameter (d_{50}) of 180µm and provides, due to its coarser grade compared to other sorbitol qualities, a flowability sufficient for direct compaction.

6.7.5.1 Neosorb P60W

Sorbitol; LOT: E041X
Roquette, Lestrem, France

6.7.6 Magnesium stearate

Lubricants, such as the most universally used magnesium stearate, are used in tableting to reduce the extent of interparticular friction as well as the friction between particles and the die during compaction and ejection phase. The radial and axial transmission of forces has improved (Koglin, 1992)., Needle-shaped magnesium stearate qualities have superior lubricant properties compared to platelet shaped ones (Steffens, 1982). Magnesium stearate of animal origin, manufactured by the use of fatty acids extracted from beef tallow, is nowadays used infrequently as of BSE, commonly known as the mad cow disease. Nowadays magnesium stearate used is more or less all of vegetable origin. Commonly used concentrations are within the range of 0.25 to 1.5 %, in some special cases up to 5 % (Ritschel, 2002).

Beside its favourable characteristic to work as a lubricant magnesium stearate has some negative influences on tablet properties, some of which have already been described previously. Particularly, its very hydrophobic character has a retarding effect on tablet disintegration and prolongs tablet dissolution (Lowenthal, 1972; Bolhuis, 1975).

6.7.6.1 Magnesium stearate Pharma veg.

Magnesium stearate, vegetable; LOT: 2079
Bärlocher, Unterschleißheim, Germany

6.8 Preparation of Tableting blends

The preparation of tableting blends used for the comparison of the compactibility profiles of the Presster and the Fette P1200 have been performed using 20 litre metal vessel on a lab-scale free-fall blender (Bohle, Enningerloh, Germany).

To guarantee enough space within the vessel during blending, the maximum batch size has been set to 5kg (Sucker, 1991).

After sieving the excipients and the lubricant by a 710 µm and 315 µm sieve respectively, the lubricant has been placed between two fractions of the excipients inside the vessel, in order to keep the adhesion of lubricant to the wall of the vessel as small as possible.

The blender has been set to work at 60 RPM for 3 minutes, while the direction of rotation of the vessel changed every 30 seconds.

The blend of Dicafos and 1 % of magnesium stearate, also used within the comparison of compactibility profiles of the Presster and the Fette P1200, was blended using a PM 1000 free fall blender (Bohle, Enningerloh, Germany) for 5 minutes at 6 RPM.

Tableting blends for both the investigation of ejection forces and take-off forces have been prepared using a Turbula mixer T2F (Bachofen, Basel, Switzerland).

After sieving the excipients and the lubricant by a 710 µm and 315 µm sieve respectively, the lubricant has been placed between two fractions of the excipients inside the 500ml glass blending vessel, which has been filled up to about two thirds of its volume. Blending took place at 60 RPM for 3 minutes.

Lubricant of all the investigations has been magnesium stearate veg. (Bärlocher, Unterschleißheim, Germany)

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8 Symbols and Abbreviations

°	degree
%	percent
A/D	analogue to digital
API	active pharmaceutical ingredient
BSE	bovine spongiform encephalopathy
CC	compaction cycle
ccm	cubic centimetre
COD	coefficient of determination, sample variance
cos	cosinus
D	tablet diameter [mm]
DAQ	data acquisition
DISLP	displacement sensor of lower punch
DISUP	displacement sensor of upper punch
ε	porosity [%]
EJ	ejection
Eq.	equation
et al.	et alii [Lat.]
EU 19	Euro 19 = Euro B
F	diametral crushing force [N]
Fig.	figure
FSO	full scale output
Hz	Hertz
kHz	kiloHertz
kN	kiloNewton
LVDT	Linear variable displacement transducer
max	maximum
min	minimum
mm	millimetre
ms^{-1}	meter per second
ms	millisecond

mV	milliVolt
MU	Mechanical Unit
N	Newton
NODP	Number of data points in terms of samples per second [S/s]
pC	pico-Coulomb
s	second
S	samples
sin	sinus
s/n	serial number
sps	samples per second
R^2	coefficient of determination, sample variance
RPM	revolutions per minute
SD	standard deviation
t	tablet thickness [mm]
Tab.	table
TO	take-off
TS	tensile strength [MPa]
V	voltage
V_c	volume of the compact at certain pressure [ccm]
V_t	"true" volume of the material determined by helium pycometric measurement
w/w	weight by weight
µm	micrometer

9 Special Notes

Data about percental content of tableting blends do refer to percent by weight (w/w), unless stated otherwise.

Trademarks have been used without special marking.

All statements within this work, as well as within any publication out of this work, concerning the Presster refer to the Presster model 2002, having the serial number 107 exclusively.