(3) T. C. Kram, *J. Pharm. Sci.*, **61**, 254(1972).

(4) J. J. Nelson, *J. Chromatogr. Sci.*, **11**, 28(1973).

(5) R. W. Roos, *J. Pharm. Sci.*, **61**, 1979(1972).

(6) R. J. Baczuk, G. K. Landrum, R. J. DuBois, and H. C. Dehm, *J. Chromatogr.*, **60**, 351(1971).

(7) W. F. Beyer, *Anal. Chem.*, **44**, 1312(1972).

(8) C. G. Scott and P. Bommer, *J. Chromatogr. Sci.*, **8**, 446 (1970).

(9) M. W. Anders and J. P. Latorre, *Anal. Chem.*, **42**, 1430 (1970).

(10) R. A. Henry, J. A. Schmit, and J. F. Dieckman, *J. Chromatogr. Sci.*, **9**, 513(1971).

(11) S. Siggia and R. A. Dishman, *Anal. Chem.*, **42**, 1223(1970).

(12) T. C. Kram, *FDA By-Lines*, **1**, 290(1971).

(13) R. A. Dishman, Ph.D. thesis, University of Massachusetts, Amherst, Mass., July 1970, p. 135.

(14) P. Vestergaard, *Clin. Chem.*, **16**, 651(1970).

(15) F. A. Fitzpatrick, S. Siggia, and J. Dingman, Sr., *Anal. Chem.*, **44**, 2211(1972).

(16) J. A. R. J. Hulsman, Ph.D. thesis, University of Amsterdam, Amsterdam, The Netherlands, 1969, p. 65.

(17) J. A. Mollica and R. F. Strusz, *J. Pharm. Sci.*, **61**, 444(1972).

(18) W. C. Landgraf and E. C. Jennings, *ibid.*, **62**, 278(1973).

(19) F. Bailey and P. N. Brittain, *J. Pharm. Pharmacol.*, **24**, 425(1972).

(20) "The United States Pharmacopeia," 18th rev., Mack Publishing Co., Easton, Pa., 1970, p. 912.

(21) "The National Formulary," 13th ed., Mack Publishing Co., Easton, Pa., 1970, pp. 876, 877.

(22) R. E. Graham, P. A. Williams, and C. T. Kenner, *J. Pharm. Sci.*, **59**, 1152(1970).

(23) P. Ascione and D. Fogelin, *ibid.*, **52**, 709(1963).

(24) C. A. Johnson, R. King, and C. Vickers, *Analyst*, **85**, 714 (1960).

(25) A. S. Meyer and M. C. Lindberg, *Anal. Chem.*, **27**, 813 (1955).

(26) J. E. Sinsheimer and E. F. Salim, *ibid.*, **37**, 566(1965).

(27) E. J. Umberger, *ibid.*, **27**, 768(1955).

(28) S. Gorog and G. Szepesi, *ibid.*, **44**, 1079(1972).

(29) C. C. Porter and R. H. Silber, *J. Biol. Chem.*, **185**, 201 (1950).

(30) W. J. Mader and R. R. Buck, *Anal. Chem.*, **24**, 666(1952).

(31) A. A. Noujaim and D. A. Jeffery, *Can. J. Pharm. Sci.*, **5**, 26(1970).

(32) G. A. Howard and A. J. P. Martin, *Biochem. J.*, **46**, 532 (1950).

(33) "Chromatographic Methods 820M9," DuPont Instruments, Wilmington, Del., Oct. 30, 1970.

(34) D. E. Guttman and P. D. Meister, *J. Amer. Pharm. Ass.*, *Sci. Ed.*, **47**, 773(1958).

(35) J. F. K. Huber and J. A. R. J. Hulsman, *J. Chromatogr.*, **62**, 79(1971).

PHARMACEUTICAL TECHNOLOGY

Tooling as a Factor in Tablet Weight Variation and Control

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Abstract ☐ The importance of punch length uniformity to the control of tablet weight variation was demonstrated in a rotary tablet press. An assessment of the weight variation of single-station compression on the multiple-station tablet press was obtained by means of a special isolation technique involving a force-actuated weight control device. Analysis of the relation between punch length and compression force pointed to the uncertainty of the relationship between tablet weight and compression force when variations of upper and lower punch lengths are considered. Control of tablet weight based on compression force signal suffers from this uncertainty, as demonstrated by experimental data.

Keyphrases ☐ Tablet weight variation—statistical contribution of individual tool parameters of rotary press ☐ Weight variation, tablets—statistical contribution of individual tool parameters of rotary press ☐ Tool parameters of rotary press—effect on tablet weight variation ☐ Punch length uniformity, rotary tablet press—effect on tablet weight variation

A foremost concern in the manufacture of tablets is the assurance of tablet weight uniformity. Studies of tablet weight variation on single-punch tablet machines (1, 2) have generally attributed the weight variation to nonuniform filling of the dies caused by variations in such parameters as granule size and distribution, bulk density, and flow properties of the granulations. In the case of the multiple-station rotary press, however, an

Table I—Summary of Experimental Parameters

Run Number	Punches	Dies	Number of Tablets in Samples	Source of Sample
1	Old[a]	Old	199	All tablets produced at time of sampling
2	New[b]	Old	200	As in Run 1
3A	New	Old	99	All tablets rejected by weight controller as "underweight"; a single lower punch, 0.25 mm. shorter than others, was used
4	New	Old	100	Tablets rejected by weight controller as "overweight" using an arbitrary upper limit
5	New	New[b]	298	All tablets produced at time of sampling

[a] Regular production punches that were used many times. Length dimensions are in Table II. [b] New punches were checked out to be within ±0.02 mm. (0.001 in.) variation. New dies were not measured.

Table II—Length Variation[a] and Cup Depth Dimensions of Old Punches[b]

Lower Punch Dimensions, mm.		Upper Punch Dimensions, mm.	
ΔL[c]	C[d]	ΔL	C
0	0.36	0	0.28
−0.02	0.36	+0.02	0.25
0	0.30	+0.05	0.25
0	0.36	+0.10	0.23
+0.05	0.28	+0.05	0.25
−0.02	0.33	+0.05	0.23
+0.02	0.28	−0.02	0.38
0	0.36	+0.10	0.23
0	0.30	+0.02	0.28
0	0.30	+0.02	0.41
0	0.36	+0.08	0.23
0	0.36	+0.05	0.28
0	0.30	+0.05	0.28
+0.05	0.28	+0.08	0.20
+0.02	0.25	−0.05	0.36
0	0.36	−0.02	0.23

[a] Length is the working length from the face of the punch tip to the flat of the punch head. [b] All dimensions are converted from the original measurements in inches. Measurements were made to the nearest 0.0254 mm. (0.001 in.). [c] ΔL = deviation of length dimension from a reference punch in millimeters. [d] C = cup depth in millimeters.

additional source of weight variation is introduced due to dimensional variations inherent in the use of a multiplicity of punches and dies. A purpose of this study was to determine, through compression study of a single product, how dimensional variation in punch length affects weight variation and what portion of the variation is contributed by each tool parameter. A comprehensive program in tool maintenance and record keeping was described previously (3, 4). Recent establishment of standard specifications (5) of tableting tools within the pharmaceutical industry provides a sound and uniform basis for pursuing a tool control program.

Progress made in recent years on strain gauge instrumentation of the rotary tablet press allows continuous monitoring of the tablet compression process in a production situation. The relationship between tablet weight and compression force is almost linear for a significant portion of the curve (6). The use of this relation to control tablet weight automatically was reported (7, 8). However, the value of such instrumentation is contingent upon the user's awareness that the weight control is of an indirect nature and subject to restraints of dimensional tolerance of the tableting tools. Part of the data gathered in this study shows the possibility of erroneous control if tablet punch dimensions are not adequately maintained.

EXPERIMENTAL

Materials—The material used was a granulation consisting of about 94% lactose with acacia and starch binders. It is a regular production lot for producing a specially shaped ovaloid tablet with a specified average weight range of 195–205 mg. based on the weighing of 10 tablets.

Equipment—A rotary tablet press[1] with 16 stations was used. The machine was equipped with strain gauges for use with a weight checking device[2].

The punches were standard 19-mm. (0.75-in.) diameter with a flat

face beveled edge tip. The tip configuration was a 12.7 × 4.8-mm. (0.5 × 0.19-in.) ovaloid with center bisection. Both the tablet press and the tooling were regular production equipment[3]. A machine speed of approximately 60 r.p.m. was used.

Method—The tablet press was set up and operated by production personnel according to standard procedures. Weight checks and hardness tests were performed prior to production runs. After about 0.5 hr. of run time, a sample of tablets was taken and bottled. These tablets were then weighed individually on an analytical balance[4] to the nearest 0.1 mg. The length of each punch was measured, using a dial comparator and a V-block, to the nearest 0.02 mm. (0.001 in.).

During this study, changes were made in the upper and lower punches as well as in the dies to evaluate their effects on tablet weight variations. In addition, the weight controller[2] was put into operation for a portion of the test run during which off-weight tablets were rejected by the control device. These rejects were individually weighed. The upper and lower weight limits were set in terms of their compression force readings according to a regression line established prior to the run. Repeated test runs established the reliability and stability of the electromechanical systems of the weight control instrument.

Table I summarizes the different parameters used in the five runs as well as the number and description of tablet samples taken in these runs.

RESULTS AND DISCUSSION

Variation of Tablet Weight—The weight data gathered from each run were treated statistically to obtain mean tablet weight, standard deviation, and frequency distribution. Figure 1 shows the frequency distribution of tablet weight for Run 1 where old punches and dies were used. The length measurement of the upper and lower punches used is shown in Table II. Figure 2 shows the frequency distribution of tablet weight when new punches with ±0.02-mm. tolerance were used. Figure 3 shows a corresponding distribution when both punches and dies were new (Run 5). The bore of the old dies, under microscopic examination, showed signs of wear. Although no attempt was made to measure the amount of wear, it was sufficient to cause frequent capping problems during all runs except Run 5, when a new set of dies was installed.

Since the purpose of this study was to determine the tooling effect on weight variation and since these effects were not time variant, all samples were collected over a period just long enough for producing a specified number of tablets. Chi-square analysis

[1] Manesty Betapress, Thomas Engineering, Hoffman Estate, Ill.
[2] The Gretag weight control instrument (TPG 410), with accept–reject mechanism as well as strain gauge installation, was provided by Thomas Engineering, Hoffman Estate, Ill.
[3] Of the Tablet Production Department.
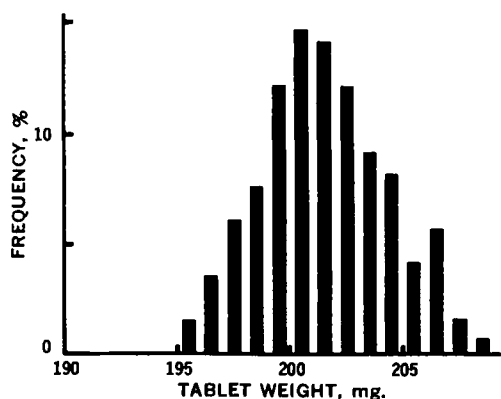[4] Sartorius model 2462, Brinkmann Instruments, Inc., Westbury, N. Y.

Figure 1—*Frequency distribution of tablet weight, Run 1, old punches and old dies. Mean sample weight = 201.4 mg., SD = 2.8 mg.*

of the tablet weight distribution showed that all samples gave normal distribution at the 95% probability level.

Table III lists the mean sample weight and the variances for Runs 1, 2, 3A, 4, and 5, where different tool parameters were used. No significance should be attached to the different values of mean weight as many weight adjustments were made throughout this study spanning several days. The tablets of Run 3A were made extra heavy by the use of an extra-short lower punch so that tablets produced at this station could be automatically rejected by the weight controller. The purpose was to isolate tablets made from a single-punch station and study the weight variation.

Effect of Tool Parameters on Weight Variation—Table III indicates that variance information may be derived from the available data to show what each parameter contributes toward the total variability of tablet weight. This follows from the statistical principle that the total variance of a system is equal to the sum of its components. The variances of Samples 1, 2, 3A, and 5 in Table III were tested and found to be significantly different at the 0.05 level or less.

In this study, the total weight variance was associated with the use of old punches and dies. The next level of variability occurred when the old punches were substituted with new punches, keeping all other parameters constant. The variability was still lowered by using new dies. The final level of variability was exhibited when only a single-punch station was involved. This "single-station" effect was achieved, as indicated earlier, by producing extra-heavy tablets through the use of an extra-short lower punch and rejecting (isolating) the tablets automatically through the tablet weight controller. The residual variability of the single-station compression stemmed primarily from variations due to granulations and the nontool part of the tablet press.
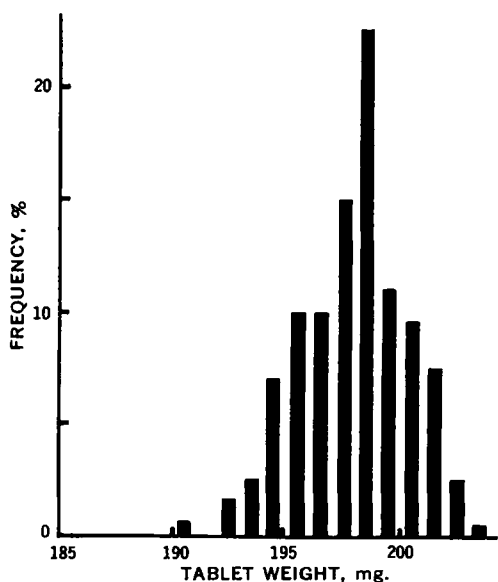
Table III—Summary of Statistical Data

Run Number	Mean Tablet Weight, $\bar{x}$, mg.	Variance, S^2	Source of Variance
1	201.4	7.97	Old punches plus old dies plus single-station variability
2	197.9	5.51	New punches plus old dies plus single-station variability
3A	205.8	1.73	Single-station variability
4	204.7	5.20	Old punches plus old dies plus single-station variability plus regression error in force-weight correlation
5	201.1	4.35	New punches plus new dies plus single-station variability

Table IV shows the variance associated with each parameter. These variance components were calculated from the data of Table III in a manner shown under the column "Reference to Variance of Table III." The subscripts for the different variances, S^2, refer to the run number. Obviously, the variance component and percentages are specific to the particular system under study and cannot be generalized to other situations. For instance, a granulation with difficult flow characteristics would have a higher proportion of the total variance associated to single-station compression. Similarly, a different set of punches with a marginal maintenance record may show a large variance and, therefore, a higher percentage of the total variance due to nonuniformity of the punches. While the comparison of variances in Table IV is not intended for generalization, such analysis is useful in pointing to the significance of good tooling as reflected in tablet weight uniformity. In the present case, as much as 45% of the weight variance was eliminated by substituting old punches and dies with new tools and a 30% reduction in variance was achieved with use of close tolerance punches (±0.02 mm.) alone.

Effect of Punch Length on Automatic Weight Control Based on Punch Force—The discussions so far have been on weight variation caused by nonuniform die fill due to variations in lower punch and die dimensions. With the availability of tablet weight control devices based on compression force, the length uniformity of the upper punches assumes added importance. The following analysis considers what happens to the compression force when the length of one or both punches is changed by a fixed amount.

The density of sulfathiazole tablets was found to be (9) linearly proportional to the logarithm of compression force for all but the
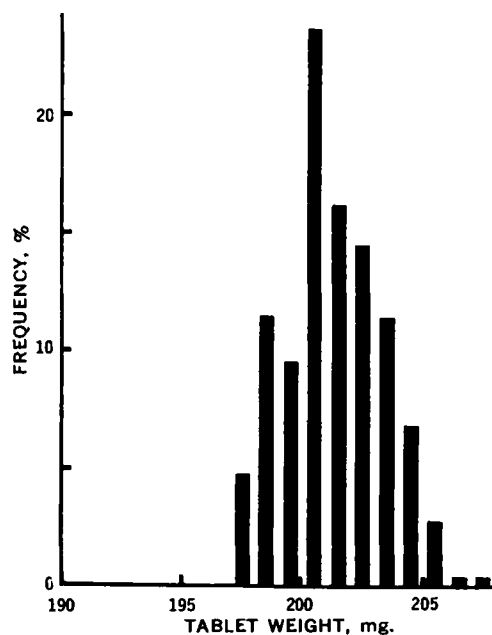

Figure 2—*Frequency distribution of tablet weight, Run 2, new punches and old dies. Mean sample weight = 197.9 mg., SD = 2.3 mg.*

Figure 3—*Frequency distribution of tablet weight, Run 5, new punches and new dies. Mean tablet weight = 201.1 mg., SD = 2.1 mg.*

Table IV—Variance Components of a Tablet Compression System Using Old Punches and Dies

Source of Variance	Reference to Variance of Table III	Variance Component, S^2	Percent of Total Variance, %
Single-station compression	S_3^2	1.73	22
Multiple-station compression with new punches and dies	$S_5^2 - S_3^2$	2.62	33
Old punches	$S_1^2 - S_2^2$	2.46	31
Old dies	$S_2^2 - S_6^2$	1.16	14
	Total variance =	7.97	100%

highest level of force. Similar relationships have been reported for p-acetanisidine (methacetin) (10) and for several alkaline halides (11). This empirical relation may be expressed as follows:

$$\ln F = \ln A + Bp_2 \qquad \text{(Eq. 1)}$$

or:

$$F = Ae^{Bp_2} = Ae^{Bp_1 V_1/V_2} \qquad \text{(Eq. 2)}$$

Differentiating gives:

$$dF = \frac{ABp_1 e^{Bp_1 V_1/V_2}}{V_2^2} (V_2\, dV_1 - V_1\, dV_2) \qquad \text{(Eq. 3)}$$

where F = compression force, p_1 = bulk density of granulation, p_2 = density of finished tablet, V_1 = volume of die fill, V_2 = volume of tablet, A = proportionality constant, and B = proportionality constant.

For very small changes in volume, Eq. 3 may be written as follows:

$$\Delta F = \frac{ABp_1 e^{Bp_1 V_1/V_2}}{V_2^2} (V_2\, \Delta V_1 - V_1\, \Delta V_2) \qquad \text{(Eq. 4)}$$

where $V_1 > V_2$, ΔF = change in compression force, ΔV_1 = change in die fill volume, and ΔV_2 = change in tablet volume.

Although data were not available to quantify the dependence of force on punch length variation according to Eq. 4, the equation does allow estimation of the direction of change in force as a result
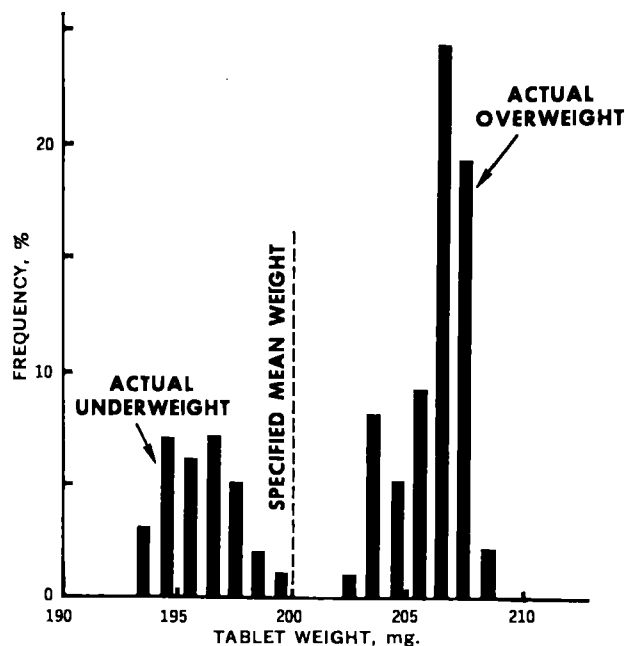
Figure 4—Frequency distribution of tablet weight, Run 3, with tablets rejected by weight controller as underweight. One lower punch is 0.25 mm. short.
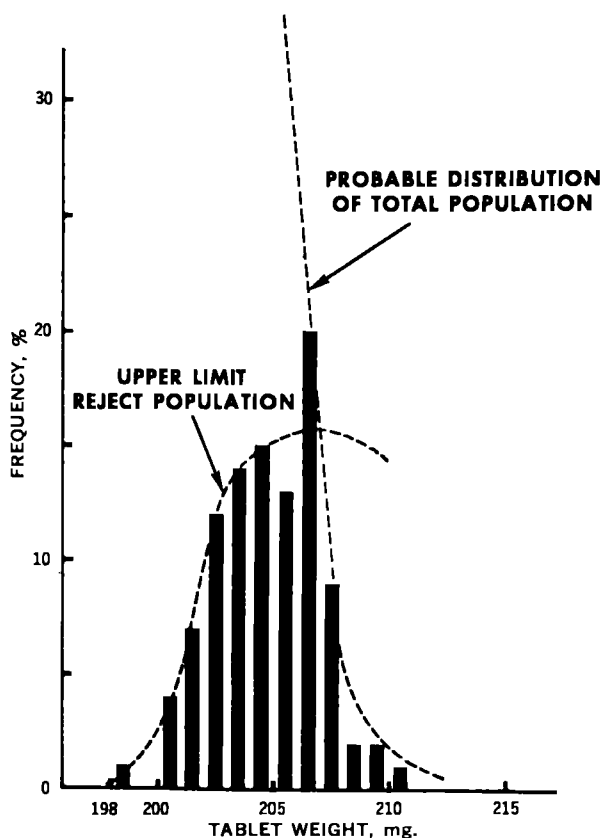
Figure 5—Frequency distribution of tablet weight, Run 4, with tablets rejected by weight controller at upper weight limit. Mean sample weight = 205 mg., SD = 2.3 mg.

of a fixed change in punch lengths in a selected combination. Table V illustrates the use of this method of estimation whereby punch length deviations of 0, +d, and −d were assumed for nine combinations. Depending upon these combinations, the punch length deviations can be translated as an increase (+) or a decrease (−) of the die fill and tablet volumes, ΔV_1 and ΔV_2. The tablet weight control device, receiving inputs of compression force, indicates deviation of the specified tablet weight in relation to the deviation of compression force, ΔF, from the set point. Thus, there is no weight deviation if $\Delta F = 0$, there is overweight if ΔF is positive, and there is underweight if ΔF is negative.

Examination of Table V reveals that it is possible to have the weight controller output contradicting the actual tablet weight. In fact, in the simplified analysis of Table V, only Cases 1, 5, and 9 give indicated weight (instrument output) in agreement with the actual tablet weight. The magnitude of the discrepancy between the indicated weight and actual weight would depend upon the extent of the punch length deviation, upper and lower punch combinations, tablet thickness, compression ratio, granulation density, and compressibility. Published data (9) were used in conjunction with Eq. 4 to gain an approximate estimate of indicated weight deviation based on deviations in punch length. Such a calculation showed that if one of the lower punches is short by 0.05 mm. (0.002 in.), the weight deviation as indicated by the weight control instrument would be about 0.7% overweight whereas the actual tablet is about 0.4% overweight. If both upper and lower punches of a station were 0.05 mm. (0.002 in.) short, then the indicated weight deviation would be about 2.5% underweight with the actual tablet weight still 0.4% overweight.

Tablet punches of wide dimensional variations are likely to produce tablets with a wide distribution of tablet weight. Under such circumstance, use of a tablet weight controller may not always assure uniformity of weight. On the contrary, erroneous control is likely, including the acceptance of rejectable tablets and rejection of acceptable tablets.

Figure 4 is a frequency distribution of tablet weight of Run 3 where an extra-short lower punch (0.25 mm. shorter than standard)

Table V—Effect of Punch Length Variation on Output Signal of Tablet Weight Controller

Case Number	Lower Punch Length[a]	Upper Punch Length[a]	ΔV_1[b]	ΔV_2[c]	ΔF[d]	Indicated Weight (from Instruments)	Actual Weight (Determined by Lower Punch)
1	Standard	Standard	0	0	0	Standard	Standard
2	Standard	+d	0	−	+	Overweight	Standard
3	Standard	−d	0	+	−	Underweight	Standard
4	−d	Standard	+	+	−	Underweight	Overweight
5	−d	+d	+	0	+	Overweight	Overweight
6	−d	−d	+	+	−	Underweight	Overweight
7	+d	Standard	−	−	+	Overweight	Underweight
8	+d	+d	−	−	+	Overweight	Underweight
9	+d	−d	−	0	−	Underweight	Underweight

[a] In this analysis, deviation from standard punch length is either +d (longer by d mm.) or −d (shorter by d mm.). [b] ΔV_1 = change in die fill volume. [c] ΔV_2 = change in tablet volume. [d] ΔF = change in compression force.

was used. The strongly bimodal distribution indicates the presence of two distinct populations within the sample. The tablets with mean weight of 195 mg. were actually underweight tablets produced at the same time as those made by the short punch station with a mean weight of 206 mg. Both groups exhibited low compression force and were rejected as underweight, although one group was actually overweight. This illustration is similar to Case 4 or 6 of Table V.

Figure 5 is a frequency distribution of tablet weight from a sample of overweight rejects. A sharp cutoff is absent at the overweight reject point. Rather, the weights are normally distributed with a standard deviation as large as that of the tablet population (Fig. 3). Underweight rejects, although not analyzed, are believed to have similar frequency distributions. Although there are other factors, tool uniformity is probably a significant factor in causing a weight distribution rather than a sharp cutoff at the rejection point. The same factor is probably also responsible for a lack of precise correlation between compression force and tablet weight. Ridgway et al. (8), in analyzing the performance of their closed-loop weight controller, experienced similar frequency distribution in the underweight and overweight rejects as well as scattering of data in the correlation between compression pressure and tablet weight.

SUMMARY

The weight variations of tablets produced on a rotary tablet press were analyzed. Estimates were made from the statistical data as to the contribution of each tool parameter to the total variance in tablet weight.

The effect of punch length variation was also explored for its interaction with tablet weight controllers which derive their input signal from compression force. Possible erroneous control is cautioned if critical tool dimensions are not adequately maintained.

REFERENCES

(1) I. Alsos, S. G. Dahl, and T. Waaler, Pharm. Acta Helv., 44, 27(1969).

(2) H. Delonca, A. Peuch, Y. Youakim, and G. Segura, ibid., 44, 464(1969).

(3) C. J. Swartz, S. Weinstein, J. Windheuser, and J. Cooper, J. Pharm. Sci., 51, 1181(1962).

(4) C. J. Swartz and J. Anschel, ibid., 57, 1779(1968).

(5) Tableting Specification Manual, IPT Standard Specifications for Tableting Tools, Academy of Pharmaceutical Sciences, Washington, D. C., 1971.

(6) E. L. Knoechel, C. C. Sperry, and C. J. Lintner, J. Pharm. Sci., 56, 116(1967).

(7) O. Schupback, F. Kestenholz, and R. Furtwangler, Pharm. Ind., 30, 743(1968).

(8) K. Ridgway, J. J. Deer, P. L. Finlay, and C. Lazarou, J. Pharm. Pharmacol., 24, 203(1972).

(9) T. Higuchi, N. Rao, L. W. Busse, and J. V. Swintosky, J. Amer. Pharm. Ass., Sci. Ed., 42, 194(1953).

(10) L. N. Elowe, T. Higuchi, and L. W. Busse, ibid., 43, 718 (1954).

(11) E. Nelson, Ph.D. dissertation, University of Wisconsin, Madison, Wis., 1954.

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