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Mass Uniformity: Influence of Operational Compression Conditions on Breakability of Scored Tablets as Part of Manufacturing Robustness Evaluation

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ABSTRACT

Dose uniformity is a key quality element of drugs. The purpose of this study was to demonstrate a practical approach to evaluate the breakability robustness as part of the tabletting validation of a scored tablet. The influence of operational compression parameters (speed and force) on the weight variabilities of half- and quarter-tablets was investigated using two types of cross-scored round tablets of identical composition but different in size. It was shown for the used veterinary model tablet that manufacturing variation of two compression parameters around the defined target values do not significantly influence the weight variability of the broken tablets. The empirical guidance was also confirmed that for the investigated dose-proportional tablets the standard deviation of the broken tablet-part weight is linearly related to the original tablet weight. There exists a strong correlation between the variability of half-tablets and of quarter-tablets: the theoretical model previously presented was refined, demonstrating that the additional variance induced by breaking is a linear function of the break-line length. As a consequence, the standard deviation of half- and quarter-parts of cross-scored round tablets, expressed in mass units, will thus remain approximately identical. Hence, the relative standard deviation (RSD) of quarter-tablet weights will nearly double when breaking half-tablets into quarter-tablets.

Key words: scored tablets, tablet breakability, weight uniformity, statistical control, compression validation, robustness development

INTRODUCTION

Tablets with single or multiple score lines allow the administration of a portion of the tablet, which can then be considered as the unit dosage of the drug. Pharmacopoeial and other regulatory documents acknowledge this, *e.g.* the EP monograph *Tablets*[(1)] clearly defines that tablets may have breakmarks. In the production section of the current EP monograph (not in the testsection), it is explicitly stated that for tablets for which a subdivision is authorized, it must be demonstrated to the satisfaction of the competent authority that the subdivided parts comply either with content-uniformity (test A of EP 2.9.6.) or mass-uniformity (EP 2.9.5.) as appropriate. From this definition, it is clear that uniformity of tablet portion after breaking or splitting is certainly a quality attribute of the tablet, although it may not be considered as a regulatory obligatory routine QC test much the same as with microbiological purity. Both examples relate to the concept of parametric release. This is confirmed by the recent proposal[(2)], stating that the breakability has to be assessed during development using mass-uniformity criteria. In the development pharmaceutics guidance CPMP/QWP/155/96[(3)], the general regulatory opinion of the authorities is expressed, stating that the practice of administration of half-tablets should be discouraged. However, the same sentence also says that where such an approach has been justified in the application, which can be based upon posology or ease of intake considerations[(2)], it is important to demonstrate the maintenance of dosage uniformity within tablet halves by breakability tests. The EC-Variations[(4)] demonstrates the abundant practice by the industry and careful acceptance by the authorities of the use of broken tablet-parts, where in the case of a change in tablet dimension (type I variation, number 40), breakability data at release as well as at end-of-shelf-life are ultimately required. Examples of the current general regulatory decisions are found in the scientific EPAR discussions of the EMEA, *e.g.* CPMP/5346/02[(5)] or CVMP/265/00[(6)].

In the US, scoring is being addressed in several FDA documents, *e.g.* MAPP5223.2 *Scoring configuration of generic drug products*[(7)]. The uniformity of dosage units (USP/NF 905) described in the USP/NF[(8)] is in general based on the weight combined with the assay of 10 dosage units. If only the weights of units are considered, compliance *sensu strictu* with the USP requirements cannot be demonstrated as such. However, if consistent content homogeneity has been demonstrated by the validation results, the weight is considered a valid dose-uniformity quality attribute.

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The regulatory interest was fuelled by an increasing number of researches and discussion papers. Previous papers often gave the breakability results and recommendations from a general pharmaco-therapeutic practical point of view[9-10], while developmental, manufacturing and quality technical aspects were seldomly discussed[11-16]. To our knowledge, the robustness of breakability variability as part of the manufacturing process characterization has not yet been studied and reported. Certain research documents discuss a number of alternative acceptance criteria[17-18], generally allowing relative mass variations of broken tablets to be higher than that of intact tablets.

In addition to the technical aspects, pharmaco-economic, in-use and clinical considerations such as posology regimen, therapeutic window, pharmaco-kinetics and related PK/PD-relations have to be taken into account to justify the existence of a breaking line and to qualify the applied breakability acceptance criteria with the regulatory-pharmacopoeial texts as general guidelines[19-21].

A previous paper[22] investigated the influence of breakability methodology on mass uniformity of half- and quarter-tablets, as well as different data acquisition, evaluation and criteria-approaches, using a discriminative model tablet.

As part of the manufacturing development, the aim of this study was to investigate the influence of operational compression parameters during tabletting on the weight variabilities of half- and quarter-tablets, as well as to compare variously sized tablets of identical composition. This study provided a practical example of robustness-verification.

MATERIALS AND METHODS

I. *Drug Dosage Form Tested*

Two types of tablets having identical composition and originating from the same granulate were used in this study. The tablets differed in size (400 mg tablet versus 1000 mg tablet). All tablets were flat and cross-scored on one side, and contained 22% m/m drug substance. The tablets were for veterinary use in the treatment of dogs: the large weight variety in the target animal species justified the requirement of a cross-scored tablet for the intended purpose.

The tablets were manufactured by typical wet granulation process using a fluidized bed granulator (Glatt WSG120) followed by powder blending in a conical blender and compression performed with a rotary tablet press equipped with 32 stations (Kilian RTS32). The tablets consisted of microcrystalline cellulose, sorbitol and dried yeast lysate as main excipients. It was previously shown that this tablet was suitable as a discriminative model tablet relative to breakability[22].

The ranges of operational compression settings for manufacturing the 400 mg and 1000 mg tablets were chosen for a manufacturing robustness assessment validation of the compression stage. Therefore, the ranges were as wide as practically possible around the operational target-values with the available compression equipment. The compression speed for the 400 mg tablet varied between 50 and 90 thousand tablets per hour, whereas for the 1000 mg tablet it varied between 40 and 70 thousand tablets per hour. The compression force was manually adjusted, with the maximum at 40 kN for the used punches. Force settings were ranked on the equipment as high, medium and low. Tablet hardness was determined as the force required to break the tablet in a diametral compression test (*i.e.* the tablet crushing strength), using a PharmaTest equipment (type PTB301).

All tested tablets were flat and round, with 11 mm (400 mg tablet) and 15 mm (1000 mg tablets) diameters. The score lines applied in these cross-scored tablets had the following specifications[23]:

1. 400 mg tablets: W (width) = 0.88 mm, D (depth) = 0.42 mm, θ = 45° and R (engraving cut radius) = 0.05 mm.
2. 1000 mg tablets: W = 1.20 mm, D = 0.58 mm, θ = 45° and R = 0.05 mm.

II. *Breakability Test Method*

The following breakability test method was applied in this robustness study by the manufacturing operators: hold the tablet between the thumb and index-finger of each hand on either side of the score line, with the score line facing upwards and without inserting the nail. Separate into two halves by a rotating movement at the joint of the first two phalanges of the index-fingers.

To validate the used breakability test method, a slightly alternative breakability test method was also applied on the 400 mg tablet compressed under medium speed and force in more controlled laboratory conditions by three persons, giving similar results (see Results and Discussion section): The two halves were separated by breaking open the tablet at the score line side.

The methods described above are applicable to break the tablets into half-tablets, as well as to break half-tablets into quarter-tablets.

III. *Data Acquisition*

The previously described protocol[22] contains all possible weight information and allows detailed investigations of all possible relationships such as left-right differences, half-to-quarter interactions. However, this protocol is not feasible and justified for routine validation purposes. For the data evaluation currently used, only one half-tablet is retained per tablet, taken alternatively from the right and left hands. Similarly, only one quarter-tablet is retained per tablet, taken alternatively from each of the 4 possible quadrants.

Breakability losses obtained from breaking tablets into half-tablets and into quarter-tablets had been investigat-

ed[22]. A mean loss per tablet of 0.3% was obtained in previous study with the applied breaking methods. Hence, for practical purposes, the losses were not measured nor included in the currently reported results.

The calculation of tensile strength σ_t ($N \cdot mm^{-2}$ or MPa) for these flat-faced tablets was determined from the mean force value F (N) at which the tablet fractured under diametral compression (hardness value), according to the following equation $\sigma_t = 2F/(\pi Dt)$, where D is the tablet diameter (mm) and t is the overall tablet thickness (mm)[24]. As the score-depth is only 0.42 mm for the 400 mg tablets and 0.58 mm for the 1000 mg tablets, we have again neglected this small deviation for practical reasons, and used the thickness of the whole tablet as t value in the tensile strength equation.

IV. *Data Analysis*

Excel was used for data preparation and processing. Statistical analyses were performed with SPSS 9.0. For all statistical tests, a critical significance level $\alpha = 0.05$ was chosen.

Graphical exploration of the data was performed *i.a.* by boxplots, visualizing the median, the 25th and 75th percentile (Tukey's hinges between which 50% of the values are located), and the smallest and largest values that aren't outliers. The outliers are individually represented in the figures, classified as the values differing more than 1.5 box-lengths from the 75th percentile (denoted as o in the Figures) and the values differing more than 3 box-lengths from 75th percentile (denoted as * in the Figures).

RESULTS AND DISCUSSION

Figures 1 and 2 present summarizing boxplots with the weights of half- and quarter-tablets for each of the tested operational compression settings from 1000 mg and 400 mg tablets respectively. Further, a tabular overview of the corresponding data (mean and standard deviation), tablet

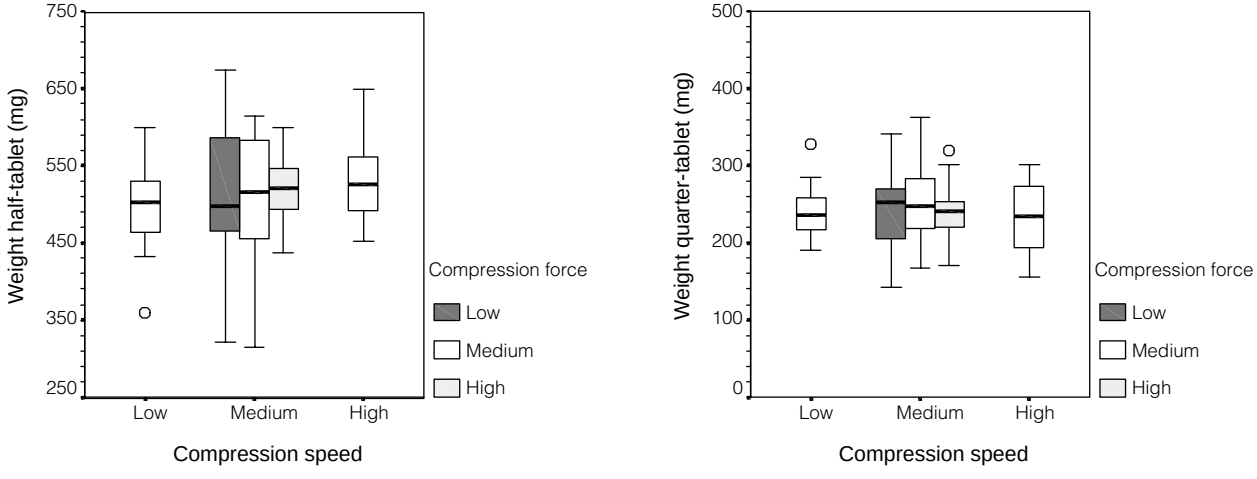

Figure 1. Boxplots with weights (mg) of half- and quarter-tablets from 1000 mg tablets of three operational compression speed and force settings (n = 20 per operational setting).

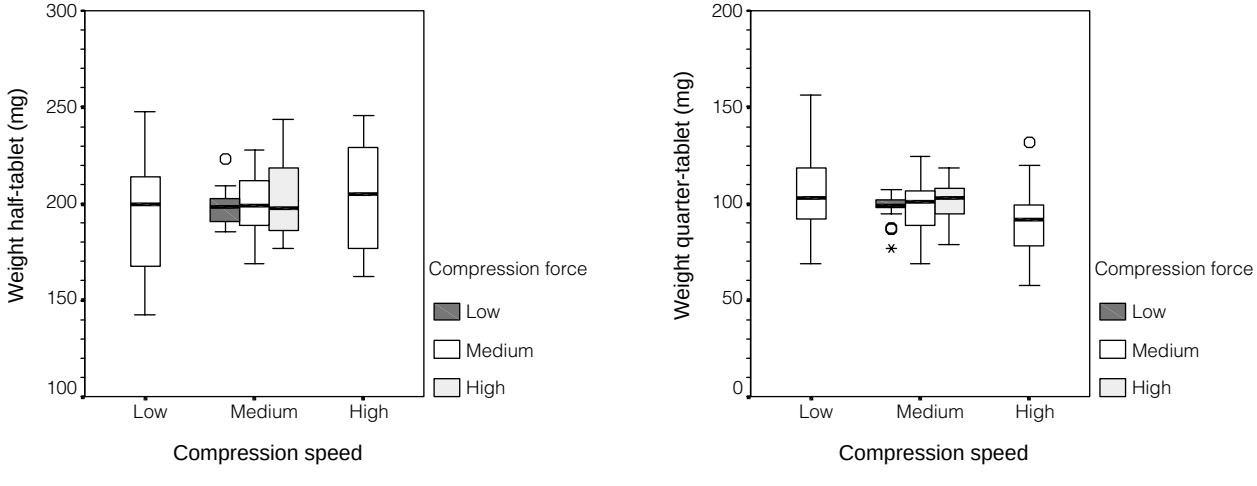

Figure 2. Boxplots with weights (mg) of half- and quarter-tablets from 400 mg tablets of three operational compression speed and force settings (n = 20 per operational setting).

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Table 1. Effect of operational compression conditions (speed and force) on tablet characteristics

Test tablet	Compression speed[a]	Compression force[b]	Weight (mg) (mean ± S.D.) (n = 20)			Hardness (N) (mean ± S.D.) (n = 10) (tensile strength in MPa)	Mean thickness (mm) (n = 10)
			Whole tablets	Half tablets	Quarter tablets		
400 mg tablet	Medium	Medium	400.1 ± 2.6	200.9 ± 15.5	98.2 ± 13.9	71.2 ± 2.8 (1.12)	3.68
	Low	Medium	402.8 ± 2.8	195.0 ± 30.0	105.2 ± 20.0	71.1 ± 2.5 (1.12)	3.69
	High	Medium	397.9 ± 3.3	203.0 ± 27.6	91.5 ± 18.6	68.6 ± 3.3 (1.07)	3.70
	Medium	Low	396.8 ± 3.3	197.8 ± 9.3	98.2 ± 7.3	47.4 ± 2.1 (0.71)	3.85
	Medium	High	399.3 ± 3.4	201.4 ± 18.5	101.9 ± 11.1	86.0 ± 3.2 (1.40)	3.56
	Overall[c]		399.4 ± 3.1	199.6 ± 20.2	99.0 ± 14.2	68.9 ± 2.8 (1.08)	3.70
1000 mg tablet	Medium	Medium	1005.6 ± 6.3	509.4 ± 81.0[d]	249.6 ± 49.9	120.2 ± 5.5 (1.01)	5.07
	Low	Medium	999.2 ± 6.9	496.7 ± 54.6	242.6 ± 32.5	116.7 ± 5.6 (0.979)	5.06
	High	Medium	991.5 ± 8.5	529.7 ± 54.6	232.9 ± 46.8	113.0 ± 3.8 (0.950)	5.05
	Medium	Low	1000.7 ± 6.6	513.3 ± 96.5[d]	243.1 ± 54.9	77.3 ± 4.6 (0.614)	5.35
	Medium	High	1003.9 ± 7.2	521.1 ± 41.7	239.8 ± 37.9	131.1 ± 5.2 (1.11)	5.03
	Overall[c]		1000.2 ± 7.1	514.0 ± 65.7	241.6 ± 44.4	111.7 ± 5.0 (0.928)	5.11

[a]For the 400 mg tablets: low, medium (= standard setting) and high speed are 50, 70 and 90 thousand tablets/hr, respectively.
For the 1000 mg tablets: low, medium (= standard setting) and high speed are 40, 50 and 70 thousand tablets/hr, respectively.
[b]Arbitrary setting on used compression equipment.
[c]Mean of all values.
[d]This high standard deviation results from the fact that the obtained breaking line does not coincide with the score-line: at least one half-tablet weight was deviating more than 30% of the target weight.

weight, hardness and thickness data are given in Table 1.

Looking at the breakability results, with much higher variabilities than the pharmacopoeial criteria which in its most general form requires a relative standard deviation of below 6.0% for n = 20 tablets [1,2,8,22], it must be emphasized that the investigated tablets are for veterinary purposes only and that they are presented with only a one-sided break-line, which contrasts the human tablet situation where quite often, double-sided break-lines are applied.

The relationships between the observed variabilities in tablet, half-tablet and quarter-tablet weights (expressed as standard deviations) on the one hand, and the tablet related characteristics hardness and thickness on the other hand can be visualized with a scatterplot matrix in Figure 3.

From this scatterplot matrix, little relationship was observed between hardness or thickness and the individual standard deviations. However, there did appear to be a relationship between the standard deviations of half- and quarter-tablets.

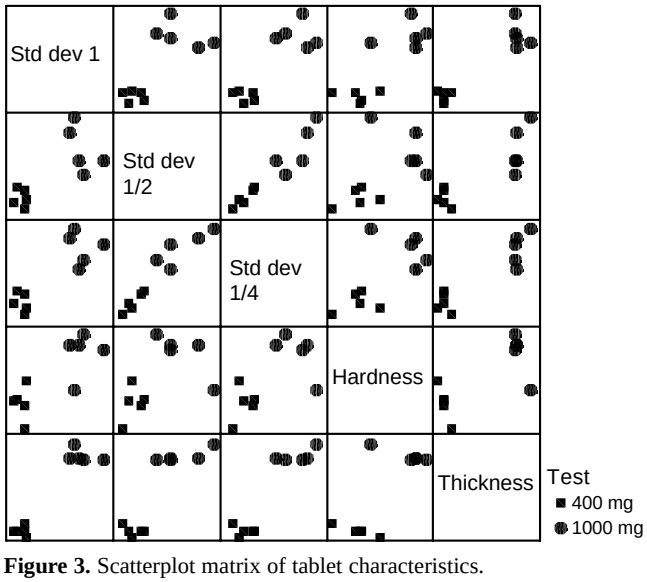

Figure 3. Scatterplot matrix of tablet characteristics.

Seen the fractional experimental design, the effects of the investigated factors within each tablet group were independently analyzed using one-way ANOVA models with 3 factor levels within each factor (*i.e.* no interactions studied). Within the 400 mg tablet group, the effect of compression speed and force on the half-or quarter-tablet weights was not statistically significant. Similar conclusions are obtained within the 1000 mg tablet group. Excluding the outliers (see footnote under the tables), the same statistical conclusions were obtained in the 1000 mg tablet group. The homogeneity of variance, a basic assumption for ANOVA, was confirmed for each of the ANOVA models using the Levene's test[26]. The results showed that the compression speed and force did not have a significant effect on the weights of the broken tablets. It was thus concluded that this manufacturing step is sufficiently robust to produce tablets with consistent breakability characteristics, leading to reproducible mass uniformity of broken tablets. Particle characteristics such as particle size distribution and powder flowability, which can affect the packing behaviour during compression and influence mass uniformity phenomena, were not part of this study on the operational tabletting stage.

Table 1 demonstrates that the tablet hardness and thickness are related to the compression settings. Using one-way ANOVA analysis followed by the Duncan test for multiple comparisons of means, it was experimentally concluded that unlike the compression force, the compression speed within the current operational settings had no significant effect on the hardness of the investigated tablets. Our observation on constant mass per tablet for the different compression set-

tings showed that the effect on hardness was inversely related to the thickness of the tablets (see Figure 3). Although in general, the lower the compression speed, the longer the contact time leading to increasing tablet strength, our results are constrained within certain operational conditions and are aimed at the evaluation of manufacturing robustness of partial tablets uniformity. In addition, the tablet friability was also investigated according to the European Pharmacopoeia (data not shown) and found to be between 0.0% and 0.2%. No observable effects of the investigated compression settings on the friability were observed. The hardness of tablets is more sensitive than the breakability variability towards the operational compression speed and force settings, confirming the usefulness of this measurement for in-process compression control.

The calculated tensile strengths for the investigated tablets ranged between 0.614 and 1.40 MPa. No direct relationship could be observed between the breakability standard deviation and the calculated tensile strength σ_t. However, since this conclusion is *sensu strictu* only valid for the investigated tablets and the crushing, diametrical hardness test method, using other tablets or even changing the test method, *e.g.* knife-edge cutting or three-point bending test, could lead to other conclusions.

From the data presented here, tablet and partial tablet weight variability in function of tablet size (400 mg versus 1000 mg) and the specific relationship between half-tablet and quarter-tablet variabilities for these 2 tablets are further investigated.

The 400 mg tablets, compressed with medium speed and force settings, were broken into half-tablets and quarter-tablets using an alternative, more controlled method in the laboratory. The tablet and broken-tablet variabilities obtained from both test-methods were statistically compared with F-tests. Two-sided significance levels p = 0.18 and p = 0.32 were obtained for half-tablets and quarter-tablets comparison respectively, confirming the similarity between the two breakability test methods.

It was observed that the whole tablet, half-tablet and quarter-tablet weight variability (expressed as standard deviation) decreased with decreasing tablet size (see Table 1). More specifically, the ratio of both tablet weights was 2.5 (1000.2 mg versus 399.4 mg), whereas the corresponding ratios of the standard deviations of whole tablet, half-tablet and quarter-tablet weights (together with their 99% confidence interval) were respectively 2.3 (1.8 - 3.0), 3.3 (2.5 - 4.3) and 3.1 (2.4 - 4.1) (see overall values in Table 1). This result indicated that the tablet and part-of-tablet weight variability (expressed as standard deviation) was a linear function of tablet weight for the currently investigated model tablets. This was in correspondence with the results obtained in a similar study[21] with a palatable bisected tablet: the half-weight variability was found to be 51 mg (17%RSD), 84 mg (11%RSD) and 204 mg (13%RSD) for the half-tablets of 600 mg (mean half-weight = 299.7 mg), 1500 mg (mean half-weight = 757 mg) and 3000 mg (mean half-weight = 1529 mg) tablets of identical shape. The breakability variability of the currently investigated dose-proportional tablets is thus a peculiar case of heteroscedasticity with constant relative standard deviation[25]. It is to be pointed out that a strict theoretical and universally applicable comparison of the two tablet sizes can in principle be confounded with the speed-factor, as both were simultaneously different in this study. However, from the presented data, it appears that the relation of the breakability variability with the tablet mass for dose-proportional tablets is a useful empirical first estimation.

The relationship between the half-tablet variability and quarter-tablet variability within one tablettype was further investigated by calculating the ratio of standard deviation of quarter-tablets to the standard deviation of half-tablets. A 95% confidence interval was constructed using an F-distribution. The results are tabulated in Table 2.

A previous paper[22] hypothesized that the variability of partial tablets (expressed as variance) within one tablet is a linear function of the length of the score (*i.e.* the longer the score, the higher the variability of the corresponding partial tablet's weight). Based on this hypothesis and disregarding the whole tablet variability, it was deduced that the theoretical expected ratio of quarter-tablet to half-tablet variability is 0.87. The experimental results (see last column in Table 2) are in-line with this theoretical value.

In general, the following mathematical model is applicable: If the variabilities of tablets, half-tablets and

Table 2. Weight variabilities related to breaking tablets into half-tablets and half-tablets into quarter-tablets (expressed as standard deviations) and ratio (with 95% confidence interval) of $s_{1/4}$ to $s_{1/2}$ for two different test tablets and various compression conditions

Test tablet	Compression speed	Compression force	s_1	$s_{1/2}$	$s_{1/4}$	s_{B1}	s_{B2}	Ratio $s_{1/4}$ to $s_{1/2}$
400 mg tablets	Medium	Medium	2.6	15.5	13.9	15.4	11.5	0.90 (0.56, 1.43)
	Low	Medium	2.8	30.0	20.0	30.0	13.2	0.67 (0.42, 1.06)
	High	Medium	3.3	27.6	18.6	27.6	12.5	0.67 (0.42, 1.07)
	Medium	Low	3.3	9.3	7.3	9.2	5.6	0.78 (0.49, 1.25)
	Medium	High	3.4	18.5	11.1	18.4	6.1	0.60 (0.38, 0.95)
1000 mg tablet	Medium	Medium	6.3	81.0[a]	49.9	80.9	29.2	0.62 (0.39, 0.98)
	Low	Medium	6.9	54.6	32.5	54.5	17.6	0.60 (0.37, 0.95)
	High	Medium	8.5	54.6	46.8	54.4	38.0	0.86 (0.54, 0.95)
	Medium	Low	6.6	96.5[a]	54.9	96.4	26.2	0.57 (0.36, 0.90)
	Medium	High	7.2	41.7	37.9	41.5	31.6	0.91 (0.57, 1.44)

[a]This high standard deviation results from the fact that the obtained breaking line does not coincide with the score-line: at least one half-tablet weight was deviating more than 30% of the target weight.

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quarter-tablets are respectively called s_1^2, $s_{1/2}^2$ and $s_{1/4}^2$, then the following mathematical relationships exist:

$$s_{1/2}^2 = \frac{s_1^2}{4} + s_{B1}^2 \quad \text{.....(1)}$$

$$s_{1/4}^2 = \frac{s_{1/2}^2}{4} + s_{B2}^2 = \frac{s_1^2}{16} + \frac{s_{B1}^2}{4} + s_{B2}^2 \quad \text{.....(2)}$$

With $\frac{s_1^2}{4}$: Intrinsic variability of half-tablets inherited from whole tablets

s_{B1}^2 : Additional variability due to breaking a whole tablet into half-tablets

$\frac{s_{1/2}^2}{4}$: Intrinsic variability of quarter-tablets inherited from halves.

s_{B2}^2 : Additional variability due to breaking a half-tablet into quarter-tablets.

The variabilities s_{B1}^2 and s_{B2}^2 induced by the breaking process can be calculated from equation (1) and (2) and the experimentally determined variances s_1^2, $s_{1/2}^2$ and $s_{1/4}^2$. An overview of the above mentioned variability components is given in Table 2.

Under the hypothesis that the variability of partial tablets (expressed as variance) is a linear function of the length of the score, the following relationship for a cross-scored round tablet is valid:

$$s_{B2}^2 = \frac{1}{2} s_{B1}^2 \text{ or } s_{B2} = 0.71 \times s_{B1} \quad \text{.....(3)}$$

In two particular cases (indicated in footnote [a] in Table 2), individual half-tablets weights were more than 30% different from the theoretical values due to irregular tablet breaking, in which the breaking line did not coincide with the score line. This off-score breaking behavior is beyond the scope of the theoretical hypothesis (see equation 3) and therefore these two cases are excluded from the linear regression model. Additional not reported data obtained with the alternative breakability method were also included in the linear regression model. The resulting experimental correlation between s_{B1} and s_{B2} is visualized in Figure 4, and the corresponding regression equation is (95% confidence intervals between brackets):

$$s_{B2} = 4.3\ (-4.6 \text{ to } 13.2) + 0.51\ (0.21 \text{ to } 0.80)\ s_{B1} \quad \text{.....(4)}$$

Therefore, the hypothesis that the variability of partial tablets (expressed as variance) is a linear function of the score length is confirmed by the available data.

Consequently, it may be concluded that the variability of broken tablets is mainly determined by the half-tablet variability, and that breaking half-tablets into quarter-tablets does not imply increase in variability. However, if relative standard deviations are considered, the RSD of quarter-tablets is approximately twice the variability of half-tablets. Moreover, this finding may also have consequences for the final choice of the form of the tablet: unlike a round tablet, will an oblong tablet have smaller and constant length of score.

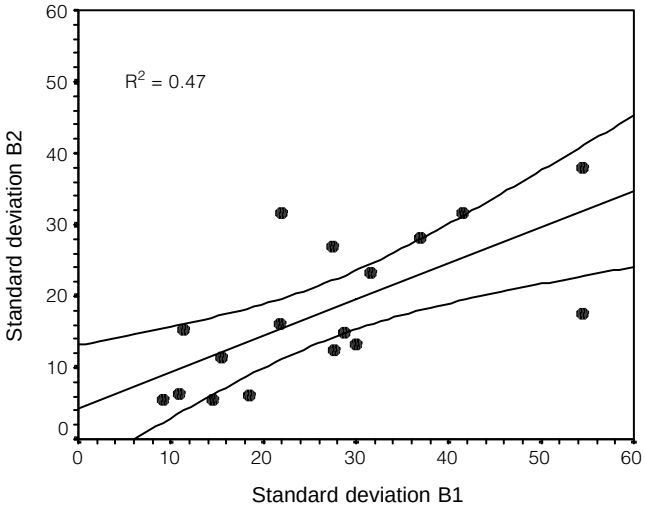

Figure 4. Scatterplot illustrating the correlation between the variability due to breaking tablets into half-tablets (B1) versus the variability due to breaking half-tablets into quarter-tablets (B2). Both variabilities are expressed as standard deviation.

While this study focused only at the operational tabletting robustness, there are still numerous remaining issues. A global mechanistic model is one of the ultimate goals yet awaiting further exploration. This model will need to consider additional factors like score line characteristics, particle properties such as particle size and size distribution and its densification packing behavior, bonding mechanisms of plastic deformation, brittle fragmentation, and relaxation phenomena. Moreover, the criteria are still a matter of discussion (for example reference 27), but should ultimately reflect a risk assessment specific for the tabletted drug under consideration.

CONCLUSIONS

The purpose of this investigation, as part of a case study of a tablet manufacturing validation, was to study the influence of the operational tabletting parameters (speed and force, and resulting physical tablet characteristics) on the weight variability of half- and quarter- tablets. The secondary purpose was to determine the possible relationship between the variabilities of the half-tablets and the quarter-tablets.

Using 400 mg and 1000 mg discriminative flat model tablets, we have demonstrated that variation of the compression speed and force around their target values does not significantly influence the weight variability of half- and quarter-tablets. Moreover, it was observed that tablet hardness is more sensitive towards the operational tabletting speed and force, confirming the discriminative power and thus possible usefulness of this physical parameter for in-process compression control.

The breakability methodology was cross-validated: a highly controlled test method executed in the laboratory, gave similar results as the applied method executed in an in-process situation at the tablet manufacturing plant.

In correspondence with other breakability studies, it was confirmed that for tablets with identical composition but different in size, the standard deviation of whole and partial tablet weights is linearly related to the tablet weight.

There exists a strong correlation between the variability of half-tablets and that of quarter-tablets. The theoretical model presented in a previous paper was further refined and verified with the current data, and it was confirmed that the additional variance induced by breaking is a linear function of the break-line length. As a consequence, the standard deviation of half- and quarter-tablets, expressed in mass units, will thus remain approximately identical for round tablets, and hence the relative standard deviation (RSD) of quarter-tablet weights will always be higher when breaking half-tablets into quarter-tablets.

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