Figure 20—Cross-sectional view of Product S, moistened (about 720X).

content and distortion caused by pressure. Fuhrer (3) mentioned that pressure distorts potato starch grains and theorized that energy-rich grains are formed, so that no additional energy is needed for swelling. Close scrutiny of the grains before and after water was added seemed to indicate that the grains are less angular, supporting the theory that there is a degree of restoration to the original grain shape due to hydration of the starch molecules. The hydration and resulting effects occur rapidly (i.e., a fraction of a second). The hydration of the hydroxy groups and sorption of water could account for the slight swelling (5–10%) of the starch (9, 11). This amount of swelling could result in about a 70% increase in volume,

and the swelling would take a few seconds. These two combined effects of the attachment of water molecules and the increase in volume of the grains cause sufficient force to break up the tablet. Channels or pores lined with starch grains were not manifest in any of the surfaces examined. Therefore, the thesis that starch grains act as as a "wicking agent" and draw water into the tablet should be layed aside. The conditions for rapid disintegration are sufficient starch agglomerates, low pressure, and presence of water.

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Dissolution Rate Studies III: Effect of Type and Intensity of Agitation on Dissolution Rate

J. TINGSTAD▲, E. GROPPER, L. LACHMAN, and E. SHAMI

Abstract □ The effect of flow rates on dissolution rates using a continuous flow, column-type apparatus was determined. The flow method of agitation is compared to three other types used with the static beaker procedure. The advantages of the column-type apparatus in attaining low intensities of agitation without sacrificing accuracy or homogeneity are discussed.

Keyphrases □ Dissolution rates—effect of flow agitation, compared to compendial methods, column-type equipment □ Agitation, column flow type—effect on dissolution rates, compared to compendial methods

The importance of low agitation intensities in detecting real differences in dissolution rates and in obtaining good in vitro–in vivo correlations in dissolution rate experiments has been established (1, 2). In addition, the importance of the accurate control of the

degree of agitation has been pointed out (2). However, the use of low agitation intensities and the accurate control of variables associated with agitation are severely limited with the static beaker method but not with the continuous flow, column-type procedure (3,
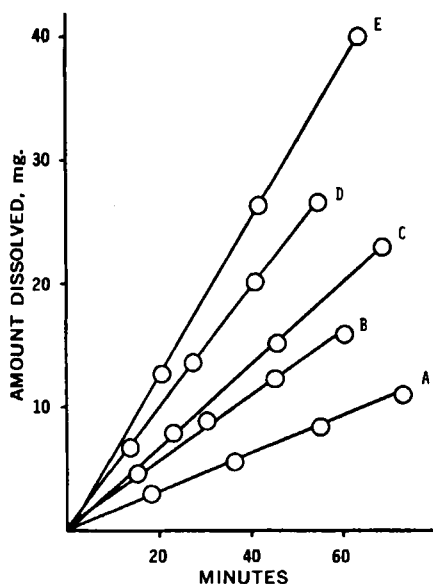
Figure 1—*Pseudo-zero-order plot showing the dissolution of salicylic acid constant-surface pellets in the 13-mm. dissolution chamber (flow method) at various flow rates. Key: A, 5.48 ml./min.; B, 13.3 ml./min.; C, 21.8 ml./min.; D, 36.6 ml./min.; and E, 47.2 ml./min. The plot for 45.1 ml./min. is too close to that for 47.2 ml./min. to be depicted here.*

4). This article reports the effect of flow rates (*i.e.*, liquid velocity) on dissolution rates using a column-type apparatus and compares the columnar flow type of agitation with that provided by: (*a*) the USP XVIII disintegration apparatus, (*b*) a three-bladed stirrer, and (*c*) the USP XVIII-NF XIII rotating basket in the static beaker method.

EXPERIMENTAL

Preparation of Constant-Surface Pellets—Constant-surface pellets of analytical grade salicylic acid (without lubricant) were prepared in the usual manner, using a 0.56-cm. (0.22-in.) circular punch and die and compressing at 2724-kg. (6000-lb.) pressure. The finished pellets weighed 200 mg. and varied less than 0.2% in weight.
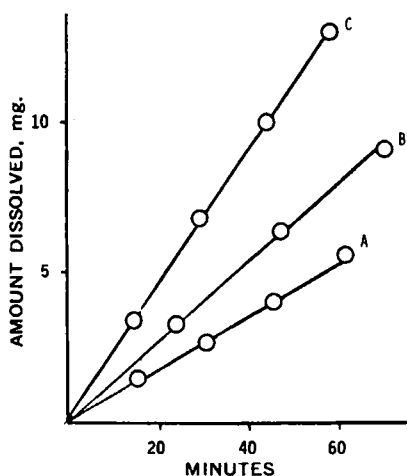

Figure 2—*Pseudo-zero-order plot showing the dissolution of salicylic acid constant-surface pellets in the 25-mm. dissolution chamber (flow method) at various flow rates. Key: A, 13.1 ml./min.; B, 21.3 ml./min.; and C, 34.1 ml./min. The plot for 36.4 ml./min. is too close to that for 34.1 ml./min. to be depicted here.*
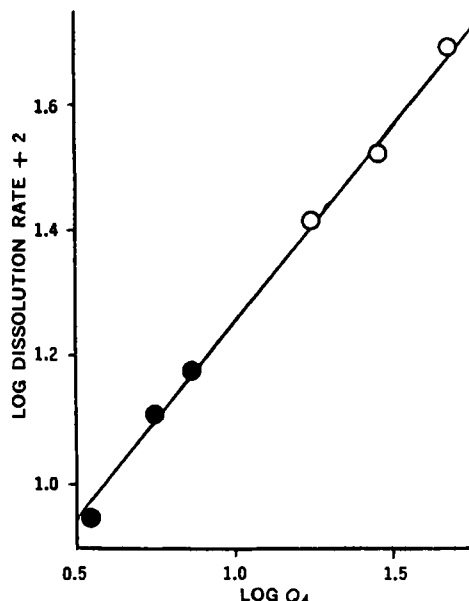

Figure 3—*Log-log plot of* Q_A *(liquid velocity) versus dissolution rate. Key:* O, *13-mm. dissolution chamber; and* ●, *25-mm. dissolution chamber. See text for further explanation.*

Procedure for Flow Method—The column-type apparatus used in these experiments was described in detail previously (5). The effluent solution was routed through a 1-cm. spectrophotometric flow cell and then into a receptacle. The temperature was 25.0 ± 0.1°, and the solvent system was 0.1 N HCl with 0.05% polysorbate 80 added to ensure uniform wetting of the solid. The flow rate was held constant for each experiment but was varied among experiments by adjusting the setting on the solid-state speed control.

Between determinations, the dissolution chamber (13- and 25-mm. size) was cleaned and the system was flushed until the UV absorbance receded to a constant value. A blank was taken, the pump was turned off, and the dissolution chamber was disassembled. The pellet was placed in a small beaker and cleansed of loose powder with solvent; then it was placed in the dissolution chamber at the center of the lower support screen. The chamber was reassembled
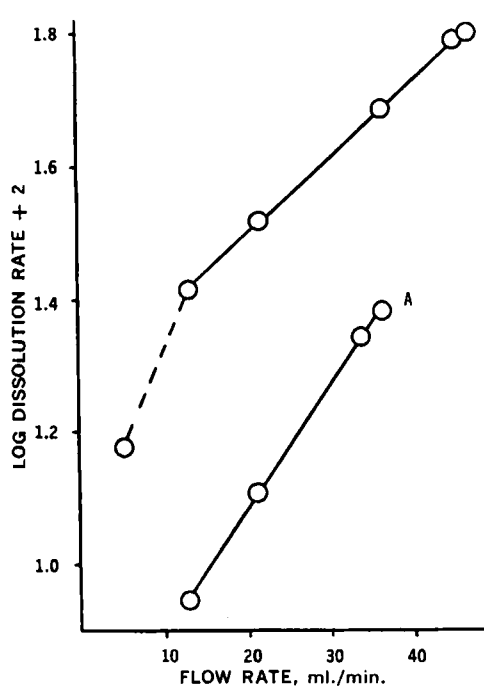

Figure 4—*Semilog plot of flow rate versus dissolution rate. Key: A, 25-mm. dissolution chamber; and B, 13-mm. dissolution chamber.*
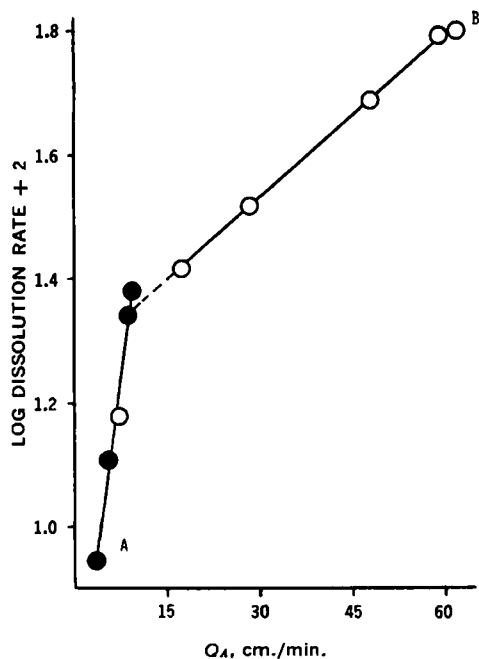
Figure 5—*Semilog plot of* Q_A *(liquid velocity) versus dissolution rate. Key: A, ●, 25-mm. dissolution chamber; and B, O, 13-mm. cell. See text for further explanation.*

and placed in the constant-temperature bath containing the solvent reservoir. The pump was activated and the system was allowed to flush for exactly 5 min.; this time was sufficient to stabilize the dissolution rate as determined by the continuous tracing on the strip chart. The effluent solution was then collected in three to five volumetric flasks of appropriate size for about 60 min. The absorbance of each fraction was determined at 303 nm., and the amount dissolved (along with the flow rate) was calculated from absorbance–volume–time measurements.

Procedure for Beaker Method—The temperature, solvent system, and pellet treatment were identical to those used in the flow method. Exactly 900.0 ml. of solvent in a 1-l. jacketed beaker was used in each case, and the volume lost through sampling was immediately replaced. Sampling was begun 5 min. after introduction of the pellet to correspond to the procedure used in the flow method. Samples were taken every 15 min. thereafter for 60 min.

When the USP–NF rotating basket was used for agitation, the pellet was placed inside it and the basket was stationed in the center
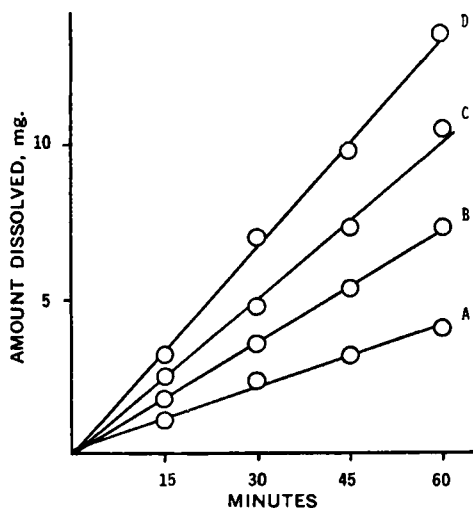

Figure 6—*Pseudo-zero-order plot showing the dissolution of salicylic acid constant-surface pellets in the beaker method using a three-bladed stirrer at various rotational speeds for agitation. Key: A, 50 r.p.m.; B, 100 r.p.m.; C, 150 r.p.m.; and D, 200 r.p.m.*
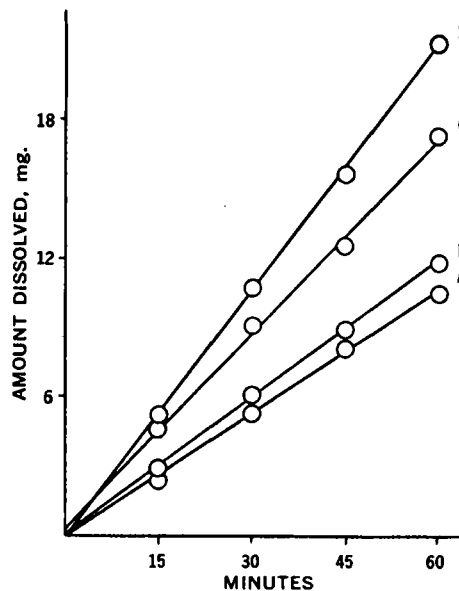

Figure 7—*Pseudo-zero-order plot showing the dissolution of salicylic acid constant-surface pellets in the beaker method using the USP disintegration apparatus (A) and the USP–NF rotating basket (B, 50 r.p.m.; C, 100 r.p.m.; and D, 150 r.p.m.) for agitation.*

of the liquid 2.0 cm. from the bottom. Samples were taken from the same position in the beaker each time. Rotational speed was varied among experiments using solid-state speed control.

With the three-bladed stirrer (1.5-cm. blades positioned in the center of the liquid 2.0 cm. from the bottom), the pellet was placed in the USP–NF basket and held stationary at the side of the beaker halfway between the top and the bottom of the liquid. Rotational speed was varied as before.

The USP disintegration apparatus was used at the official speed only. The pellet was not placed on the screen but on the bottom of the beaker to avoid physical abrasion by the vertical motion of the screen. Experiments with both the flow and beaker methods were conducted in duplicate.

RESULTS

Flow Method—The dissolution of the salicylic acid pellets at various flow rates using the 13- and 25-mm. dissolution chambers
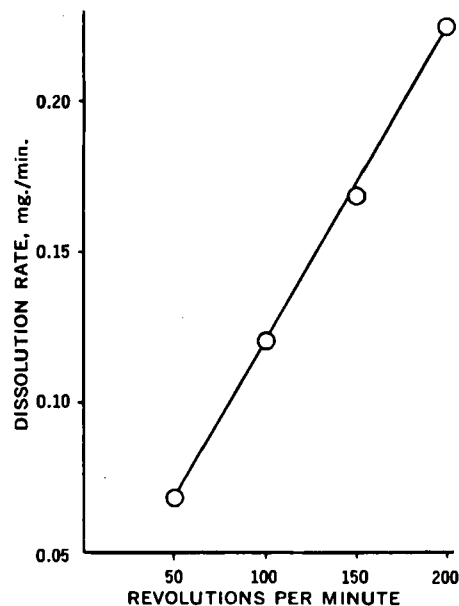

Figure 8—*Plot showing the effect of rotational speed on dissolution rate using the three-bladed stirrer.*
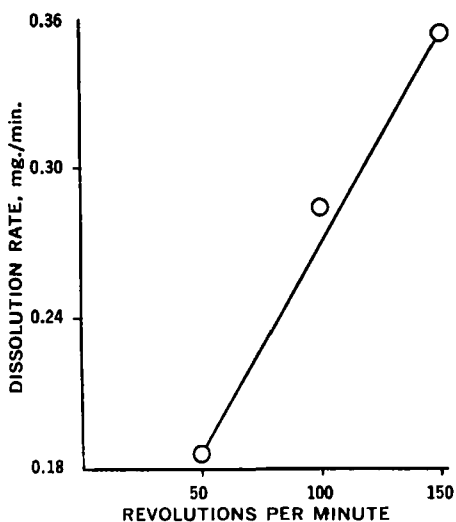
Figure 9—*Plot showing the effect of rotational speed on dissolution rate using the USP-NF rotating basket.*

is shown in Figs. 1 and 2, respectively. In this type of system the usual correlation between dissolution rate and flow rate takes the form:

$$\text{dissolution rate} \propto (Q_A)^{0.2-0.5} \qquad \text{(Eq. 1)}$$

where Q_A is the liquid velocity (centimeters per minute) and equals the flow rate (milliliters per minute) divided by the cross-sectional area of the dissolution chamber (0.765 and 3.87 cm.[2] for the 13- and 25-mm. units, respectively). Thus, a plot of log dissolution rate *versus* log liquid velocity yields a straight line with a slope of 0.2–0.5. The slope of the line in Fig. 3 is 0.6.

For each individual dissolution chamber, the dissolution rate was found to vary logarithmically with the flow rate within a certain range (Fig. 4), and a plot of liquid velocity *versus* log dissolution rate yields the two-slope linear relationship shown in Fig. 5.
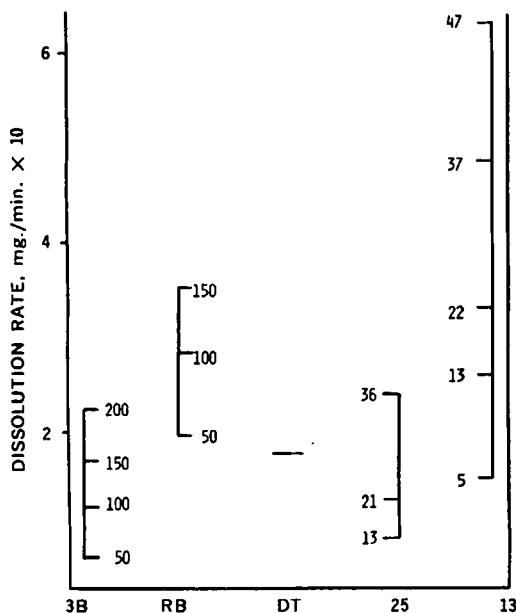

Figure 10—*Nomogram showing the relative effect of agitation on dissolution rate for the flow method (13- and 25-mm. chambers at various flow rates in milliliters per minute) and the beaker method (DT, USP disintegration apparatus at official speed; RB, USP-NF rotating basket at various rotational speeds in revolutions per minute; and 3B, three-bladed stirrer at various rotational speeds in revolutions per minute).*
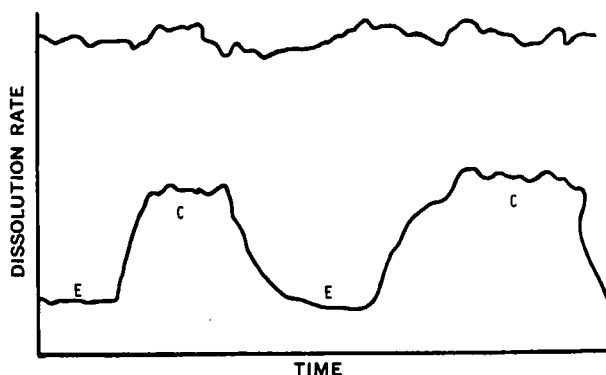

Figure 11—*Continuous UV tracings of dissolution rate versus time for salicylic acid constant-surface pellets. Lower curve (25-mm. chamber at flow rate of 80 ml./min.) shows sharp rise in dissolution rate when pellet is moved from edge (E) of lower support screen to center (C). Upper curve is standard tracing at nonturbulent flow rate (25-mm. chamber at 13.1 ml./min.).*

Beaker Method—The dissolution behavior of the pellets in the beaker experiments is shown in Figs. 6 and 7. A linear relationship was found between dissolution rate and agitation intensity for the three-bladed stirrer for the 50–200-r.p.m. range (Fig. 8). A similar relationship was found for the USP-NF rotating basket between 50 and 150 r.p.m. (Fig. 9). These results are similar to those obtained by Levy *et al.* (6).

Comparison of Methods—An estimate of the equivalence of agitation intensity from one method to the next, under the conditions of these experiments, can be made quickly using the nomogram in Fig. 10.

DISCUSSION

Flow Method—The discrepancy between the slope of the line in Fig. 3 and the "theoretical" range of 0.2–0.5 is probably because the dissolving solid was a single pellet rather than a packed bed of nondisintegrating granules (3). The data points obtained at 34 and 36 ml./min. with the 25-mm. chamber and those determined at 45 and 47 ml./min. with the 13-mm. unit were not included in this plot. Although these points exhibited a reasonable degree of correlation (and their exclusion did not result in an appreciable change in the value of the slope), their deviation from the straight line and the semilog nature of the plots in Fig. 4 made their exclusion seem appropriate.

At present, we have no theoretical explanation for the deviations nor for the apparent semilog relationship between dissolution rate and flow rate/liquid velocity. A partial explanation could involve: (a) the geometry of the dissolution chambers, (b) the drag associated with solvent flowing past the cylindrical pellets, and (c) the involvement of more "actual" surface area of the pellet due to increased fluid velocity. The validity of the semilog relationship and of the dual slope nature of the plots (under the conditions of these experiments) is strengthened by the fact that the nonlinear point (5.48 ml./min. flow rate) for the 13-mm. cell in Fig. 4 falls on the line for the 25-mm. unit in Fig. 5 (open circle on plot A).

The plots in Figs. 4 and 5 were not extended beyond 36 ml./min. for the 25-mm. chamber or beyond 47 ml./min. for the 13-mm. unit because results were too erratic with faster flow rates. Apparent dissolution rates above those limits were lower than those for lower flow rates. The cause of this anomaly is the greatly increased turbulence at higher flow rates. The pellets did not remain in the center of the lower support screen but tended to slide along the screen until they reached an eddy (usually close to the edge) and then stopped. At these higher flow rates (up to 80 ml./min.), the dissolution rate varied noticeably, depending upon where the pellet was located on the screen. This can be seen clearly in Fig. 11 (lower curve) where the continuous differential plot of dissolution rate *versus* time, obtained from the recording spectrophotometer, shows a marked increase when the pellet was moved from the edge to the center of the screen.

As expected, this phenomenon is especially apparent with the larger chamber. The problem does not seem to occur to any ap-

preciable extent at lower flow rates. This finding gives rise to the interesting observation that, for constant-surface pellets, the system is, in a sense, more "homogeneous" at lower agitation intensities. Determination of solvent flow patterns in the dissolution chambers at different flow rates would aid in the selection of proper flow rates for any particular system. Such studies, using the method described by Withey and Bowker (7), are in progress in these laboratories.

Beaker Method—In a previous publication (5) dealing with tablet formulations, the three-bladed stirrer (50 r.p.m.) method of agitation resulted in a faster dissolution rate than the rotating basket method (100 r.p.m.). Yet the nomogram in Fig. 10 shows that the three-bladed stirrer, even at 200 r.p.m., produced a slower dissolution rate than the rotating basket at 100 r.p.m. The following explanation emphasizes the inherent difficulties associated with the beaker system. When working with disintegrating tablets, the granules fall out of the basket and are then subject to lower (actual) agitation intensities beause they are not in close proximity to the basket. This problem is compounded by the fact that the basic design of the basket makes it a poor stirring device for the solvent. The three-bladed stirrer was designed to agitate and therefore provided greater agitation than did the rotating basket in the tablet formulation experiments, especially after disintegration took place. However, with the nondisintegrating pellet the solid remains in the basket and is continuously subjected to the recorded rotational speed. Furthermore, in these experiments, the pellet was in the stationary basket well removed from the three-bladed stirrer; thus the agitation intensity near the pellet was considerably less than that near the blades. With the USP disintegration apparatus, the dissolution of the pellet was undoubtedly slowed by positioning it on the bottom of the beaker.

These results indicate that, with the beaker method, unwanted variations are likely, depending on the nature of the dissolving solid (disintegrating or nondisintegrating) and the particular conditions of the experiment (placement of the solid in relation to the stirrer, *etc.*). In addition, the "constant" stirring does not yield a constant (effective) agitation intensity throughout experiments with disintegrating tablets; the agitation near the intact tablet is quite different from that near disintegrated particles dispersed throughout the medium.

Comparison of Methods—The inherent deficiencies of the beaker method are essentially absent with the flow method. First, after defining the cell size, the only variable under nonturbulent flow conditions is the flow rate. Even under turbulent flow conditions, the problems seen with the pellet are reduced with disintegrating tablets, since the granules are usually small enough to circulate throughout the dissolution chamber.

Second, in light of the importance of low agitation intensities, it is encouraging to see (Fig. 10) that flow rates of less than 10 ml./min. with the 25-mm. cell yield agitation intensities lower than those provided by the three-bladed stirrer at 50 r.p.m. The inherent advantages of the flow method are emphasized by the fact that the lower flow rates needed for more laminar flow are most likely to yield meaningful *in vitro–in vivo* correlations.

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Evaluation of Tablet Breaking Strength Testers

FRANK W. GOODHART▲, J. RONALD DRAPER, DOUGLAS DANCZ, and FRED C. NINGER

Abstract □ The objective of this study was to determine the relative merits of various tablet hardness testers now used along with one new tester, the Heberlein (Tester A). The Instron Tension-Compression machine (Tester B) was used as the standard machine to which all comparisons were made. A force washer was calibrated using the Instron machine, and the identical force washer anvil setup was used on various air-operated testers for comparative measurements. The air-operated testers studied were the Strong-Cobb (Tester C1) and three modified Strong-Cobb testers (Testers C2, C3, and C4). At an Instron breaking load of 6.00 kg., Testers C2, C3, and C4 gave scale readings (kilograms per square inch) of 9.60, 9.53, and 10.2, while Tester C1 gave a reading of 10.8. Tester A results were 10–15% higher than those of Tester C1 when the units of comparison were Strong-Cobb units. The kilogram scale on Tester A gave values about 10% higher than those of Tester B. A review of the current literature on this subject is given together with a theoretical analysis of tablet breaking. From the results obtained, it is apparent that there are distinct advantages to using a hardness tester with a mechanical drive rather than a pneumatic type, because more uniform force application rates may be achieved and there is less maintenance work and less need for calibration checks.

Keyphrases □ Tablets, strength—evaluation and comparison of six testers, theoretical aspects of tablet breaking □ Strength, tablets—evaluation and comparison of six testers, theoretical aspects of tablet breaking □ Hardness testers for tablets—mechanical *versus* pneumatic driven, theoretical aspects of tablet breaking, calibration method for force response

The determination of tablet breaking strength (tablet hardness test) has become an important measurement in the formulation and manufacture of compressed tab-lets. During formulation, breaking strength is determined along with friability and disintegration–dissolution measurements since these factors are often inter-