

Comparative Investigations of Tablet Crushing Force Testers

Jørn M. Sonnergaard^a, Christina G. Jensen^a, Laerke Poulsen^a, and Kenneth B. Lokind^b

Department of Pharmaceutics, The Danish University of Pharmaceutical Sciences^a, Copenhagen (Denmark), and Novo Nordisk A/S, Bagsvaerd^b (Denmark)

Summary

The performance of 16 tablet breaking force testers was evaluated in terms of accuracy, reproducibility and repeatability. Three tablet formulations with different plastic or brittle deformation mechanisms and with target breaking forces of 50, 100 and 150 N were tested.

Statistically significant differences were observed between the estimated mean values of the investigated testers. The approximate accuracy measured as the percentage difference from the grand mean mostly lay in the interval $\pm 10\%$. The reproducibility expressed as the relative standard deviation between the testers estimated by the concept of components of variance was 5–7 % depending on the model tablet excipient. The standard deviation within testers (repeatability) was affected by the type of model formulation showing increasing

variability with increasing brittleness of the compressed material. No specific effect of altering the speed of platens on the mean values or the variability was observed.

It is concluded that, compared to other quality methodologies of solid dosage forms with a suspected variability, there is generally no reason to question the standard and performance of the breaking force testers used today in the pharmaceutical industry.

Zusammenfassung

Vergleichende Untersuchung von Tabletten-Bruchkrafttestern

Die Leistung von 16 Tabletten-Bruchkrafttestern wurde im Hinblick auf Präzision, Reproduzierbarkeit und Wiederholbarkeit der Ergebnisse untersucht. Drei Tablettenformulierungen mit verschiedenen plastischen oder spröden Eigenschaften und mit Zielbruchkräften von 50, 100 und 150 N wurden verwendet.

Zwischen den geschätzten Mittelwerten der Ergebnisse der untersuchten Tester wurden statistisch signifikante Unterschiede beobachtet. Die Annäherung der Präzision, gemessen als prozentualer Unterschied vom Mittel insgesamt, lag meist im Bereich von $\pm 10\%$. Die Reproduzierbarkeit, ausgedrückt als relative Standardabweichung der Werte der einzelnen Tester untereinander und geschätzt nach dem Konzept der Varianzkomponenten (components of variance), war 5 bis 7 % in Abhängigkeit vom Exzipienten der Modelltabletten. Die Standardabweichung der Werte einzelner Tester wurde von der Art der Modellformulierung beeinflusst und zeigte eine zuneh-

mende Variabilität mit zunehmender Brüchigkeit des verpreßten Materials. Änderungen der Geschwindigkeit der Preßwerkzeuge führte zu keinen spezifischen Auswirkungen auf Mittelwerte oder Variabilität.

Es wird geschlossen, daß es – im Vergleich mit anderen Qualitätsprüfmethoden für feste Arzneiformen mit möglicher Variabilität der Ergebnisse – im allgemeinen keinen Grund gibt, die Standards und die Leistung der heute in der pharmazeutischen Industrie verwendeten Bruchkrafttester in Frage zu stellen.

Key words

- Crushing force testers, accuracy, methodology, repeatability, reproducibility
- Solid dosage forms
- Tablets

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1. Introduction

In industrial production and quality control, the resistance to crushing or the breaking force of tablets is a pivotal quality parameter in the characterisation of the mechanical properties of the compacts. As stated in the specifications for a given product it is important that the crushing force is measured in a precise and repeatable system using appropriate and reliable instruments and that the result is independent of the breaking tester used.

Different tablet breaking force testers were investigated and compared in the early seventies [1–3] but since then the technical evolution has greatly improved the performance and facilities of the testers. The relative standard deviations were shown to be considerably larger on old-fashioned manually operated equipment than on modern motorised equipment. Schmidt and Römpf [4] recently investigated the operation of three modern force testers. In this investigation special attention was made to the calibration and to the effect of the speed of the jaws.

An important aspect in the investigation of a given quality parameter over a longer period of time is the stability and robustness during storage. However, only few investigations deal with the effect of long-term storage on the crushing force of compacts. It seems to be generally accepted [5–7] that sodium chloride tablets increase their strength upon storage. Follier and Dodelker [7] measured the strength of tablets 3 min and 24 h after compaction and found a decrease in strength between 20 and 30 % in a number of relevant pharmaceutical excipients.

The effect of rate of loading or the speed of the jaws on force measurements has been investigated with contradictory conclusions. An increasing tablet strength with increasing rate was observed over a wide range of speed settings [8, 9], and an increase in the speed of the jaws from 0.5 to 2.3 mm/s on a standard force tester increased the breaking force of between 4 and 8 % [4]. In contrast to these observations compacts made of acetylsalicylic acid and ammonium sulphate showed decreasing tensile strength when the speed of the jaws varied from 0.008 to 1.67 mm/s [10].

The advantage of testers operating with a constant loading of force rather than the traditional constant displacement of the jaws has recently been discussed [4, 11]. If, however, the tablet under pressure is considered to be an elastic body, no difference between these two methods is expected. According to Hook's law, an elastic deformation will show a simple linear relationship between applied force and deformation. This close-to-linear or linear relationship was observed by Schmidt and Römpf [4] on commercial force testers, where deviations occurred in the initial and final stage of the loading. Likewise, it is apparent by recalculation of the data of Rees et al. [8] who worked on an Instron tester that this interdependence between the applied load and the crosshead movement exists as shown in Fig. 1. The dif-

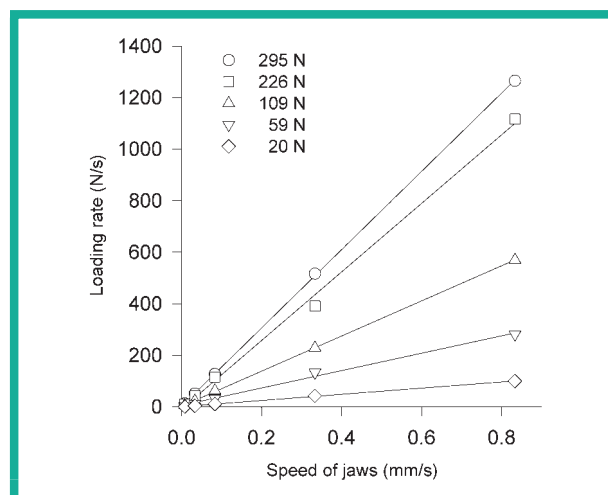


Fig. 1: Linear relationship between loading rate and speed of jaws with different average crushing force. Data from Rees et al. [8].

ferent slopes are clearly related to the strength of the examined tablets. Due to their higher elastic modulus rigid tablets will show a substantially greater slope in the relationship between the movement of the jaws and the loading force.

It is interesting to notice that the loading rate data in Fig. 1 can be represented by a simple multiple relationship:

$$Lr = 5.487 \times Cm \times St \quad (\text{Eq. 1})$$

Where Lr is the loading rate, Cm the crosshead movement and St the average crushing force of the investigated tablets. This equation describes (determined through R^2) 99.2 % of the total variability in the loading rate. According to the USP Advisory Panel on Physical Test Methods [11] it is recommendable to keep the loading rate constant since compressive loads can build up rapidly with constant movement and lead to uncontrolled crushing and greater variability. This statement is not supported by the data of Rees et al. and the standard deviations reported by Schmidt and Römpf [4].

In inter-laboratory investigations where analytical methods or procedures are compared, the one-way analysis of variance is truly the most effective way of detecting any systematic difference between laboratories. The informative value of a statistically significant difference may, however, be of limited value as minor differences without any practical importance may be distinguished due to a very small intra-laboratory variability. It appears that the focus in the ANOVA table should rather be put on the variability between laboratories also known as the reproducibility. This quality parameter is most accurately estimated by the components of variance concept. As the laboratories or methods are considered to be arbitrarily selected (random factor model) from a large population, the interpretation of the analysis of variance is different from the fixed factor model.

Table 1: Random factors one-way ANOVA with k groups and n replicates from which the variance components are estimated.

ANOVA source	Sum of squares	Degrees of freedom	Mean squares	Expected mean square
Groups/ Treatment	SSg	k-1	SSg / (k - 1)	$\sigma g^2 \times n + \sigma e^2$
Error	SSe	n × (k - 1)	SSe / (n × (k - 1))	σe^2
Total	SSt	n × k - 1		

From the one-way analysis of variance the variance components are calculated as shown in Table 1 [12, 13].

Substituting σ in Table 1 with the estimator S the expected mean square (EMS) of the k groups (testers, laboratories, methods) is the sum of the between-groups variance (Sg^2) multiplied by the number (n) of replicates and the within-groups variance (Se^2).

$$Se^2 + n \times Sg^2 = SSg / (k - 1) \quad (\text{Eq. 2})$$

The total variance (St^2) of the measurements is consequently calculated as:

$$St^2 = Sg^2 + Se^2 \quad (\text{Eq. 3})$$

The purposes of this investigation are:

- To describe and evaluate the performance in terms of accuracy and precision of breaking force testers in operation in the pharmaceutical industry today. In order to decrease the influence of intra-batch variability expected to be present in commercial tablets model tablets were produced on a single-stroke machine at low speed.
- To evaluate the effect of different rates of platen movement on the average strength and on the variability in cases where the tester has this feature.
- To investigate the effect of excipients with different compressibility characteristics on the accuracy and precision of the crushing force testers.

2. Materials and methods

2.1. Materials

Microcrystalline cellulose (Avicell® PH 102, FMC, Philadelphia, PA, USA), lactose monohydrate (Tablettose® 80, Meggle Milch-industrie, Wasserburg, Germany) and magnesium stearate (Unichem, Copenhagen, Denmark) were used as purchased.

2.2. Model tablets

Tablets were compressed based on three model formulations: plastic deforming microcrystalline cellulose (MCC), lactose monohydrate (LAC) consolidating by a brittle mechanism and a 50 % w/w mixture (MCCLAC). 3 kg powder was mixed in an Erweka Cubusmixer AR400 (Erweka, Heusenstamm, Germany) for 3 min at 30 rpm with 0.5 % magnesium stearate, afterwards the powder blends were sieved through a 710 µm sieve. The tablets were compressed on a Fette Exacta single-punch tablet machine (Fette, Schwarzenbek, Germany). 400 mg tablets were compressed with 12 mm flat faced punches with bevel edges at a speed of 60 rpm. From all three mixtures

Table 2: Basic characteristics of the model tablets (n = 20).

	Mass (mg)	CV (%)	Height (mm)	CV (%)
MCC50	395.8	0.87	4.39	0.19
MCC100	397.1	0.23	3.72	0.25
MCC150	398.1	0.23	3.43	0.36
MCCLAC50	399.2	0.24	3.24	0.37
MCCLAC100	397.3	0.37	2.94	0.26
MCCLAC150	398.2	0.21	2.76	0.35
LAC50	399.6	0.40	2.84	0.42
LAC100	397.6	0.38	2.67	0.88
LAC150	400.0	0.33	2.62	0.50

tablets were compressed with target crushing forces of 50, 100 and 150 N. The heights of 20 tablets were measured on a Mitutoyo Indicator (Mitutoyo, Tokyo, Japan). Details of the basic tablet characteristics are listed in Table 2.

2.3. Crushing force testers

The radial crushing force of the nine tablet formulations (n = 20) was measured on 16 different testers from three manufacturers: Schleuniger (Schleuniger, Solothurn, Switzerland), models 2E (n = 3), 6D (n = 7), 8M (n = 2); Pharma Test (Pharma Test Apparatebau, Hainburg, Germany), model PTB 311 (n = 2); Erweka (Erweka, Heusenstamm, Germany), models TBH 28 (n = 1), TBH 30 (n = 1). The testers were deliberately not calibrated prior to the measurements as the normal calibration schedule of the laboratory was conformed.

2.4. Correction of data due to the effect of ageing

In order to eliminate the effect of storage upon the measurements as the investigation took place over a longer period of time, the strength was measured on the same instrument (S6D1) 20, 41, 50 and 60 days after manufacturing. The apparent straight line relationship between time and force was used to correct the data of all other measurements.

2.5. Effect of speed

The effect of the speed of the jaws on the mean value and the variability was investigated on all nine tablet batches on three testers. Model S8M2 at nine speed settings from 0.25 to 4.75 mm/s and model S8M1 and Er30 at seven respectively six speed settings from 0.75 to 4.75 mm/s.

2.6. Data handling

Excel® (Microsoft) and Statgraphics® Plus (Manugistics) were used in the statistical analysis and other calculations. Since crushing force data has been shown not to deviate from the normal distribution [14], parametric statistical methods were applied.

Outliers in the individual sets of data were identified according to Eq. 4 [13, 15].

$$G = \frac{\max |Xe - \bar{X}|}{S} \quad (\text{Eq. 4})$$

Where Xe is the extreme value in the data, X is the mean value and S' is the overall standard deviation including the extreme value. The critical levels of G are tabulated [15] or may be calculated from the t-distribution [13]. With n = 20 and 5 % significance level an outlier is suspected when G exceeds the value 2.71. The identified outliers were not omitted from the investi-

gation as they were considered to be an unavoidable element of the methodology in the measurement of tablet breaking force.

Components of variance were calculated from the ANOVA tables of the nine model tablets based on the data corrected for effect of ageing.

3. Results and discussion

From the basic characteristics of the tablets shown in Table 2 it is apparent that the variations of mass and dimension as planned and expected are very low within the model tablets. Attempts to correlate the mass and height of 20 tablets to the strength of the individual tablets were unsuccessful. It is thus concluded that the crushing force data are stochastically independent variables with homogeneity better or at the same level as the resolution of the testers.

3.1. Effect of ageing

The effect of storage on the average strength values of tablets made of microcrystalline cellulose and lactose is illustrated in Fig. 2. The physical stability of lactose tablets is seen to be markedly more influenced by the ageing and the negative slope which is in general increasing with increasing strength. The standard deviation of the measurements seems to be unaffected by the ageing. The negative slope of the regression lines used as the correction factor on all measurements are listed in Table 3 and the results presented in Table 4.

3.2. Detection of outliers

Among the 2880 individual observations of breaking force, 16 measurements were identified as outliers according to Eq. 4 (Table 3). Although outliers were detected in all batches there is a tendency towards extended occurrence for tablets made of the brittle lactose. The occurrence of outliers among the testers (Table 5) must – considering the relative few observations – be regarded as randomly distributed. It is noticeable that in all cases the outliers were minimum values in the data sets. This is probably due to the previously [14] observed phenomenon of the effect of microscopic fragments of material sticking to the jaws giving rise to an uneven load on the tablets.

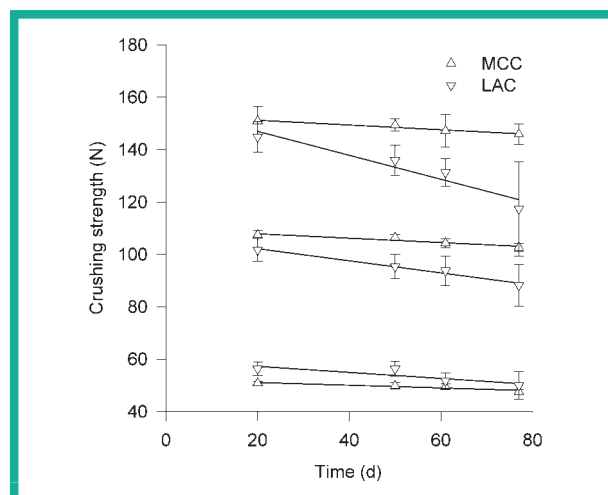


Fig. 2: Effect of storage upon crushing force of tablets made of microcrystalline cellulose (MCC) and lactose (LAC). Apparatus: Schleuniger 6D (S6D1). Error bars indicate the standard deviation ($n = 20$).

3.3. Effect of speed

Characteristic examples of the relationship between the speed of the jaws and crushing force are illustrated in Fig. 3. In general, no significant effect of the speed was observed, neither on the mean value nor on the standard deviation. Only the Erweka tester model 30 showed in few cases a small rate dependent increase in force values but this trend was constrained and observed only at the slow speed settings. These observations are in contrast to other results [8 – 10] and may be partially explained by higher rates and the more limited range of speed settings on commercial testers. In this study the speed was increased by factor 20 where other investigators increased the speed by factor 200 [10].

3.4. Accuracy

Accuracy is defined as the closeness of agreement between the observed value and the true value. Since no true value exists in this case the accuracy of the involved testers was evaluated through a comparison between the equipment mean value and the overall grand mean. Statistically tested through ANOVA, a highly significant difference between the 16 testers for all the

Table 3: Results of the investigation listed according to the model tablets ($n = 320$). Reproducibility and repeatability are characterised as the standard deviation calculated from components of variance.

Model tablet	Grand mean (N)	Correction factor (N/day)	Corrected grand mean (N)	Number of outliers	Reproducibility (%)	Repeatability (%)
MCC50	49.5	-0.053	51.7	0	4.8	1.8
MCC100	102.2	-0.084	105.6	0	5.0	1.9
MCC150	144.6	-0.090	148.4	3	5.5	2.2
MCCLAC50	54.0	-0.039	55.6	2	5.1	3.1
MCCLAC100	100.9	-0.059	103.3	0	5.8	2.2
MCCLAC150	152.8	-0.114	157.5	1	6.4	2.0
LAC50	56.6	-0.115	61.4	2	6.5	5.5
LAC100	95.8	-0.230	105.4	4	6.0	6.5
LAC150	130.0	-0.458	149.0	4	7.1	8.3

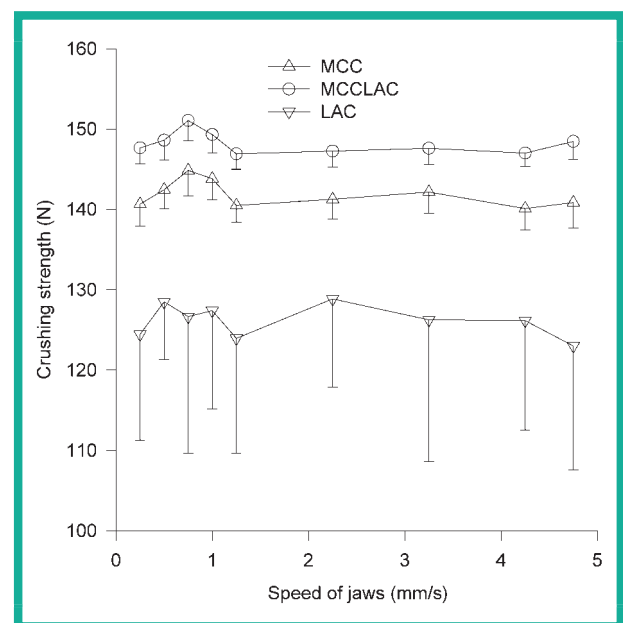
Table 4: Results of the investigation listed according to the testers. Mean values of crushing strength (upper row, N) and coefficient of variation (lower row, %), n = 20.

Formula	MCC 50	MCC 100	MCC 150	MCC-LAC 50	MCC-LAC 100	MCC-LAC 150	LAC 50	LAC 100	LAC 150
S2E1	51.8 1.7	104.4 1.7	145.2 3.3	55.6 1.7	100.5 2.2	153.8 1.6	61.0 4.6	103.9 5.3	144.9 4.3
S2E2	53.7 2.0	102.9 1.8	143.9 2.2	57.0 3.2	99.4 2.7	148.8 2.2	59.8 4.6	95.9 6.3	135.6 8.2
S2E3	51.9 2.0	99.0 1.6	136.2 2.7	52.3 7.7	94.6 1.9	141.0 1.8	60.3 6.0	97.9 6.9	132.2 12.3
S6D1	51.5 1.2	108.6 1.7	152.2 3.6	56.4 2.1	107.1 1.8	161.7 1.7	57.9 4.3	105.0 4.2	151.3 3.8
S6D2	50.5 1.7	106.4 2.3	149.4 1.8	54.8 2.2	103.2 2.7	158.3 1.3	58.1 5.2	101.9 4.5	143.9 7.8
S6D3	51.5 1.9	109.3 2.1	153.9 1.2	56.2 2.5	107.5 2.5	164.6 2.4	59.9 3.9	100.8 6.3	150.6 6.4
S6D4	53.2 1.3	111.3 2.0	158.9 2.1	58.9 3.4	109.8 1.9	170.3 1.7	69.3 4.6	118.2 5.6	165.6 4.7
S6D5	53.6 2.0	111.0 1.4	156.8 1.8	57.6 3.0	109.1 2.1	168.3 1.2	62.7 5.3	110.1 7.7	161.9 5.1
S6D6	53.5 1.6	112.3 2.3	159.2 2.3	58.0 2.3	109.6 2.2	168.3 1.9	63.3 5.5	110.3 7.8	157.5 6.5
S6D7	53.6 1.7	110.9 1.9	159.0 1.7	57.8 3.0	110.0 1.8	170.6 1.4	64.8 4.7	114.0 5.2	162.9 4.3
S8M1	48.9 1.5	102.3 1.6	144.4 1.6	51.2 2.3	96.9 2.6	150.4 1.6	58.6 5.2	98.8 6.7	139.6 9.5
S8M2	53.8 1.5	108.2 0.9	150.4 1.7	57.4 2.2	105.0 1.9	157.6 1.5	68.2 5.2	110.7 9.0	160.8 7.6
PH1	48.7 1.9	98.0 1.7	135.7 1.5	52.0 2.3	94.7 2.5	144.7 1.3	56.7 3.2	99.5 3.0	142.9 5.1
PH2	53.1 2.3	102.7 2.1	140.3 2.3	54.4 2.4	97.4 2.2	144.9 2.5	57.9 7.4	109.6 6.3	154.7 9.9
Er28	44.6 2.7	94.9 2.1	137.1 2.6	50.3 3.6	97.1 2.7	149.2 3.3	56.5 7.5	100.3 5.5	132.7 8.4
Er30	53.1 1.7	108.1 2.3	151.9 1.6	59.6 2.5	111.2 2.0	167.3 3.0	66.8 7.6	109.7 9.7	147.1 18.4

MCC: microcrystalline cellulose, LAC: lactose.

Table 5: Characteristics of the crushing force testers with the time between production and measurement and time elapsed since last calibration. n.c.: not calibrated.

Manu- facturer	Model	Time/ test (days)	Time/ cali- bration (days)	Rate (mm/s)	Number of outliers
Schleuniger	S2E1	1	n.c.	—	1
	S2E2	36	n.c.	—	0
	S2E3	50	181	—	0
	S6D1	14	15	—	1
	S6D2	37	43	—	1
	S6D3	37	2	—	0
	S6D4	50	57	—	1
	S6D5	51	84	—	1
	S6D6	51	84	—	1
	S6D7	51	84	—	1
	S8M1	56	n.c.	1	0
	S8M2	87	n.c.	1	1
Pharma- tester	PH1	10	441	—	1
	PH2	10	1	—	2
Erweka	Er28	50	55	—	2
	Er30	73	0	2.3	3

**Fig. 3: Example of the relationship between speed of jaws and the uncorrected crushing force for tablets with target force 150 N. Apparatus: Schleuniger 8M (S8M2). Error bars indicate the standard deviation (n = 20).**

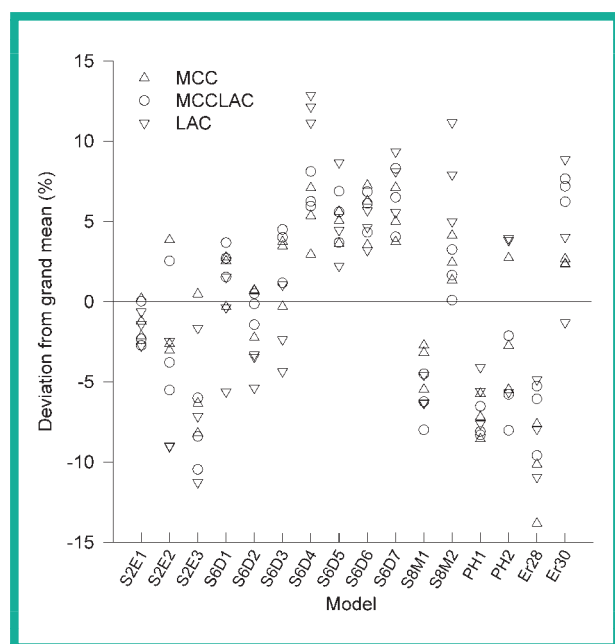


Fig. 4: Apparent accuracy of the 16 testers calculated as the percentage deviation of the mean value ($n = 20$) from the grand mean ($n = 320$).

nine model tablets was observed. This difference is illustrated in Fig. 4 where the deviation from the grand mean is normalized as the percentage deviation. The deviation between the testers mostly lies in an interval between $\pm 10\%$ and only few measurements are outside this interval. No tendency towards a relationship between the individual equipment and the type of model substance or the target breaking force was observed. Nor was any deviation found to be related to the time elapsed since the last calibration. It is also characteristic that the accuracy seems to be independent of the manufacture, model or age of the tester.

3.5. Precision

Precision is the variability or the degree of scatter between a series of measurements obtained from multiple sampling. In this case two aspects of precision are relevant: The repeatability and the reproducibility. The intermediate precision expressing the within-equipment or laboratory variations on different days, different analysts etc. is considered to be unimportant in this investigation.

3.5.1. Repeatability

Repeatability which is the precision over a short period of time and here referred to as the within-testers standard deviation is based on 20 measurements. The average or overall repeatability is calculated from the ANOVA tables of the nine model formulations as the residual standard deviation with 304 degrees of freedom. It is evident from the data in Table 3 that the over-

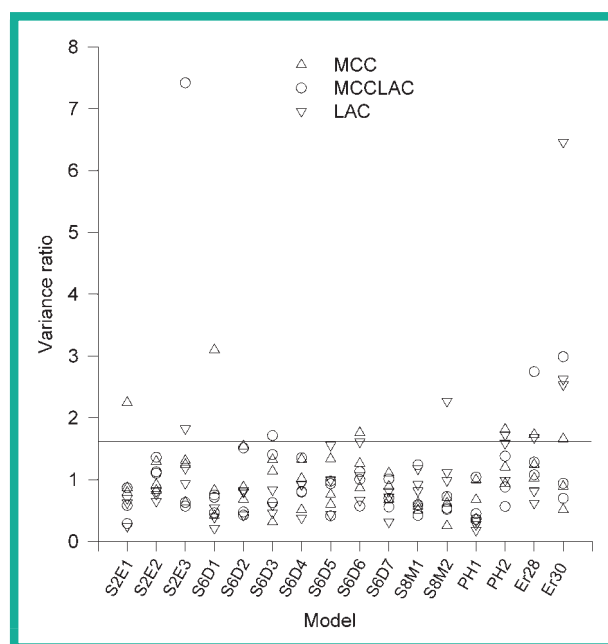


Fig. 5: Repeatability of the 16 testers represented as the variance ratio between the individual tester and the residual variance of the remaining testers. The straight line is the variance ratio corresponding to the $F_{0.05}$ value with 19 and 285 degrees of freedom.

all repeatability is dependent on the tableted material as the relative standard deviation is increasing with increasing brittleness. The statistical test on the difference between the repeatability of the testers (Bartlett's test) showed statistical difference ($p < 0.05$) in most cases. These differences are visualised in Fig. 5 as the variance ratio between the individual variance and the residual variance of the remaining 15 testers computed from the ANOVA table. It is expected that the influence of outliers is more pronounced on the standard deviation than on the mean value of a given set of data. This influence is seen in Fig. 5 where the large variance ratios are mostly caused by the outliers. The majority of the calculated ratios are below the theoretical F-value and are thereby not considered to be statistically significant.

The relationship between the repeatability and characteristics of the tablet material implies the need for a larger sample size in order to estimate the mean value of a given batch better than suggested by the European Pharmacopoeia [16] where only 10 tablets are tested. As the crushing force test is extremely easy and rapid to perform it is thus suggested that the number of tablets is increased to 20 and that the results are submitted as the mean and standard deviation of the data.

3.5.2. Reproducibility

The reproducibility expresses the precision between laboratories or equipment. As mentioned earlier, the testers are randomly selected and the most correct way to express the reproducibility is through the standard deviation calculated by components of variance. The

relative standard deviations expressing the reproducibility are listed in Table 3 and show a small increase with the target crushing force and with the brittleness of the tableted material.

4. Conclusions

- The apparent accuracy of the 16 testers presented as a percentage deviation from the grand mean only in few cases exceeds $\pm 10\%$.
- The overall repeatability for the 16 testers is estimated at 2 % for microcrystalline cellulose tablets increasing to 6–8 % for lactose tablets.
- The reproducibility among the testers is estimated at 5–7 % with a minor dependency of the material or target crushing force.
- It is suggested that the sample size in the Ph. Eur. test for resistance to crushing is increased to 20.
- Due to the low variability and the acceptable physical stability microcrystalline cellulose seems promising as a basic material in a potential calibration tablet.
- No substantial effect of the speed of the jaws was observed on neither the mean values nor on the variability.
- The reproducibility is most correctly calculated by means of the variance components concept.

5. References

- [1] Ritschel, W. A., Skinner, F. S., Schlumpf, R., Vergleichende Untersuchungen mit verschiedenen Geräten zur Bestimmung der Druckfestigkeit von Tabletten, *Pharm. Acta Helv.* **44**, 547 (1969)
- [2] Goodhart, F. W., Draper, J. R., Dancz, D. et al., Evaluation of tablet breaking strength testers, *J. Pharm. Sci.* **62**, 297 (1973)
- [3] Bavitz, J. E., Bohidar, N. R., Karr, J. I. et al., Performance of tablet breaking strength testers, I: Intralaboratory comparison and prediction, *J. Pharm. Sci.* **62**, 1520 (1973)
- [4] Schmidt, P. C., Römpf, H., Resistance to crushing of tablets. Do we need a more precise description of the method in the European Pharmacopoeia? *Pharmeuropa* **12**, 573 (2000)
- [5] Bhatia, R. P., Lordi, N. G., Conductivity and hardness change in aged compacts, *J. Pharm. Sci.* **22**, 896 (1979)
- [6] Karehill, P. G., Nyström, C., Studies on direct compression of tablets. XXII. Investigation of strength increase upon ageing and bonding mechanisms for some plastically deforming materials, *Int. J. Pharm.* **64**, 27 (1990)
- [7] Follonier, M., Doelker, E., Accelerated ageing test for predicting the short-term change of the mechanical strength of compressed tablets, *Eur. J. Pharm. Biopharm.* **39**, 267 (1993)
- [8] Rees, J. E., Hersey, J. A., Cole, E. T., The effect of rate of loading on strength of tablets, *J. Pharm. Pharmacol.* **22**, 64S (1970)
- [9] Degennaro, M. D., Geiger, B. S., The effect of loading rate on apparent tablet hardness, *Can. J. Pharm. Sci.* **15**, 58 (1980)
- [10] Newton, J. M., Ingham S., Onabajo, O. O., The effect of strain rate on mechanical strength of tablets, *Acta Pharm. Technol.* **32**, 61 (1986)
- [11] Augsburg, L. L., Wurster, D. E., New general test chapter Tablet breaking force, *Pharmacopeial Forum* **26**, 513 (2000)

[12] Montgomery, D. C., Design and analysis of experiments, 5th ed., J. Wiley & Sons, New York (2001)

[13] NIST/SEMATECH e-Handbook of Statistical Methods, <http://www.itl.nist.gov/div898/handbook/11/20/02>

[14] Sonnergaard, J. M., Distribution of crushing strength of tablets, *Int. J. Pharm. Biopharm.* **53**, 353 (2002)

[15] Davies, O. L., Goldsmith, P. L., Statistical methods in research and production, 4th ed., Longman Group, London (1976)

[16] European Pharmacopoeia, 4th ed., General Chapters 2.9.8. "Resistance to crushing of tablets", p. 201, Council of Europe, Strasbourg (2001)

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Correspondence:

Dr. Jørn Møller Sonnergaard,
Department of Pharmaceutics,
The Danish University of Pharmaceutical Sciences,
Universitetsparken 2,
2100 Copenhagen (Denmark),
e-mail: jms@dfh.dk