Performance of Tablet Breaking Strength Testers I: Intralaboratory Comparison and Prediction

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Abstract □ Two motorized and two manually powered instruments were used to measure the breaking strength of tablets of three different shapes, each of two sizes and each at three different target breaking strength values. The experimental results were statistically analyzed. The uniformity among breaking strength testers was compared and these results are presented. A high correlation among devices was observed, allowing for the derivation of regression equations which could be used to predict precisely the breaking strengths from one instrument to another. Manually operated instruments tended to yield lower and more variable values than those of their electrically powered counterparts. Tablet shape and size were also found to affect the uniformity and consistency of tablet breaking strengths.

Keyphrases □ Tablet breaking strength—comparison among six different tablets and four hardness testers, effect of tablet tester, tablet size and shape, and target breaking strength □ Instruments for testing tablet breaking strength—characterization, comparison, effect of tablet shape and size, regression equations to predict breaking strength values □ Breaking strength testers for tablets—comparison among six different tablets and four hardness testers

Resistance to breaking, more commonly referred to as hardness, is one of the most important parameters measured as indexes of a pharmaceutical tablet quality. Available to the development pharmacist is a wide and ever increasing variety of instruments[1] designed for measuring this property.

Frequently during the development of a pharmaceutical tablet formulation, the researcher, either out of personal preference or because of availability limitations, uses one instrument for making breaking strength measurements on the formulation he or she is developing. In the interest of consistency, this instrument is usually used throughout the development program. The assignment of specifications for the final product is then based on the specific tablet tester used. It has been observed that the breaking strength of the same product can be different when a tablet tester other than the one specified is used for measurement. Such occurrences frequently arise in multinational organizations where more than one manufacturing site exists. Presently, there are no known procedures available to the pharmacist for converting specifications based on one device to those of another.

A resolution of this problem was, in part, the purpose of the work described here. More specifically, an attempt was made to: (*a*) characterize a selected number of tablet breaking strength testers with respect to their uniformity, consistency, and average values for a number of selected target breaking strengths; (*b*) compare the testers with respect to their averages and variances; (*c*) study the effect of tablet shape and size on tablet breaking strength values associated with each tester; (*d*) study the combined effect of the three factors (tablet testers, shape and size, and target breaking strength) on values; and (*e*) estimate the correlation between breaking strength values associated with the tablet testers and develop regression equations to predict breaking strength values of one instrument from those of another.

[1] A partial list would include the Stokes (formerly Monsanto) tester (Stokes Compacting Division, Pennwalt Corp., Warminster, Pa.), the Heberlein tester (Cherry-Burell, Park Ridge, Ill.), the Ahiba tester (Gubelin International Corp., Mount Kisco, N. Y.), the Pfizer tester (Chas. Pfizer & Co., Brooklyn, N. Y.), the Strong-Cobb tester (Strong-Cobb Inc., Cleveland, Ohio), and the Erweka tester (Chemical and Pharmaceutical Industry Co., New York, N. Y.).

HISTORICAL

In marked contrast to the past, a large number of instruments for measuring tablet breaking strength has been made available recently to the pharmaceutical industry. It was not until the early 1930's that the first instrument for measuring tablet breaking strength, the Monsanto (now Stokes) tester, became available. Since, then, elaborate studies on tablet breaking strength and related equipment have been completed and reported. Nutter Smith (1–5) for example, studied and discussed conditions that influence the resistance of tablets to normal "wear and tear"; two devices, one each for testing the breaking point of tablets and effects of abrasion; and two instruments for measuring the surface hardness of tablets. None of the equipment Nutter Smith studied, however, other than the Stokes tester has received wide acceptance in the industry.

In the decade of 1940–1950, the Strong-Cobb testing device became available and continues to enjoy wide appeal. Subsequently, Fairchild and Michel (6) described and evaluated the Pfizer tablet tester and compared it against the Stokes tester for ease of operation, accuracy, and reliability. In 1961, Endicott *et al.* (7) reported on an instrument they developed and evaluated which produced values of tablet breaking strength expressed in terms of fracture resistance. De Lonca *et al.* (8) reported on work with two devices (the Dynestat and Erweka) for measuring tablet breaking strength, and in 1968 Brook and Marshall (9) pointed out that variations observed on four devices involved in their studies were partly due to inaccuracies in equipment mechanisms and emphasized the need for calibration when comparing the results of one machine to another. In none of this work, however, was there an attempt to relate values obtained on one instrument to those of another.

EXPERIMENTAL

Tablets evaluated in this study contained the following: hydrous dibasic calcium phosphate NF, 32%; lactose USP, 32%; microcrystalline cellulose NF, 32%; starch USP, 3.5%; and magnesium stearate USP, 0.5%. The formulation was manufactured in one batch large enough to conduct all experiments.

All tablets were compressed on a single-punch press[2] operated at a rate of 90 tablets/min. Tablets of three different shapes, each in two sizes at target breaking strengths of 4, 8, and 12 kg., were prepared. The tablet sizes and shapes selected for the study were: Tablet I, round, standard concave, 7.14 mm. (0.28 in.) in diameter; Tablet II, round, standard concave, 10.3 mm. (0.40 in.) in diameter; Tablet III, capsule shaped, deep concave, 3.97 × 9.52 mm. (0.15 × 0.37 in.); Tablet IV, capsule shaped, deep concave, 4.76 × 11.9 mm.

[2] Model E, Stokes Compacting Division, Pennwalt Corp., Warminster, Pa.

Table I—Comparison of Averages[a] of Tablet Breaking Strength Testers

Tablet	Target Hardness, kg.	Statistical Intercomparison[b] T-3	T-4	T-2	T-1
I	4	3.90 ± 0.10[c]	4.90 ± 0.12[a]	4.66 ± 0.11[a]	4.25 ± 0.10[b]
II	4	4.22 ± 0.08[c]	5.32 ± 0.10[a]	5.25 ± 0.10[a]	4.49 ± 0.09[b]
III	4	4.53 ± 0.18[c]	6.18 ± 0.25[a]	5.95 ± 0.24[a]	5.61 ± 0.23[a]
IV	4	4.95 ± 0.19[b]	6.38 ± 0.24[a]	5.86 ± 0.22[a]	5.99 ± 0.22[a]
V	4	3.91 ± 0.13[b]	5.20 ± 0.17[a]	5.14 ± 0.17[a]	5.76 ± 0.19[c]
VI	4	3.89 ± 0.11[c]	5.13 ± 0.15[a]	5.16 ± 0.15[a]	5.67 ± 0.17[b]
I	8	8.15 ± 0.10[a]	10.07 ± 0.13[b]	9.72 ± 0.12[b]	9.37 ± 0.12[d]
II	8	8.96 ± 0.12[c]	11.25 ± 0.15[b]	10.89 ± 0.15[b]	9.89 ± 0.13[a]
III	8	9.01 ± 0.24[b]	11.51 ± 0.30[c]	10.69 ± 0.28[a,c]	9.97 ± 0.26[a]
IV	8	8.86 ± 0.22[a]	12.00 ± 0.30[b]	10.88 ± 0.27[c]	9.65 ± 0.24[d]
V	8	8.80 ± 0.38[b]	11.31 ± 0.49[a]	9.99 ± 0.43[c]	11.33 ± 0.49[a,c]
VI	8	7.89 ± 0.11[c]	10.31 ± 0.14[a]	9.37 ± 0.13[b]	10.57 ± 0.15[a]
I	12	13.02 ± 0.16[c]	14.86 ± 0.18[a]	14.44 ± 0.18[a,b]	13.94 ± 0.17[b]
II	12	12.16 ± 0.19[a]	14.73 ± 0.24[b]	13.46 ± 0.22[c]	12.74 ± 0.20[d]
III	12	12.24 ± 0.29[a]	14.62 ± 0.35[b]	13.23 ± 0.31[c]	12.47 ± 0.30[a,c]
IV	12	12.64 ± 0.25[a]	15.30 ± 0.30[b]	13.93 ± 0.28[c]	11.59 ± 0.23[d]
V	12	12.54 ± 0.16[a]	15.15 ± 0.20[b]	13.11 ± 0.17[c]	15.88 ± 0.21[d]
VI	12	12.59 ± 0.20[a]	15.29 ± 0.24[b]	13.23 ± 0.21[c]	14.07 ± 0.22[d]

[a] The values are the geometric average and its standard error, respectively, based on Cochran's approximation (12). [b] Two testers' averages are not statistically different (at $p = 0.05$) if they have at least one superscript in common. Two testers' averages are statistically different (at $p < 0.05$) if they have different superscripts. Note: These intercomparisons in this section are designated with superscript letters.

(0.18 × 0.46 in.); Tablet V, oval, deep concave, 5.56 × 10.3 mm. (0.21 × 0.40 in.); and Tablet VI, oval, deep concave, 7.14 × 12.7 mm. (0.28 × 0.50 in.).

The following four testers were evaluated: T-1, a manually powered, spring-loaded tester[3]; T-2, a motorized tester[4] whose function is derived from a counterweight principle; T-3, a manually operated tester[4] whose function is derived from a counterweight principle; and T-4, a motorized, spring-loaded tester[5].

To achieve the target breaking strengths desired, an arbitrary tablet weight for each size and shape was selected. This weight of powder mix was introduced into the corresponding die and pressure was exerted onto the mass. The resulting tablet was then measured for breaking strength on tester T-3. If the target value was not achieved, a new charge of powder mix of the same weight was introduced into the die and a different pressure was exerted. The resulting tablet was again measured for breaking strength. This procedure was repeated, if necessary, until the correct pressure to achieve the desired tablet breaking strength was reached. Once the correct set of machine adjustments was obtained, 500 tablets were compressed, keeping tablet weights ±4% of target and tablet thicknesses ±1% of target. When this operation was completed, a new size or shape was chosen and the same procedure was repeated until all of the different sizes, shapes, and target breaking strengths were manufactured.

The design protocol called for obtaining at random, for each shape and size, samples of four tablets each for testing on the four testers (involving random assignment of tablets to testers). The four breaking strength values for each occasion were determined concurrently. This procedure was repeated sequentially until 10 such samples of four were collected at each of the target values of 4, 8, and 12 kg. Only one operator was involved in the completion of all operations.

DISCUSSION

The discussion presented here is based upon the results of the statistical analysis of the 720 breaking strength values obtained from the randomized design of experiment described in the previous section. To compare the breaking strength values (Table I) generated by the testers in this study, both the ANOVA and Duncan's multiple range test (10) were used. The Levene (11) test of homogeneity of average absolute mean deviations (Table II) was employed for comparing the variability of instruments. The results of the regression analysis are presented in Table III; linear regressions were the best fit for the data and polynomial regressions were tried but did not contribute substantially to the fit.

[3] Stokes tester.
[4] Heberlein tester.
[5] Ahiba tester.

Using known breaking strength values experimentally obtained, one can now predict the breaking strength value from one tester to another using the following equation:

$$Y = A + BX_0 \qquad \text{(Eq. 1)}$$

where Y is the predicted breaking strength value, A and B are the numerical coefficients from Table III, and X_0 is the experimentally obtained breaking strength value associated with a given tester.

For instance, if one wishes to predict breaking strength values for T-4 from an experimentally obtained breaking strength value associated with T-3, Eq. 1 has the following form:

$$\text{(T-4)} = A + B\text{(T-3)} \qquad \text{(Eq. 2)}$$

The 95% confidence limits of the predicted breaking strength value can be computed by inserting the appropriate X_0 value into the formula given in the last column of Table III. The explicit expression of the confidence limits formula for the predicted values

Table II—Comparison of Variability[a] (Uniformity) among the Testers

Tablet	Target Hardness, kg.	Statistical Intercomparison[b] T-3	T-4	T-2	T-1
I	4	0.12[b]	0.16[b,c]	0.30[a,c]	0.42[a]
II	4	0.23[a]	0.19[a]	0.15[a]	0.15[a]
III	4	0.39[b]	0.50[b]	0.48[b]	0.81[a]
IV	4	0.42[a]	0.38[a]	0.42[a]	0.70[a]
V	4	0.25[a]	0.65[b]	0.25[a]	0.42[a,b]
VI	4	0.22[b]	0.38[a,b]	0.37[a,b]	0.51[a]
I	8	0.23[a]	0.29[a]	0.33[a]	0.37[a]
II	8	0.33[a]	0.25[a]	0.32[a]	0.36[a]
III	8	0.42[b]	0.43[b]	0.45[b]	1.20[a]
IV	8	0.75[a]	0.62[a]	0.51[a]	0.54[a]
V	8	1.02[a]	1.07[a]	1.50[a]	1.02[a]
VI	8	0.33[a]	0.41[a]	0.17[a]	0.27[a]
I	12	0.13[a]	0.42[b]	0.56[b]	0.51[b]
II	12	0.47[a]	0.60[a]	0.47[a]	0.45[a]
III	12	0.67[a]	0.82[a]	0.55[a]	0.97[a]
IV	12	0.40[a]	0.82[a]	0.69[a]	0.75[a]
V	12	0.40[a,b]	0.25[a]	0.45[a,b]	0.63[b]
VI	12	0.35[a]	0.39[a]	0.55[a,b]	0.78[b]

[a] The values are the average absolute mean deviations based on 10 observations. [b] Two testers' average absolute mean deviations are not statistically different (at $p = 0.05$) if they have at least one superscript in common. Two testers' average absolute mean deviations are statistically different (at $p < 0.05$) if they have different superscripts. Note: These intercomparisons in this section are designated with superscript letters.

Table III—Regression Equation, Prediction Efficiency (RSQ, %), and Formula for 95% Confidence Limits of Predicted Values

Tablet	(X)	(Y)	A	B	RSQ, %[a]	Formula for[b] 95% Confidence Limits
I	T-3	T-2	0.718	1.065	97.8	$\pm[0.053990 + 0.003873 (X_0 - 8.35833)^2]^{1/2}$
	T-3	T-4	0.812	1.087	98.4	$\pm[0.039932 + 0.002865 (X_0 - 8.35833)^2]^{1/2}$
	T-3	T-1	0.403	1.052	97.4	$\pm[0.062581 + 0.004489 (X_0 - 8.35833)^2]^{1/2}$
	T-2	T-4	0.245	1.009	98.3	$\pm[0.043070 + 0.002665 (X_0 - 9.61667)^2]^{1/2}$
	T-2	T-1	−0.195	0.977	97.3	$\pm[0.065084 + 0.004027 (X_0 - 9.61667)^2]^{1/2}$
	T-4	T-1	−0.338	0.959	97.0	$\pm[0.070593 + 0.004215 (X_0 - 9.95000)^2]^{1/2}$
	T-2	T-3	−0.473	0.918	97.8	$\pm[0.046570 + 0.002882 (X_0 - 9.61667)^2]^{1/2}$
	T-4	T-3	−0.647	0.905	98.4	$\pm[0.033239 + 0.001985 (X_0 - 9.95000)^2]^{1/2}$
	T-1	T-3	−0.153	0.925	97.4	$\pm[0.055006 + 0.003468 (X_0 - 9.20000)^2]^{1/2}$
	T-4	T-2	−0.073	0.974	98.3	$\pm[0.041563 + 0.002482 (X_0 - 9.95000)^2]^{1/2}$
	T-1	T-2	0.458	0.996	97.3	$\pm[0.066321 + 0.004182 (X_0 - 9.20000)^2]^{1/2}$
	T-1	T-4	0.638	1.012	97.0	$\pm[0.074544 + 0.004700 (X_0 - 9.20000)^2]^{1/2}$
II	T-3	T-2	1.168	1.029	96.0	$\pm[0.071829 + 0.006600 (X_0 - 8.45833)^2]^{1/2}$
	T-3	T-4	0.562	1.168	96.8	$\pm[0.074404 + 0.006836 (X_0 - 8.45833)^2]^{1/2}$
	T-3	T-1	0.320	1.032	97.2	$\pm[0.049175 + 0.004518 (X_0 - 8.45833)^2]^{1/2}$
	T-2	T-4	−0.521	1.110	96.5	$\pm[0.081118 + 0.006753 (X_0 - 9.87500)^2]^{1/2}$
	T-2	T-1	−0.589	0.976	96.0	$\pm[0.071472 + 0.005950 (X_0 - 9.87500)^2]^{1/2}$
	T-4	T-1	−0.032	0.870	97.4	$\pm[0.046970 + 0.003061 (X_0 - 10.44170)^2]^{1/2}$
	T-2	T-3	−0.752	0.933	96.0	$\pm[0.065085 + 0.005419 (X_0 - 9.875)^2]^{1/2}$
	T-4	T-3	−0.192	0.828	96.8	$\pm[0.052774 + 0.003439 (X_0 - 10.44170)^2]^{1/2}$
	T-1	T-3	−0.069	0.942	97.2	$\pm[0.044891 + 0.003765 (X_0 - 9.05000)^2]^{1/2}$
	T-4	T-2	0.801	0.869	96.5	$\pm[0.063498 + 0.004138 (X_0 - 10.44170)^2]^{1/2}$
	T-1	T-2	0.975	0.983	96.0	$\pm[0.072005 + 0.006039 (X_0 - 9.05000)^2]^{1/2}$
	T-1	T-4	0.311	1.119	97.4	$\pm[0.060452 + 0.005070 (X_0 - 9.05000)^2]^{1/2}$
III	T-3	T-2	2.075	0.917	92.7	$\pm[0.102592 + 0.009850 (X_0 - 8.61667)^2]^{1/2}$
	T-3	T-4	1.685	1.057	91.7	$\pm[0.157331 + 0.015105 (X_0 - 8.61667)^2]^{1/2}$
	T-3	T-1	2.098	0.850	81.7	$\pm[0.251962 + 0.024191 (X_0 - 8.61667)^2]^{1/2}$
	T-2	T-4	−0.337	1.116	92.6	$\pm[0.140218 + 0.014855 (X_0 - 9.97500)^2]^{1/2}$
	T-2	T-1	0.490	0.896	82.2	$\pm[0.245761 + 0.026037 (X_0 - 9.97500)^2]^{1/2}$
	T-4	T-1	1.166	0.765	80.6	$\pm[0.267204 + 0.021067 (X_0 - 10.79170)^2]^{1/2}$
	T-2	T-3	−1.474	1.012	92.7	$\pm[0.113207 + 0.011994 (X_0 - 9.97500)^2]^{1/2}$
	T-4	T-3	−0.749	0.868	91.7	$\pm[0.129197 + 0.010186 (X_0 - 10.79170)^2]^{1/2}$
	T-1	T-3	−0.444	0.961	81.7	$\pm[0.284846 + 0.030917 (X_0 - 9.42500)^2]^{1/2}$
	T-4	T-2	1.016	0.830	92.6	$\pm[0.104348 + 0.008227 (X_0 - 10.79170)^2]^{1/2}$
	T-1	T-2	1.326	0.918	82.2	$\pm[0.251785 + 0.027329 (X_0 - 9.42500)^2]^{1/2}$
	T-1	T-4	0.861	1.054	80.6	$\pm[0.367857 + 0.039928 (X_0 - 9.42500)^2]^{1/2}$
IV	T-3	T-2	1.387	1.002	89.0	$\pm[0.190114 + 0.018582 (X_0 - 8.84167)^2]^{1/2}$
	T-3	T-4	1.470	1.106	88.3	$\pm[0.248939 + 0.024331 (X_0 - 8.84167)^2]^{1/2}$
	T-3	T-1	3.059	0.686	80.2	$\pm[0.177767 + 0.017375 (X_0 - 8.84167)^2]^{1/2}$
	T-2	T-4	0.098	1.089	96.4	$\pm[0.075905 + 0.006583 (X_0 - 10.24170)^2]^{1/2}$
	T-2	T-1	2.302	0.666	85.3	$\pm[0.132575 + 0.011497 (X_0 - 10.24170)^2]^{1/2}$
	T-4	T-1	2.445	0.594	83.3	$\pm[0.150480 + 0.010613 (X_0 - 11.25000)^2]^{1/2}$
	T-2	T-3	−0.259	0.889	89.0	$\pm[0.168681 + 0.014628 (X_0 - 10.24170)^2]^{1/2}$
	T-4	T-3	−0.137	0.798	88.3	$\pm[0.179625 + 0.012668 (X_0 - 11.25000)^2]^{1/2}$
	T-1	T-3	−1.829	1.169	80.2	$\pm[0.302970 + 0.050469 (X_0 - 9.12500)^2]^{1/2}$
	T-4	T-2	0.279	0.886	96.4	$\pm[0.061730 + 0.004354 (X_0 - 11.25000)^2]^{1/2}$
	T-1	T-2	−1.436	1.280	85.3	$\pm[0.254659 + 0.042421 (X_0 - 9.12500)^2]^{1/2}$
	T-1	T-4	−1.547	1.402	83.3	$\pm[0.355431 + 0.059208 (X_0 - 9.12500)^2]^{1/2}$
V	T-3	T-2	1.874	0.899	89.2	$\pm[0.190797 + 0.014619 (X_0 - 8.45000)^2]^{1/2}$
	T-3	T-4	1.382	1.090	89.4	$\pm[0.275469 + 0.021106 (X_0 - 8.45000)^2]^{1/2}$
	T-3	T-1	1.414	1.137	94.0	$\pm[0.162287 + 0.012434 (X_0 - 8.45000)^2]^{1/2}$
	T-2	T-4	0.105	1.108	83.6	$\pm[0.426812 + 0.036136 (X_0 - 9.46667)^2]^{1/2}$
	T-2	T-1	0.076	1.157	87.9	$\pm[0.324653 + 0.027486 (X_0 - 9.46667)^2]^{1/2}$
	T-4	T-1	0.902	0.956	88.2	$\pm[0.318191 + 0.018346 (X_0 - 10.59170)^2]^{1/2}$
	T-2	T-3	−0.949	0.993	89.2	$\pm[0.210832 + 0.017850 (X_0 - 9.46667)^2]^{1/2}$
	T-4	T-3	−0.237	0.820	89.4	$\pm[0.207299 + 0.011952 (X_0 - 10.59170)^2]^{1/2}$
	T-1	T-3	−0.659	0.826	94.0	$\pm[0.117882 + 0.006561 (X_0 - 11.02500)^2]^{1/2}$
	T-4	T-2	1.476	0.754	83.6	$\pm[0.290667 + 0.016759 (X_0 - 10.59170)^2]^{1/2}$
	T-1	T-2	1.084	0.760	87.9	$\pm[0.213412 + 0.011877 (X_0 - 11.02500)^2]^{1/2}$
	T-1	T-4	0.420	0.923	88.2	$\pm[0.307132 + 0.017093 (X_0 - 11.02500)^2]^{1/2}$
VI	T-3	T-2	1.794	0.919	97.3	$\pm[0.045277 + 0.003546 (X_0 - 8.13333)^2]^{1/2}$
	T-3	T-4	0.870	1.154	97.9	$\pm[0.055393 + 0.004338 (X_0 - 8.13333)^2]^{1/2}$
	T-3	T-1	2.406	0.949	93.3	$\pm[0.123906 + 0.009703 (X_0 - 8.13333)^2]^{1/2}$
	T-2	T-4	−1.132	1.229	96.3	$\pm[0.095999 + 0.008662 (X_0 - 9.26667)^2]^{1/2}$
	T-2	T-1	0.619	1.026	94.6	$\pm[0.099812 + 0.009006 (X_0 - 9.26667)^2]^{1/2}$
	T-4	T-1	1.674	0.824	95.7	$\pm[0.079378 + 0.004566 (X_0 - 10.25830)^2]^{1/2}$
	T-2	T-3	−1.677	1.059	97.3	$\pm[0.052167 + 0.004707 (X_0 - 9.26667)^2]^{1/2}$
	T-4	T-3	−0.564	0.848	97.9	$\pm[0.040687 + 0.002340 (X_0 - 10.25830)^2]^{1/2}$
	T-1	T-3	−1.820	0.983	93.3	$\pm[0.128344 + 0.010411 (X_0 - 10.12500)^2]^{1/2}$
	T-4	T-2	1.228	0.784	96.3	$\pm[0.061199 + 0.003520 (X_0 - 10.25830)^2]^{1/2}$
	T-1	T-2	−0.070	0.922	94.6	$\pm[0.089731 + 0.007279 (X_0 - 10.12500)^2]^{1/2}$
	T-1	T-4	−1.504	1.162	95.7	$+[0.111941 + 0.009080 (X_0 - 10.12500)^2]^{1/2}$

[a,b] Formulas for calculating RSQ(%) and 95% confidence limits can be found in the text.

Table IV—Comparison of Averages[a] of Size-Shape Groups[b]

Target Hardness, kg.	Device	Tablet I	Tablet II	Tablet III	Tablet IV	Tablet V	Tablet VI
4	T-3	3.9[a]	4.22[b]	4.53[b]	4.95[c]	3.91[a]	3.89[a]
4	T-2	4.66[a]	5.25[b]	5.95[c]	5.86[c]	5.14[b]	5.16[b]
4	T-4	4.90[a]	5.32[a]	6.18[b]	6.38[b]	5.20[a]	5.13[a]
4	T-1	4.25[a]	4.49[a]	5.61[b]	5.99[b]	5.76[b]	5.67[b]
8	T-3	8.15[a]	8.96[b]	9.01[b]	8.86[b]	8.80[b]	7.89[a]
8	T-2	9.72[a]	10.89[c]	10.69[b,c]	10.88[c]	9.99[a,b]	9.37[a]
8	T-4	10.07[a]	11.25[b]	11.51[b,c]	12.00[c]	11.31[b,c]	10.31[a]
8	T-1	9.37[a]	9.89[a,b]	9.97[a,b]	9.65[a]	11.33[c]	10.57[b,c]
12	T-3	13.02[b]	12.16[a]	12.24[a]	12.64[a,b]	12.54[a,b]	12.59[a,b]
12	T-2	14.44[c]	13.46[a,b]	13.23[a]	13.93[b,c]	13.11[a]	13.23[a]
12	T-4	14.86[a]	14.73[a]	14.62[a]	15.30[a]	15.15[a]	15.29[a]
12	T-1	13.94[c]	12.74[b]	12.47[b]	11.59[a]	15.88[d]	14.07[c]

[a] The values are the geometric averages based on 10 observations. [b] Two groups are not statistically different ($p = 0.05$) if they have at least one superscript in common. Two groups are statistically different ($p < 0.05$) if they have different superscripts. Note: These intercomparisons in this section are designated with superscript letters.

has the following form (10):

$$\hat{Y}_0 \pm t_{0.05} S_{yx} \sqrt{\frac{1}{n} + \frac{(X_0 - \bar{X})^2}{[X^2]}} \qquad \text{(Eq. 3)}$$

Comparisons of the averages and variabilities of breaking strengths among size-shape groups were also made and are presented in Tables IV and V, respectively.

The results given in Table I indicate that, in most cases, the two motorized testers yielded breaking strength values significantly higher than those of the manually operated instruments. T-4 generally gave higher readings than T-2, and these differences were significant for the five cases in the 12-kg. group. Breaking strength values generated with T-3 were significantly lower than those of the other three testers in 17 of the 18 possible cases. In the 12-kg. group, all devices were significantly different from one another in four out of six cases; that is, the two manually operated and the two motorized testers were significantly different from each other in this group.

With the data in Table IV, it is possible to make 15 comparisons derived from the combination of six categories taken two at a time within any given row. Such an exercise reveals that there are significant differences among many size-shape groups. The two sizes associated with the round shape (Tablets I and II) had significantly different breaking strength values in eight of the 12 possible cases. This result is somewhat surprising and unexplainable. Size made a difference in three out of 12 comparisons in each of the capsule-shaped (Tablets III and IV) and oval-shaped (Tablets V and VI) groups, but the effect of size was not pronounced in the capsule- and oval-shaped groups for the target values of 8 and 4 kg., respectively.

An analysis of the data presented in Table II shows that T-1 maintained a higher level of variability than the other testers in more than half of the possible cases. However, there was no significant difference in variability when all testers were compared in 10 out of 18 cases. Furthermore, there was no significant difference among T-3, T-4, and T-2 as far as their variabilities in 16 out of 18 cases.

Table V reveals that, except for the oval shape (Tablets V and VI) at the 8-kg. target, there were significant differences in variability related to a size-shape grouping in only two cases.

The use of the equation for predicting breaking strength values from one instrument to another is evident from Table III. The correlation between any two testers under consideration can be obtained by taking the square root of the RSQ value [RSQ(%)/100] noted in Table III. RSQ(%) is calculated as follows:

$$\text{RSQ}(\%) = \frac{B^2[X^2]100}{[Y^2]} \qquad \text{(Eq. 4)}$$

where B is the linear regression coefficient, $[X^2]$ is the corrected sum of squares for X's, and $[Y^2]$ is the corrected sum of squares for Y's.

The values of the correlation coefficients ranged from 0.90 to 0.99 in this study (the theoretical range here is from 0.0 to 1.0). One must be aware, however, that accurate predictions can be obtained only if: (*a*) the X_0 value is the average of exactly 10 breaking strength values experimentally derived, (*b*) the X_0 value lies between 3.0 and 15.75 kg., and (*c*) the experimental conditions are as close to those described in this paper as possible.

CONCLUSION

The characterization and comparison of tablet breaking strength

Table V—Variability[a] Comparison of Size-Shape Groups[b]

Target Hardness, kg.	Device	Tablet I	Tablet II	Tablet III	Tablet IV	Tablet V	Tablet VI
4	T-3	0.12[a]	0.23[a,b]	0.39[b,c]	0.42[c]	0.26[a,b,c]	0.22[a,b]
4	T-2	0.30[a,b,c]	0.15[a]	0.48[c]	0.42[b,c]	0.25[a,b]	0.37[b,c]
4	T-4	0.16[a]	0.19[a]	0.50[b,c]	0.38[a,b,c]	0.65[c]	0.38[a,b]
4	T-1	0.42[a,b]	0.15[a]	0.81[b]	0.70[b]	0.42[a,b]	0.51[a,b]
8	T-3	0.23[a]	0.33[a]	0.42[a,b]	0.75[b,c]	1.02[c]	0.33[a]
8	T-2	0.33[a]	0.32[a]	0.45[a]	0.51[a]	1.50[b]	0.17[a]
8	T-4	0.29[a]	0.25[a]	0.43[a]	0.62[a]	1.07[b]	0.41[a]
8	T-1	0.37[a]	0.36[a]	1.20[b]	0.54[a]	1.02[b]	0.27[a]
12	T-3	0.13[a]	0.47[b,c]	0.67[c]	0.40[a,b,c]	0.40[a,b,c]	0.35[a,b]
12	T-2	0.56[a]	0.47[a]	0.55[a]	0.69[a]	0.45[a]	0.55[a]
12	T-4	0.42[a]	0.60[a,b]	0.82[b]	0.82[b]	0.25[a]	0.39[a]
12	T-1	0.51[a]	0.45[a]	0.97[a]	0.75[a]	0.63[a]	0.78[a]

[a] The values are the average absolute mean deviations based on 10 observations. [b] Two groups are not statistically different ($p = 0.05$) if they have at least one superscript in common. Two groups are statistically different ($p < 0.05$) if they have different superscripts. Note: These intercomparisons in this section are designated with superscript letters.

testers offered considerable insight into the performance capability of the instruments studied. The characterization information is fundamental to any developmental work in this area. The study also revealed a sufficiently high correlation among the tablet testers to permit precise prediction of breaking strength values. It is possible now to expand the study to evaluate breaking strength testers of the same kind in interlaboratory crossover experiments.

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Semiautomated UV Analysis of Caffeine in Aspirin–Phenacetin–Caffeine Tablets

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Abstract □ A semiautomated individual tablet assay was developed for caffeine in aspirin–phenacetin–caffeine formulations. Caffeine and phenacetin are extracted from the bicarbonate tablet solution with chloroform. The caffeine and some phenacetin are extracted from the chloroform with acid, and an additional chloroform wash of the acid phase removes any phenacetin. The caffeine is determined by UV spectroscopy in the acid at 266 nm. at a rate of 20 tablets/hr. The coefficient of variation for 10 determinations of one sample solution was 1.72. The difference in results between the NF XIII method and the proposed method, expressed as percent of declared, did not exceed 2.6% when 10 different products were analyzed.

Keyphrases □ Aspirin–phenacetin–caffeine tablets—semiautomated UV analysis of caffeine □ Caffeine in aspirin–phenacetin–caffeine tablets—semiautomated UV analysis □ UV spectrophotometry—analysis, caffeine in aspirin–phenacetin–caffeine tablets

Aspirin, phenacetin, and caffeine in pharmaceutical preparations are determined quantitatively by the official NF procedure (1). Since the monograph employs a partition chromatographic separation on a diatomaceous earth[1] column (2), the content uniformity requirement for caffeine in the tablets is extremely time consuming.

An automated method for caffeine in blood converts the caffeine to an aromatic amine, with subsequent diazotization for color determination (3). This procedure could not be used in the presence of phenacetin.

Caffeine has been reported to fluoresce in chloroform, where the excitation at 280 nm. causes emission that can be measured at 310 nm.[2]. With filter fluorometer equipment normally applied to an automated analyzer[3], excitation energy from the source lamp is rather weak at 280 nm. In addition, the fluorescence is not strong and linearity may be difficult to achieve.

In the method reported here, the caffeine and phenacetin are extracted from the bicarbonate solution with chloroform. The caffeine is extracted from the chloroform with dilute sulfuric acid, which is washed with chloroform to remove any phenacetin from the acid phase. The caffeine is determined by measuring its UV absorbance at 266 nm.

EXPERIMENTAL

Apparatus—The following were used: Liquid sampler II[4] (20/hr.), proportioning pump[4] I, and a spectrophotometer[5] equipped with a 10-mm. flow cell[6].

Reagents—The following were used: 4 *N* sulfuric acid; 0.1 *M* $NaHCO_3$; and chloroform, reagent grade, free of UV-absorbing impurities.

Standard Preparation—Place 82 mg. of caffeine in a 250-ml. volumetric flask with 25 ml. of 0.1 *M* $NaHCO_3$, and heat on a steam bath 4–5 min. to dissolve. Cool and dilute to volume with 0.1 *M* $NaHCO_3$. The concentration of the standard solution is 0.328 mg./ml.

Sample Preparation—For tablets declared to contain 30 mg.

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