DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 21(19), 2201-2212 (1995)

DETERMINATION OF TABLET HARDNESS WITH STRAIN GAUGE EQUIPPED INSTRUMENTS

Martin Krieger[1], Franz J. Fähler[2] and Konrad Baumgartner[1]
[1] Sandoz Pharma Ltd., CH-4002 Basle
[2] Pharmatest Apparatebau GmbH, D-63512 Hainburg

ABSTRACT

A multisite study covering hardness testers of 3 different manufacturers was performed in order to asses the variability and reproducibility of hardness determination. A direct tabletting mixture was used to produce tablets of three different nominal hardnesses (30, 50 and 100 N). These tablets were tested on 8 individual strain-gauge equipped hardness testers. The differences were found to be significant for all instruments (deviations of the average values of 7 to 10%) as well as for instruments of the same manufacturer (deviations of 5 to 7%). However, reproducibility of individual instruments was good. Furthermore, instrument settings such as feeding speed and feeding force did not have a strong influence on hardness determination. Preliminary data gained with a prototype electromechanical test tablet demonstrated the internal linearity of the tested instruments but also revealed differences in signal characteristics of the strain gauges. The dynamic instead of the so far used static weight calibration of strain-gauge equipped hardness testers seems thus necessary and feasible. For the time being, hardness determinations from different instruments cannot be compared directly but have to be regarded as relative (and not absolute) measurements of hardness.

[1] address correspondence to: M. Krieger, Sandoz Pharma Ltd., 310/330, CH-4002 Basle, Switzerland.

INTRODUCTION

Monitoring of tablet hardness has always been a means for controlling the tabletting process and an indicator for the tablet quality. The determination of tablet or core hardness has moved from mechanical methods to electro-mechanical instruments equipped with strain gauges and computer control. Unfortunately, the reproducibility and robusteness of hardness determination of tablets has not improved accordingly. With the requirements of cGMP, these previously unrecognized characteristics have become a matter of interest for all those involved in manufacturing and quality control of tablets. The following report was performed as a multisite study with eight different electro-mechanical hardness testers from 3 different manufacturers.

MATERIALS AND METHODS

For the presented study, placebo tablets were produced using a direct tabletting mixture. The composition per tablet is indicated below. Direct tabletting was chosen for achieving a rather broad range of tablet hardness from 30 to 50 and 100 N respectively.

Characteristics of Test Tablets

Weight per tablet	**Composition**	
110.0 mg	Lactose	55.0 mg
	Cellulose, microcrist. gran.	52.8 mg
Diameter	Aerosil	0.2 mg
7 mm	Stearic acid	2.0 mg

Tablets used for Multisite Study

Hardness	**Batch 1**	**Batch 2**	**Batch 3**
Hardness, nominal	30 N	50 N	100 N
Hardness, produced (mean ± sdev)	29.2 ± 3.2 N	52.1 ± 3.3 N	100.3 ± 5.9 N

The hardness of these test tablets was monitored with the same instrument (WHT-1) at the beginning, during production and at the end of tabletting using the standard IPC procedure for 20 tablets. For the multisite study, samples were distributed simultaneously in air-tight brown glass bottles. At least 50 tablets of each batch (30, 50 or 100 N) were tested with the respective instruments.

Instruments tested in Multisite Study

In the presented study, we only included electro-mechanical instruments equipped with strain gauges. All instruments were previously calibrated according to the manufacturers' instructions. The instruments were located in Basle at the

solid forms dept., at process technology, quality assurance and research labs, and in Locarno (QA).

Manufacturers and Models of Hardness Testers assessed

Pharmatest	:	WHT-1, PTB 301
Erweka	:	TBH-28DR
Pelui	:	HT-300

Instrument names or model designations specific to a manufacturer and used throughout the text should be considered as registered trademarks. Statistical analysis of data was performed with spreadsheet tools.

RESULTS

We monitored tablet hardness with storage time and performed the multisite hardness testing within the same week as shown below. During the testing week of the multisite study, the average tablet hardness decreased only marginally as shown in Fig.1 and was thus regarded as constant.

Fig. 2 demonstrates that the variability of individual hardness values was considerable. Statistical (ANOVA) analysis showed that the differences of means were highly significant (at α = 5%). Interestingly, even the means measured on identical instrument models were significantly different (Table 1).

However, the reproducibility of a single instrument was usually satisfactory as demonstrated in Fig. 3 below. Due to the high variation of tablet hardness *per se* (S_{rel} for the presented data were between 3.6 and 5.5%) ANOVA analysis did not reveal a difference at α =5 % between the individual experiments shown below.

Furthermore, adjusting of instrument parameters did not significantly alter the hardness readings as shown in Fig. 4. Averages varied from 84.4 to 87.2 N (S_{rel} 3.2 - 6.1%) and again no significant difference of means could be found with ANOVA analysis at the α = 5% level. The results for the 30 N and the 50 N test tablets were comparable (data not shown).

With the present evidence of the variability of hardness determination, the calibration of the electromechanical instruments has become a topic of interest. The standard calibration procedures have to be considered as static, since the strain gauges are calibrated by exposing them to a defined standard weight only. Dynamic calibration simulating the breakage of a tablet should therefore produce a more satisfactory calibration. Since mechanical devices were shown to be unreliable, the prototype of an electro-mechanical test tablet provided by a manufacturer of hardness testers (Pharmatest) was taken as a starting point for our own

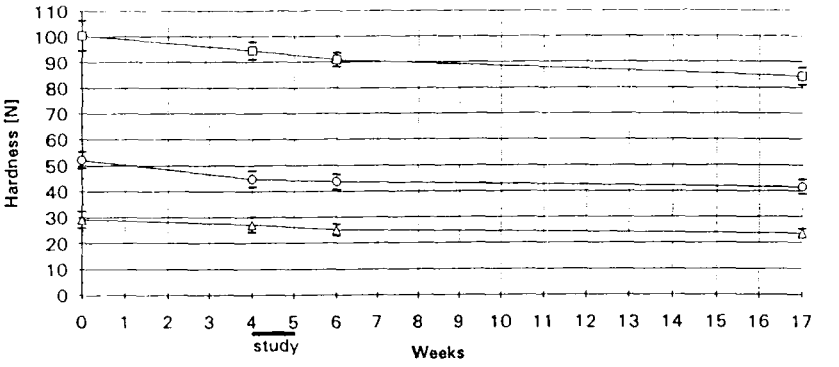

FIGURE 1. Hardness of test tablets for multisite study. Tablets were produced in week 0 with nominal hardnesses of 30, 50 and 100N and later assessed for hardness after storage in week 4, 6 and 17. Means ± standard deviation of 20 tablets are indicated, determined on the same hardness tester (WHT-1). Squares, 100N tablets; circles, 50N tablets; triangles, 30N tablets.

experiments involving a custom-built electromechanical test tablet. A drawing of the working principle of such an electro tablet is shown in Fig. 5. This device showed linear behaviour over a wide range of hardness as shown in Fig. 6.

When the different hardness testers were assessed with this electrotablet, large differences in hardness response were found. All instruments showed a linear increase of hardness but the intercepts and slopes differed widely (Fig. 7.) This finding confirmed the previous impression that static calibration of the strain gauges is not sufficient for calibration of hardness testers. We did not find a clear-cut rank correlation for the instruments by comparing data obtained either with tablets or with the electrotablet. This is possibly due to the as yet unavailable long term stability of the prototype electrotablet, which indicates the difficulty of obtaining reliable precision data.

The normalization of these instrument readings is shown in Fig. 8. One hardness tester was taken as a reference (WHT-1) and the other instrument readings were adjusted to the same intercept and slope.

In contrast to the results obtained with tablets, we were able to detect significant influences ($p(F)=1.95\times10^{-9}$ in ANOVA analysis) of instrument settings as shown in Fig. 9 due to the vastly reduced variability of hardness determination (S_{rel} 0.25-0.9%) with the electrotablet.

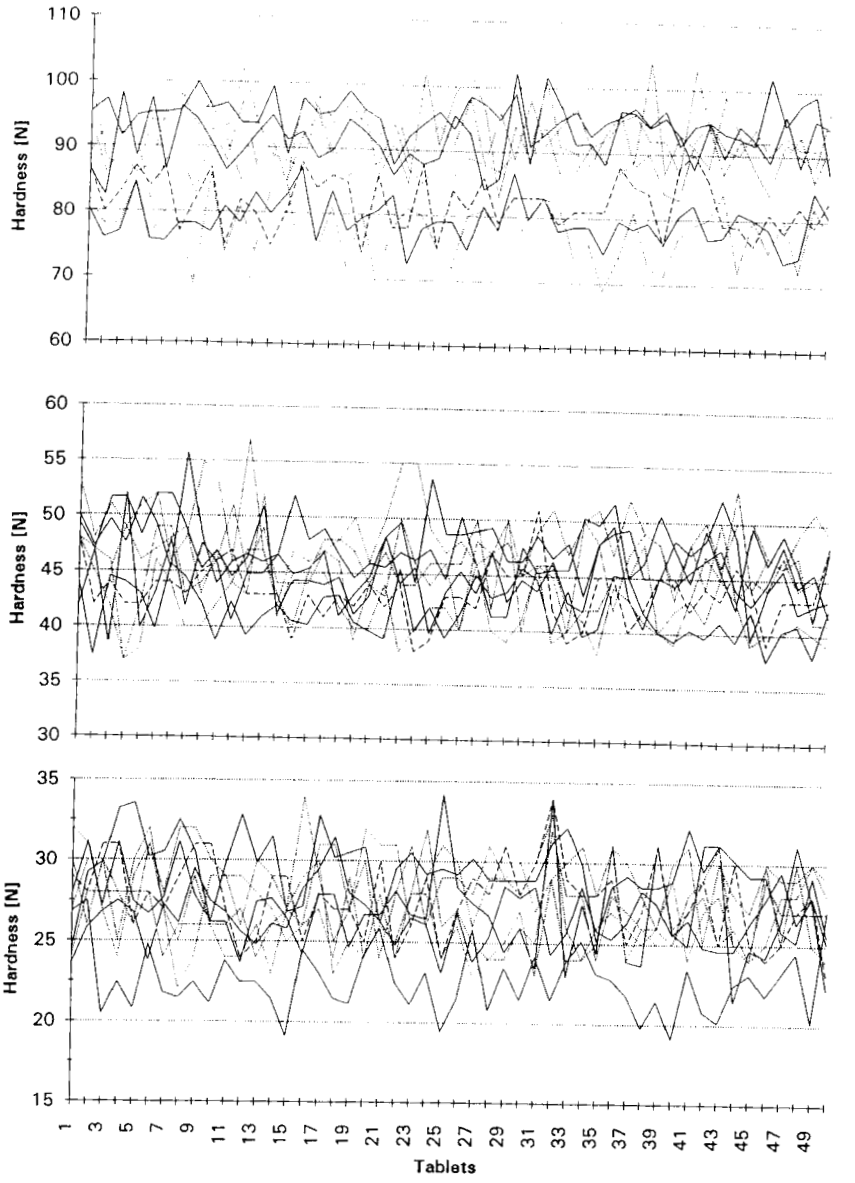

FIGURE 2. Variability of individual hardness measurements. 50 Tablets with nominal hardnesses of 30, 50 and 100 N were tested each on 8 different instruments. Solid lines, Pharmatest; dotted lines, Erweka; dashes, Pelui.

TABLE 1. ANOVA Analysis of Data presented in Fig. 2.

100 N tablets	p(F)	range of averages
all instruments	$p = 6.95 \times 10^{-105}$	77.6 - 94.4 N
Pharmatest instruments	$p = 8.09 \times 10^{-51}$	79.2 - 94.4 N
Erweka instruments	$p = 1.55 \times 10^{-45}$	77.6 - 92.8 N

50 N tablets	p(F)	range of averages
all instruments	$p = 1.84 \times 10^{-42}$	41.6 - 48.9 N
Pharmatest instruments	$p = 1.16 \times 10^{-14}$	41.6 - 46.5 N
Erweka instruments	$p = 5.92 \times 10^{-23}$	42.0 - 48.9 N

30 N tablets	p(F)	range of averages
all instruments	$p = 3.83 \times 10^{-13}$	26.1 - 30.0 N
Pharmatest instruments	$p = 3.03 \times 10^{-7}$	26.5 - 29.0 N
Erweka instruments	$p = 3.53 \times 10^{-9}$	26.1 - 29.1 N

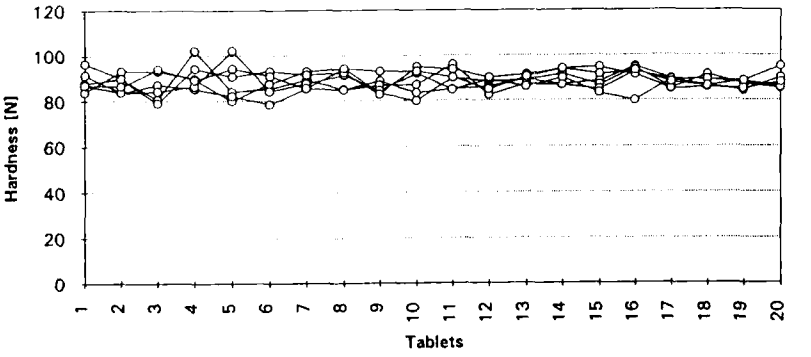

FIGURE 3. Reproducibility of a single instrument. Six samples of 20 test tablets were tested each on the same instrument (WHT-1). Averages varied from 86.6 to 90.5 N.

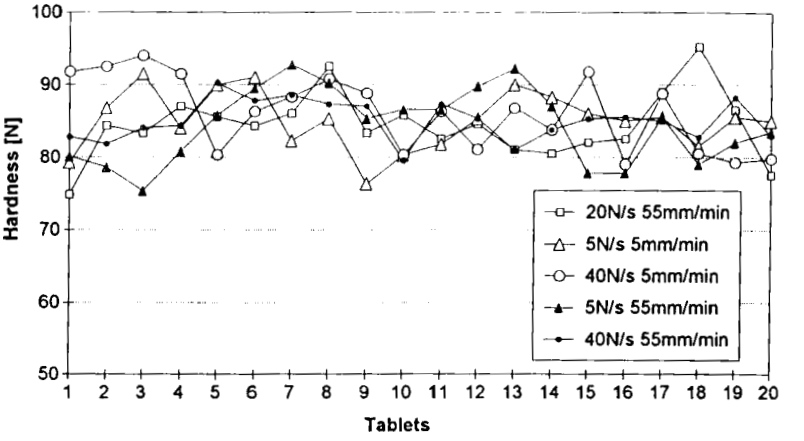

FIGURE 4. Influence of instrument parameters. Feeding speed [mm/min] and feeding force [N/s] were varied for hardness determination (WHT-1). 20 tablets each were tested at the instrument settings indicated.

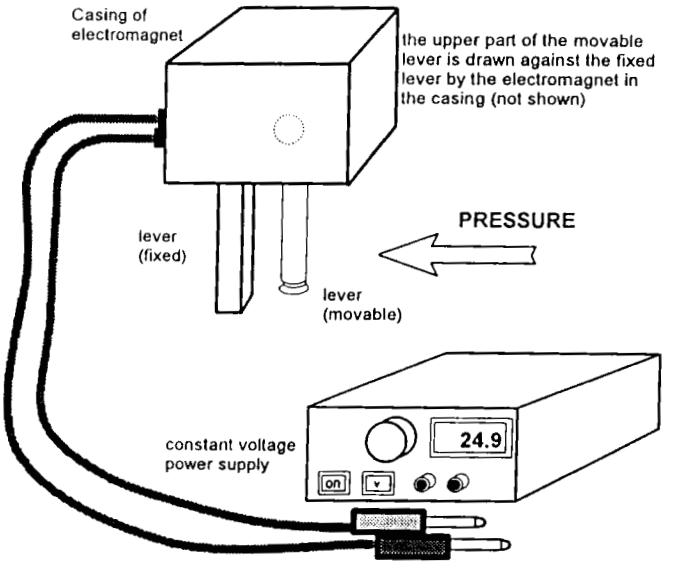

FIGURE 5. Principal drawing of electrotablet (prototype). The LED display indicates the stabilized voltage provided by the power supply.

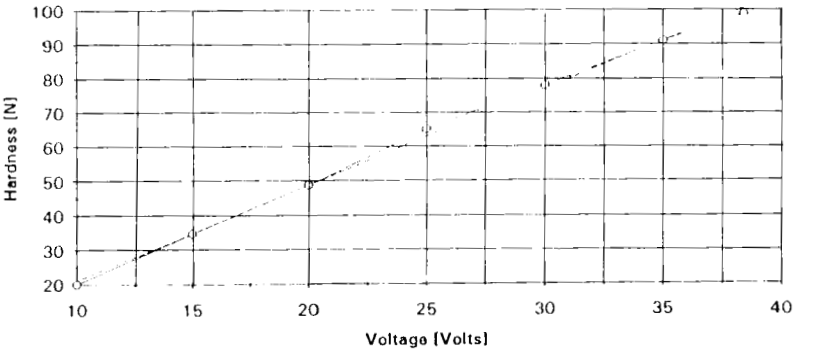

FIGURE 6. Linearity of electrotablet. The averages of 20 values are indicated at 10, 15, 20, 25, 30, 35 and 38 Volts. Linear regression of data is shown as a dashed line, r^2=0.998.

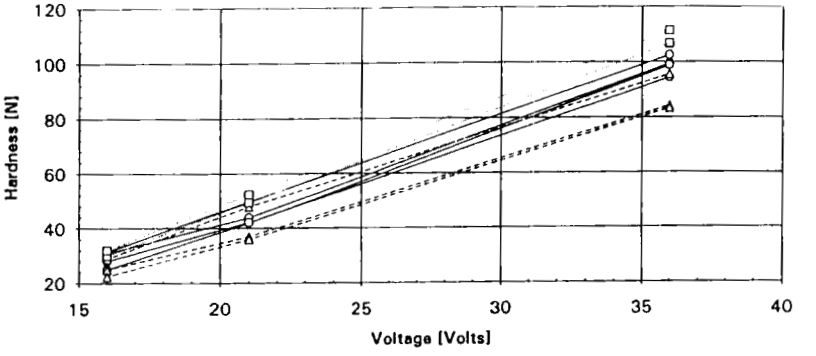

FIGURE 7. Calibration of hardness testers with a prototype electrotablet. Readings were taken at 16, 21 and 36 Volts respectively resulting in nominal hardnesses of approx. 30, 50 and 100 N. Solid lines, WHT-1, dashed lines, PTB301, dotted lines, TBH 28.

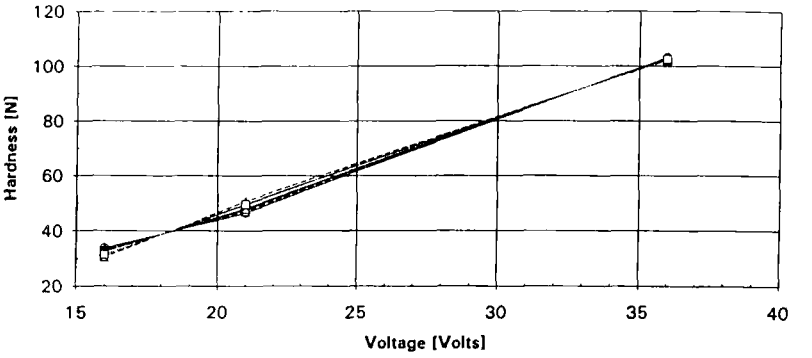

FIGURE 8. Dynamic calibration of hardness testers. Slope and offset of linear regression data was normalized with respect to an arbitrarily chosen reference instrument (WHT-1). Solid lines, WHT-1, dashed lines, PTB301, dotted lines, TBH 28.

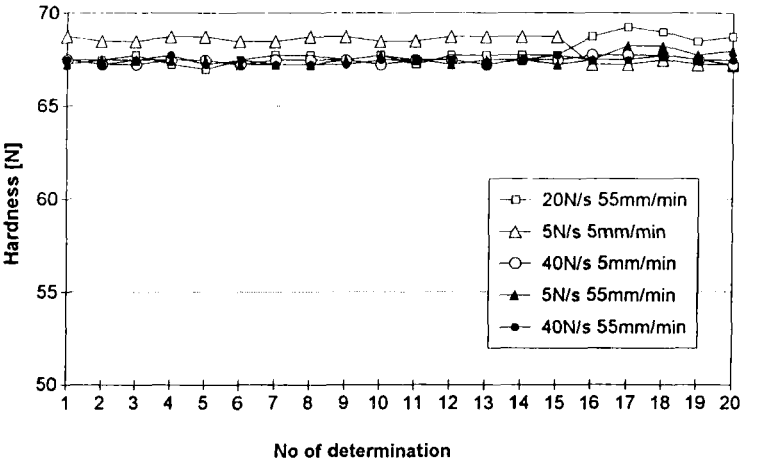

FIGURE 9. Influence of instrument settings detected by electrotablet. 20 individual determinations were performed on a WHT-1 at the parameter settings indicated. Voltage was held constant at 25V, averages varied from 67.4 to 68.3N.

Even though the linearity of the electrotablet was impressive, as demonstrated by the regression data, the hardness data produced by this method showed subtle variations at the beginning of a data series. (Fig. 10). The hardness measured with the electrotablet showed usually a slight decrease during the first five determinations. For instance at 21 Volts (not included on the graph), the standard deviation of values 1-25 was 1.57 (S_{rel} 2.7%) whereas for values 5-25, a reduced standard deviation of 1.04 (S_{rel} 1.8%) was found with averages of 57.3 N and 57.8 N respectively. This difference in standard deviations was significant in the F-test ($p = 2.5 \times 10^{-14}$). In addition to that, some signals showed some drift, e.g. at 10 Volts in Fig. 10.

In our experience, the time intervals between individual hardness determinations should be kept constant with $\Delta t_{min} > 3$sec for improving the stability of measuring conditions. Furthermore, reproducibility of electrotablet measurements varied somewhat during testing periods, demonstrating that dynamic calibration with electrotablets still needs further development effort.

DISCUSSION

As the recent (Jan. '95) earthquake in Japan (and others) demonstrate, the predictability of breakage events remains an unsolved problem. This behaviour is also found with many other physical processes on a very broad range of scales. What remains constant, is the non-linearity and non-equilibrium conditions under which deformation and breakage occurs. (1-3) In the case of tablets, this may lead to single values during hardness determinations that lie way above or below an expected hardness range. Nevertheless, tablet hardness is usually regarded as a variable with a normal distribution.

In our multisite study, we tested 30, 50 and 100 N tablets produced with the same direct tabletting mixture. We included tablets of one size only (7 mm) since we did not consider the size of tablets as critical for the variability of hardness determination. The variability is a phenomenon which is found with tablets of all sizes. We found significant differences between hardness testers, suggesting that not only tablet characteristics but also the measuring of tablet hardness is a source of hardness variability. This was to our disappointment, since we included only calibrated electro-mechanical instruments equipped with strain gauges in our multisite study.

The possible causes for these observations are manifold. The strain gauges used for measuring may have altered signal characteristics leading to wrong hardness results because of wear or erroneous overloading. In addition to that, subtle differences in the peak detection software and the internal precision in the evaluation of the force vs. time signals used for the control of the hardness determination as well as differences in the internal mechanics may also lead to the observed

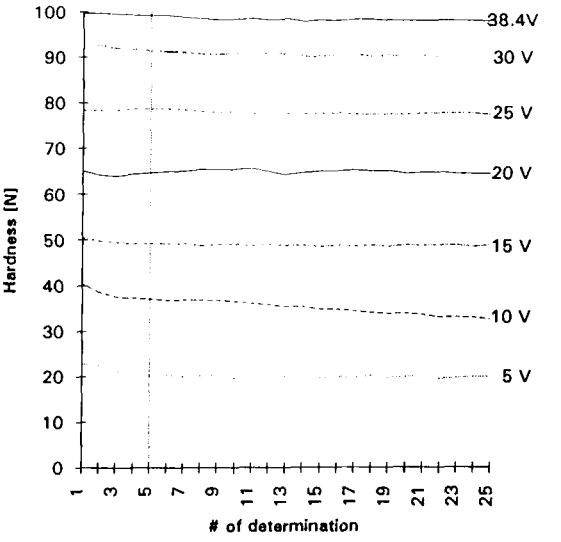

FIGURE 10. Stability of hardness determinations with prototype electro-tablet. 25 measurements each were performed on a WHT-1 at the voltages indicated at right.

variations. Surprisingly, even instruments from the same manufacturer and of the same model type produced different results.

Our data obtained with a prototype electro-tablet demonstrate that dynamic calibration of hardness testers may be at least a partial solution on the instrument side of hardness determination. All instruments tested showed reproducible, linear behaviour in a broad range of hardness. However, there is no instrument which allows adjusting of both y-intercept and slope of the calibration line. This dynamic calibration is not an absolute method, since the correlation to the static weight calibration is unknown. Therefore, instrument readings of dynamically calibrated hardness testers may not be regarded to be in Newtons but rather to be in arbitrary units. In order to obtain more comparable data from different hardness testers, new instruments have to be developed. The description of such a more standardized instrument should include detailed information on the working principles employed including the appropriate force control method to be used (preferrably constant force increase) with linearization and breakage detection criteria as well as standard measuring intervals. However, dynamic and absolute calibration of hardness testers remains a problem to be solved. Recent advances in material sciences may allow the development of such methods in the future (4-6).

CONCLUSIONS

For the pharmaceutical industry, testing of tablet hardness is a standard IPC method. However, the tablet hardness itself has hardly any direct relevance to the product quality. It has a meaning as readily available information for process control if the hardness correlates with important quality characteristics such as dissolution rate, breakability of divisible tablets and the qualification of the tablets for transportation in bulk and packaging (including unpacking by the consumer). Additionally, the compression force-hardness profiles provide information on the optimal compression force to be used. Thus, tabletting with high compression forces can be avoided, which reduces the machine and tooling wear. Also, the negative influence of high compression forces on the product quality can be avoided which cannot always be detected by in process control tests. Such characteristics are mainly dissolution rate and the potential for structural damage of tablets (lamination, capping) related to elastic recovery during decompression.

As long as there are no hardness testers on the market which can be calibrated dynamically, the exact testing of tablet hardness remains difficult. Therefore, tablet hardness may usually not be regarded as an exact product quality but rather as easily available information for process control.

REFERENCES

1. P. Meakin, Science, 252, 226 (1991).
2. K. Marshal in "Theory and practice of industrial pharmacy", L. Lachmann et al. eds., 3rd ed, Lea & Febiger, Philadelphia, 1986, p 87.
3. B. Wuetrich,. New Scientist, 141, 29 (1994).
4. D. Rittel, H. Maiger and H. D. Bui, Scr. Metall. Mater. (USA), 26, 1593 (1992).
5. Y. Xu and A. Shukla, J. Test Eval. (USA) 21, 178 (1993).
6. T. Kobayashi, I. Yamamoto and M. Niinomi, J. Test Eval. (USA) 21, 145 (1993).