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Research paper

Distribution of crushing strength of tablets

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Abstract

The distribution of a given set of data is important since most parametric statistical tests are based on the assumption that the studied data are normal distributed. In analysis of fracture mechanics the Weibull distribution is widely used and the derived Weibull modulus is interpreted as a material constant. However, the estimation of this parameter is laborious and subject to estimation problems. It is shown that the Weibull modulus is inherently connected to the coefficient of variation and that the information obtained from the modulus is unclear. The distribution of crushing strength data from nine model tablet formulations and four commercial tablets are shown to follow the normal distribution. The importance of proper cleaning of the crushing strength apparatus is demonstrated.

Keywords: Methodology; Weibull distribution; Normal distribution; Crushing strength; Tablets; Weibull modulus; Coefficient of variation

1. Introduction

When W. Weibull in 1951 presented his paper 'A statistical distribution function with wide applicability' [1] he may not have realized how predicative this title would be. A basic search in the ScienceDirect database (Elsevier) reveals more than 500 articles from 1997 to 2001 where the Weibull distribution is used. The scientific disciplines are spread from economics [2] through meteorology [3] to microbiology [4]. Most frequently, however, the Weibull distribution appears in material sciences like ceramics and metallurgy [5–9] where this method predominates in the analysis of the heterogeneity in fracture mechanics. Critical scientists have warned against this widespread use of the Weibull distribution [8,10,11]. Gorski [10] was concerned about the lack of consistency in the estimation of the parameters from a given set of data. According to Gorski: "...the great flexibility of the Weibull function, so often praised, is in reality, a serious liability" and "To date, nobody has been able to present a sufficient argument for the Weibull case".

In pharmaceutical sciences the Weibull function has been implemented in several different fields. The variability of tablet tensile strength [12–14] or pellet strength [15] is reported to follow the Weibull distribution. Under the name Rosin-Rammler-Sperling-Bennett or RRSBW the function is used in particle size analysis [16,17]. Furthermore, the function is used in dissolution rate modelling [18,19], stability testing [20], fitting of force–time profiles in compression studies [21] and in the characterization of the crushing strength–compaction pressure relationship [22].

The general concept in Weibull analysis of fracture mechanics is based on the simple principle that the strength of a chain is determined by the weakest link. This results in application of the extreme value distributions described by Gumbel [23] among which the Weibull distribution or the third asymptotic distribution of smallest values has gained most attention. A logical consequence of this principle is that longer chains or threads will be weaker than short ones due to the greater probability for weak bonds. There is no indication, however, that large tablets are weaker than small ones. On the contrary, the crushing strength is normalized by dividing by the dimension of the tablet to obtain the tensile strength.

Daniels [24] developed an alternative physical model for the breaking strength of bundles of n parallel threads: After rupture of one thread the load is still supported by the remaining threads until the next one breaks, and so on. If S is the total load and x_i $(i = 1, 2, 3...n)$ is the breaking strength of the individual threads, then it can be shown that S^*, the breaking load of the bundles of n threads, is normally distributed. Thus, the analogy to the crushing strength of tablets where the bonds between individual parti-

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cles substitutes the strength of the threads in a bundle seems to be clear.

The statistical distribution of tablet crushing strength or tensile strength is important since parametric inference tests like the *t*-test, *F*-test, analysis of variance and regression analysis require normal distribution of the random variable. The primary aim of this investigation is therefore to investigate whether the normal distribution is representative for a random sample of tablet crushing strength data and whether the Weibull modulus is more informative as a material characteristic than the coefficient of variation.

2. Theory

2.1. The Weibull and the normal distribution parameters

The three-parameter Weibull distribution, We(β, k, x_0) has the density function:

$$f(x) = \frac{k}{\beta}\left(\frac{x - x_0}{\beta}\right)^{k-1} \exp\left[-\left(\frac{x - x_0}{\beta}\right)^{k}\right] \quad (1)$$

and cumulative distribution function:

$$F(x) = 1 - \exp\left[-\left(\frac{x - x_0}{\beta}\right)^{k}\right] \quad (2)$$

where β is the scale parameter, k is the shape parameter or the Weibull modulus and x_0 the position parameter. When the position parameter equals zero the equations describe the two-parameter Weibull distribution which is most frequently used in fracture mechanics. For $k = 1$ and $x_0 = 0$ the equations describe the exponential distribution.

The mean value *E(x)* of the Weibull distribution is:

$$E(x) = x_0 + \beta \times \Gamma\left(1 + \frac{1}{k}\right) \quad (3)$$

where Γ is the gamma-function.

The variance *V(x)* is:

$$V(x) = \beta^2 \times \left[\Gamma\left(1 + \frac{2}{k}\right) - \Gamma^2\left(1 + \frac{1}{k}\right)\right] \quad (4)$$

The flexibility of the distribution is illustrated in Fig. 1 where the two-parameter Weibull distribution densities with three different sets of parameters are shown with the skewness of We$(5, 2, 0) = 0.605$, of We$(8, 3.44, 0) = 0$ and of We$(13, 6, 0) = -0.364$. The positive skewness corresponding to upwards-tailed probability curves is characteristic in particle size distributions and dissolution rate curves, so the shape parameters in these fields are mostly under 3.44. Negative skewness and thereby k values higher than 3.44 are often seen in fracture mechanics. It is characteristic that the patterns in Fig. 1 does not change with $x_0 > 0$, as the curves are displaced in parallel along the x-axis. The symmetrical or pseudosymmetrical [23] Weibull curve in Fig. 1 can hardly be distinguished from the normal curve with mean = 7.2 and standard deviation = 2.4 (No(7.2, 2.4)), and have only slight deviations at the upper and lower bounds.

Several investigators have compared the applicability of different statistical distributions with focus on the Weibull and the normal distribution to fit fracture data of various materials [5–9,12,25,26]. The general conclusions in these investigations are that the normal distribution fits the data to the same degree or better than the Weibull distribution. This does not imply that all fracture test are normally distributed but indicates that with a limited sample size it could be impossible with known inference tests to verify that the Weibull distribution gives a better approximation to the data. Only one reference is found where the normal distribution is neglected as a suitable descriptive distribution [26], but this conclusion is drawn without any statistical proof.

If a normally distributed random variable No(100,15) is mapped in a Weibull plot (Fig. 2), a curve concave to the x-axis is generated through the transformation. Without critical examination of the residuals this deviation might be disregarded and the Weibull model could be accepted.

2.2. Estimation of the parameters

While the parameters in the normal distribution No(μ,σ) are easily calculated, the problems in estimation of β and in particular the shape parameter k in the two-parameter Weibull distribution have been subject to much examination. Three estimation methods: the linear regression of transformed variables, the moment method and the maximum-likelihood method are reported to give different results [10,27–29].

In the linear regression technique the cumulative frequency *F(x)* in the two-parameter Weibull distribution is transformed from Eq. (2) to:

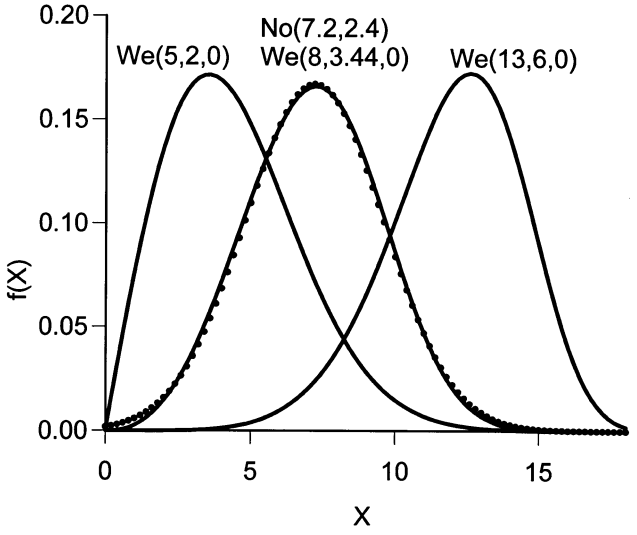

Fig. 1. Weibull density distributions We(β, k, x_0) with different parameters β, k, x_0 (with $x_0 = 0$) and the normal density distribution No(mean, standard deviation) equivalent to the symmetrical Weibull curve (dotted curve).

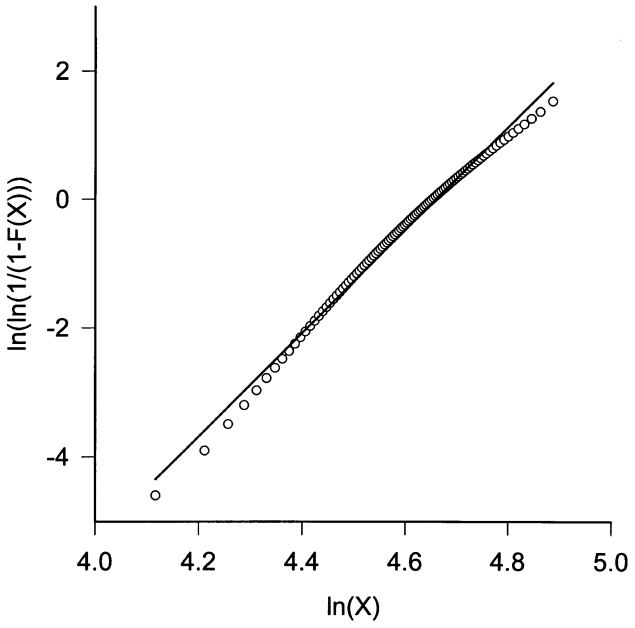

Fig. 2. Weibull plot of a normal distributed variable, No(100,15).

$$\ln\left[\ln\left(\frac{1}{1-F(x)}\right)\right] = k \times \ln(x) + k \times \ln(1/\beta) \quad (5)$$

from which the Weibull modulus is derived as the slope of the regression line. In Eq. (5) $F(x)$ can be estimated by four different methods [30,31] as $F(x) = j/(n+1)$, $F(x) = (j-0.3)/(n+0.4)$, $F(x) = (j-0.5)/n$ or $F(x) = (j-3/8)/(n+1/4)$, where n is the sample size and j is the observation number in increasing order.

2.3. Relation between the Weibull modulus and the coefficient of variation

In fracture mechanics, including the investigation of tablet and pellet strength, special attention is drawn to the Weibull modulus which is interpreted as a material constant [13,25] or more specifically as inversely proportional to the brittleness of the material [14,15]. It is generally recognized that the parameter expresses the variability or has relation to the coefficient of variation (CV) [9,31] and this relation is made quantitative by the equation $k \approx 1.2/\mathrm{CV}$ [12,32]. The relationship between k and CV is, however, more precise than this equation expresses. When the theoretical coefficient of variation of the two-parameter Weibull distribution is calculated by dividing the square root of Eq. (4) with Eq. (3) β disappears and the coefficient of variation only depends on k. This relation with k values ranging from 3.5 to 28.5 is illustrated graphically in Fig. 3.

A simple regression model ($k = 1.277 * 1/\mathrm{CV} - 0.59$) gives the residual standard deviation 0.01717. This is close to the equation reported by Ghong and Li [28] who found $k = 1.272 * 1/\mathrm{CV} - 0.525$ (k range 2–25). Although the relationship seems linear the residuals reveal a significant deviation. A better approach is obtained by the multiple regression equation Eq. (6) which predicts the shape parameter k with the residual standard deviation 0.00014.

$$k = 1.282 * 1/CV + 0.536 * CV - 0.72 \quad (6)$$

This distinct relationship between the Weibull modulus and the inverse coefficient of variation may explain why the shape parameter is considered to be a material characteristic. If the modulus is constant for a given material it means that the standard deviation is proportional to the mean value of the measurement, and consequently that the relative standard deviation or CV is constant. This phenomenon is frequently seen in many technical disciplines. With this unique relation Eq. (6) might be an alternative and simpler method in estimation of the Weibull modulus than other approaches. However, an interesting and more fundamental question is whether the information gained by the estimation of the Weibull modulus is more valuable and useful than the information obtained from the simple and well-known coefficient of variation. If the purpose of the Weibull analysis is to investigate or to compare the brittleness of materials or tablets, other techniques like the work of failure proposed by Lharib and Wells [33] seem more promising and less laborious.

3. Materials and methods

3.1. Materials

Microcrystalline cellulose (Avicel PH 102, FMC, Philadelphia, PA, USA), lactose monohydrate (Tablettose 80, Meggle Milchindustrie, Germany) and magnesium stearate (Unichem, Copenhagen, Denmark) were used as purchased.

Commercially available tablets, bevel edged, unscored and without engravings: Atropin 0.25 mg, conventional

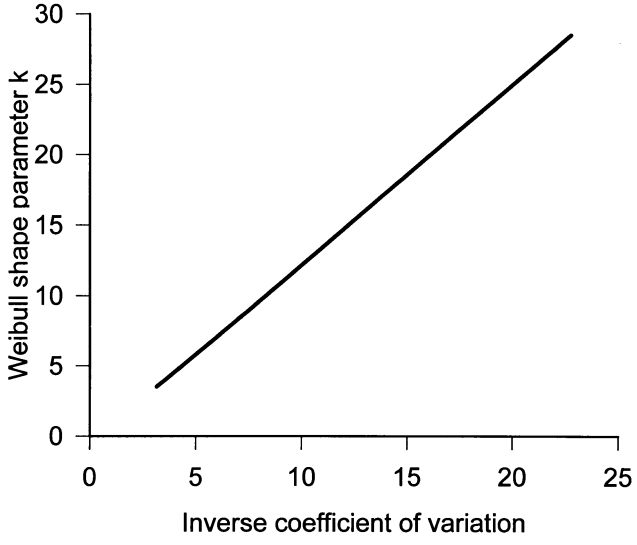

Fig. 3. Relationship between the Weibull shape parameter k and the inverse coefficient of variation.

Table 1
Basic characteristics of the investigated tablets

	Mass (mg)	CV (%)	Height (mm)	CV (%)	n
MCC50	395.8	0.87	4.39	0.19	20
MCC100	397.1	0.23	3.72	0.25	20
MCC150	398.1	0.23	3.43	0.36	20
MCCLAC50	399.2	0.24	3.24	0.37	20
MCCLAC100	397.3	0.37	2.94	0.26	20
MCCLAC150	398.2	0.21	2.76	0.35	20
LAC50	399.6	0.40	2.84	0.42	20
LAC100	397.6	0.38	2.67	0.88	20
LAC150	400.0	0.33	2.62	0.50	20
Atropin	97.7	1.60	2.68	1.25	100
Lucosil	664.1	0.44	4.21	0.28	25
Solvezink	1303	0.99	3.78	1.60	25
Alminox	953.2	0.65	4.50	0.34	25

tablets, diameter 6.0 mm, lot no. 10133011, Nycomed DAK A/S, Denmark; Alminox, chewing tablets, diameter 15.1 mm, lot no. 10132742, Nycomed DAK; Lucisil, conventional tablets, diameter 13.1 mm, lot no. 2500DK101, A/S Rosco, Denmark; Solvezink 45 mg Zn^{2+}, effervescent tablets, diameter 18 mm, lot no. 2003-11 BL260, Astra, Denmark.

3.2. Methods

Three model substances were used in the investigation: microcrystalline cellulose (MCC), lactose monohydrate (LAC) and a 50% w/w mixture (MCCLAC).

Powder (3 kg) was mixed in an Erweka Cubusmixer AR400 for 3 min at 30 rpm with 0.5% magnesium stearate. The powder blends were subsequently sieved through a 710-μm sieve.

Tablets were compressed on a Fette Exacta (60 rpm, 400 mg, 12 mm, flat-faced, bevel-edged punches). From all three mixtures tablets were compressed with target crushing strengths 50, 100 and 150 N. Details are given in Table 1.

The radial crushing strength ($n = 100$) was measured on a Schleuniger 6D (Schleuniger, Solothurn, Switzerland). The crushing strength measurements of Alminox tablets were repeated (Alminox1) without proper cleaning of the surface of the jaws as prescribed by the European Pharmacopoeia. The height of the first 20 tablets were measured on a Mitutoyo Indicator (Mitutoyo, Tokyo, Japan). If a correlation between the height and the crushing strength could be established ($P <= 0.01$), the height of all 100 tablets were measured (Atropin tablets).

3.3. Statistical analysis

Goodness-of-fit was tested with the χ^2-analysis (Statgraphics, Manugistics). The Kolmogorov–Smirnov test used for this purpose [5,7] is not accessible in this case since the premise that the parameters in the distribution are known a priori and not estimated is not satisfied. Microsoft Excel was used in regression analysis and other calculations. In the estimation of the shape parameter k through linear regression (Eq. (5)), the cumulative frequency was estimated as $F(x) = (j - 0.5)/n$.

4. Results and discussion

From the basic characteristics of the tablets shown in Table 1 it is apparent that the variations of mass as planned and expected are very low within the model tablets. The commercial tablets, presumably produced on a rotary tablet machine at a much faster rate have, in general, a higher although acceptable mass variability. The question is whether this variation in mass and the consequently variation in compaction pressure have a marked effect on the crushing strength variation. Attempts to correlate the weight and height of 20 tablets to the strength of the individual tablets were in general unsuccessful. Only the small Atropin tablets showed a significant positive correlation between height and crushing strength. Examination of the conditional distribution where the crushing strength is corrected for the tablet height did not, however, lead to any significant reduction in the standard deviation nor was the basic distribution of the crushing strength markedly influenced by this correlation.

The distributions of the crushing strengths of the three tablet batches with a target value of 50 N are shown in Fig. 4 with the calculated normal cumulative distribution. From a graphical judgement there is an excellent agreement between the observations and the normal curve and it is indicated that the variation of the pure lactose tablets (LAC50) is greater than the other formulations. The crush-

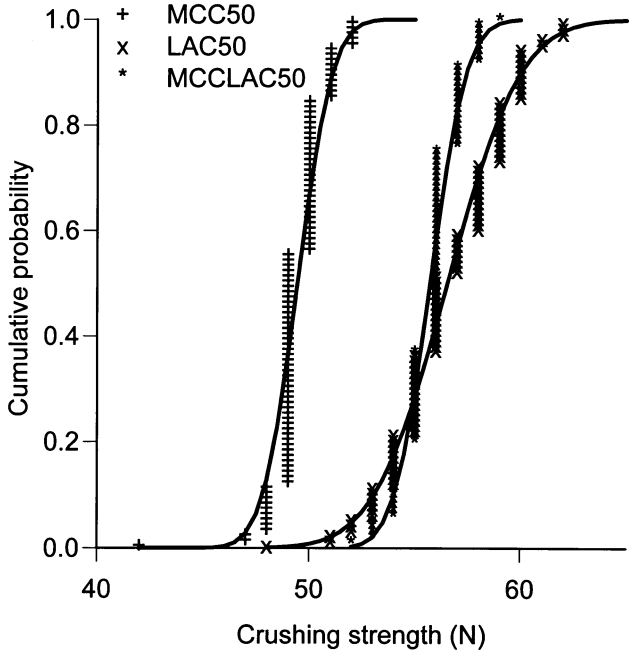

Fig. 4. Cumulative normal probability plot of crushing strength of three model tablets with target crushing strength 50 N.

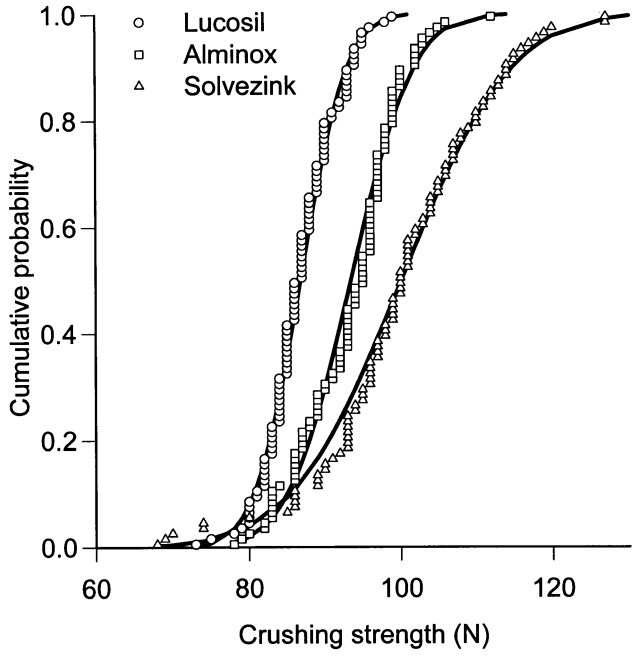

Fig. 5. Cumulative normal probability plot of crushing strength of three commercial tablets.

ing strength of three commercial tablets illustrated in Fig. 5 with the estimated normal distribution shows again a good fit to this distribution.

The main results of the investigation summarized in Table 2 show that the coefficient of variation is small for tablets made of microcrystalline cellulose and for the mixture with lactose. A pairwise *F*-test revealed no significant difference between the variances of these observations. In contrast, the variance of the brittle lactose tablets is significantly higher than the MCC and MCCLAC tablets ($P < 0.001$). The variation in crushing strength of the commercial tablets is, as expected, higher than the model tablets.

An estimated skewness close to zero of a given set of data indicates the symmetry of the underlying distribution and is one of the indications of a normal distribution. The skewness parameters in Table 2 are in general grouped around zero. The negative skewness in MCC50 is attributed to one single outlier (42N); if this is excluded then it is calculated to be −0.41 whereas the distinct skewness of Alminox1 is caused by a substantial number of small values (Fig. 6).

The χ^2-tests for goodness-of-fit are in favour overall of the normal distribution. One of the problems in this test is the correct grouping of data when the standard deviation is small compared to the resolution (1 N) of the measurements. The significant deviation from the normal distribution observed for MCC50 and MCCLAC50 tablets seems mainly to be caused by this classification problem.

According to the European Pharmacopoeia monograph: *2.9.8. Resistance to crushing of tablets*, care should be taken that all fragments of tablets have been removed before each determination. The importance of this statement is illustrated in an experiment where only a loose brushing of the jaws was performed and residues of crushed tablets were left sticking to the jaws. Alminox chewing tablets contain a large amount of mannitol, an excipient expected to adhere to metal surfaces, and were therefore selected for this test. The graphical depiction (Fig. 6) shows that the procedure results in a number of measurements in the lower end of the normal range of crushing strengths. This phenomenon might lead to a false acceptance of the Weibull distribution as an appropriate distribution for crushing strength measurements.

Even though the crushing strength is shown to be normally distributed it is possible to calculate a Weibull modulus from Eq. (5). The results of these calculations are shown in Fig. 7, where the correlation between the inverse coefficient of variation and the Weibull modulus is evident even when the distribution is normal.

5. Conclusions

- No statistical evidence against the hypothesis that the

Table 2
Results of the crushing strength measurements and of the statistical tests on the goodness-of-fit to the normal and the Weibull distribution ($n = 100$)

	Crushing strength (N)	CV (%)	Skewness	P (χ^2-test, normal)	P (χ^2-test, Weibull)
MCC50	49.4	2.58	−1.72	0.01	<0.01
MCC100	106.7	2.00	0.34	0.31	<0.01
MCC150	149.0	1.76	0.33	0.29	<0.01
MCCLAC50	55.7	2.39	−0.22	0.04	<0.01
MCCLAC100	103.0	2.29	0.09	0.18	<0.01
MCCLAC150	159.9	1.95	0.04	0.49	<0.01
LAC50	56.5	4.79	−0.23	0.25	0.13
LAC100	105.6	5.32	0.00	0.68	0.05
LAC150	134.5	5.02	−0.17	0.36	0.23
Atropin	38.8	11.14	0.69	0.22	<0.01
Lucosil	86.8	5.56	0.05	0.88	0.08
Solvezink	100.1	11.43	−0.41	0.30	0.23
Alminox	93.5	7.01	0.20	0.10	0.19
Alminox1	90.1	12.79	−1.49	<0.01	0.02

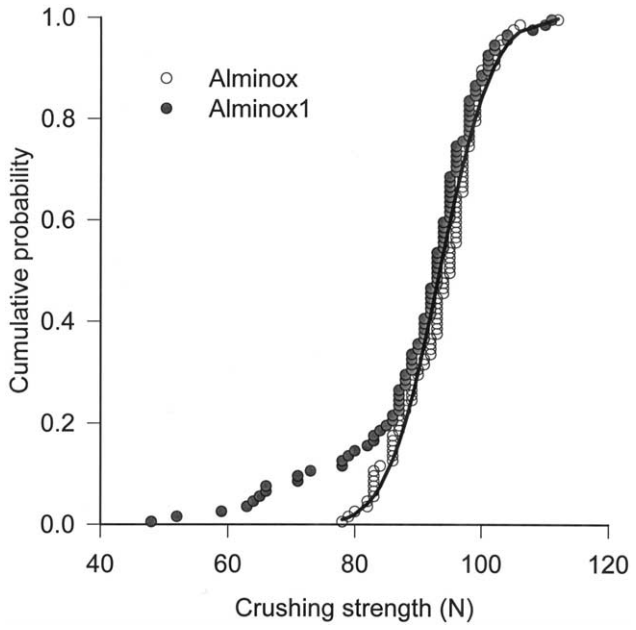

Fig. 6. Cumulative probability plot of crushing strength of Alminox tablets with and without proper cleaning of the jaws.

crushing strength of the investigated tablets were normally distributed was found.

- A strong and significant relationship between the Weibull modulus and the coefficient of variation of Weibull distributed data was found by theoretically based calculations. Approximately the same relationship was observed by analysis of experimental data even if the data were normally distributed.

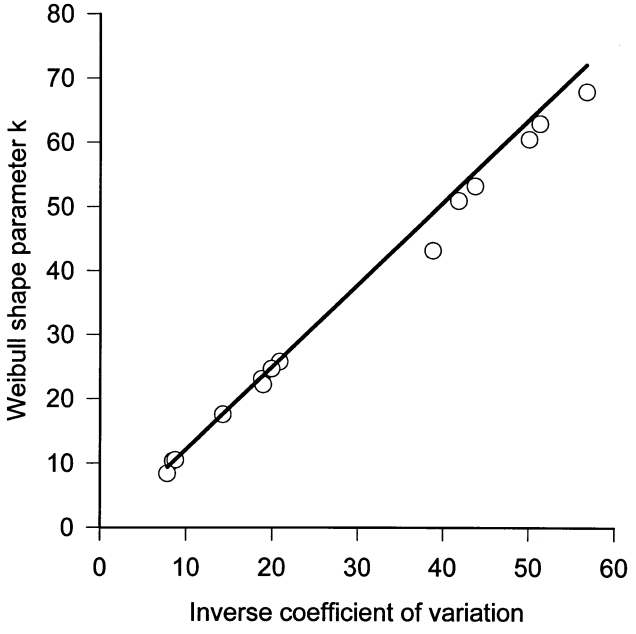

Fig. 7. Relationship between the estimated Weibull shape parameter k and the inverse coefficient of variation of the crushing strength measurements. The solid line is calculated from Eq. (6).

- A simple and fast method for estimation of the Weibull modulus based on the coefficient of variation is proposed.
- The importance of careful removal of fragments on the crushing strength apparatus was demonstrated.

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