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Variability of Uniformity of Weight Test as an Indicator of the Amount of Active Ingredient in Tablets

By J. M. AIRTH, D. F. BRAY, and C. RADECKA

Fifty-four samples, embracing five drugs sold as compressed tablets, were obtained. Individual tablet weights were determined and individual chemical assays were carried out on 10 tablets from each sample. There was little or no relationship between the amount of active ingredient and tablet weight for promazine tablets in which the active ingredient formed a small proportion (15–23 per cent) of tablet weight, but this relationship was high for tolbutamide tablets in which the active ingredient formed a large proportion (73–90 per cent) of tablet weight. This observation suggests that the uniformity of weight test may sometimes be usefully employed instead of individual tablet chemical assays when the proportion of active ingredient in the tablets is high and that the emphasis in developing direct measures of content uniformity should be placed on preparations containing small proportions of active ingredient. The present data do not confirm the observation of Moskalyk *et al.* (1961) that "Greater deviations 'in active ingredient' were found to occur in lighter weight tablets" within preparations.

THE UNIFORMITY of weight test has been included in the "British Pharmacopoeia," the "United States Pharmacopeia," and the "National Formulary" for many years. Its purpose has been to provide an indication of the amount of active ingredient in each tablet. The validity of such a test depends, of course, on the assumption that the amount of active ingredient is directly proportional to the weight of the tablet. While various aspects of the uniformity of weight test have been studied previously (see for example *References 1–3*), general recognition of its inadequacy in certain situations has only recently been recognized. The 17th revision of the U.S.P. and the 12th edition of the N.F. included for the first time a content uniformity test for certain tablets. While determinations of the amount of active ingredient in individual tablets will be necessary for some preparations, there seems little point in taking these more costly observations in cases where the uniformity of weight test gives comparable results. It is the purpose of this paper to present some data which suggest that the uniformity of weight test may be satisfactory for some tablet preparations, but inadequate for others.

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MATERIALS AND METHODS

Samples of five drugs sold in compressed tablet form were procured from Canadian retail outlets in bottles of 100 tablets. A total of 54 samples from 36 different companies were obtained. In general, not more than one sample of each drug was obtained from each company, and in fact 53 of the possible 180 company-compound combinations are represented.

TABLE I.—METHODS OF ASSAY

Drug	Samples, No.	S.D., % Recovery	Analytical Method
Promazine hydrochloride	5	0.37	Milne and Chatten (4)
Isoniazid	7	0.60	Scott (5)
Phenylbutazone	13	0.60	B.P. (6) with refinement to permit assay of 100 mg. of drug
Phenobarbital	7	0.60	Chatten (7) and/o Mattson (8)
Tolbutamide	22	0.32	U.S.P. (9)

Ten tablets were taken from each bottle for chemical assay. Two methods of selecting the tablets for assay were used. In 18 samples, 10 tablets were chosen in an essentially random manner. In the remaining 36 samples, 100 tablets were weighed and the 3 lightest, the 4 medium, and the 3 heaviest were selected for analysis.

The 10 selected tablets from each sample were individually weighed to the nearest 0.1 mg. and individually chemically assayed by the appropriate method indicated in Table I.

A single determination was carried out on each tablet by one of the authors (Radecka). Experience in this laboratory has shown that the assay error is uniformly small for all methods reported here. Values are given in Table I as standard deviations of per cent recovery.

RESULTS AND DISCUSSION

Linear regression techniques were used to study the relationship between amount of active ingredient and tablet weight. The slope (b) of the least squares regression line fitted to the data from each sample was compared with the one which indicated no relationship between active ingredient and tablet weight (β_0), and with the one which assumed the amount of active ingredient to be directly proportional to tablet weight (β_1). The former theoretical line passes through the bivariate mean of the sample data and has slope (β_0) equal zero, while the latter passes through the origin, and has slope $(\beta_1) = \frac{\Sigma xy}{\Sigma x^2}$ which in these data is extremely close to $\bar{y}/\bar{x}$, where y is the amount of active ingredient in a tablet in mg., and x is the tablet weight in mg.

A better estimate of β_1 could be obtained if the tablets had been procured directly from the manufacturer along with data indicating the actual amounts of active ingredient and other materials used. The authors have assumed that such data would give estimates of β_1 which would be essentially similar to those reported here.

It follows, therefore, that any given sample can be placed into one of four categories on the basis of the calculated value of the regression (b) of active ingredient on tablet weight ($P = .05$):

I, not significantly different from either β_0 or β_1.
II, significantly different from β_1, but not β_0.
III, significantly different from both β_1 and β_0.
IV, significantly different from β_0, but not β_1.

Both category I and category II imply the absence of a slope, and hence indicate no useful relationship between active ingredient and tablet weight. In contrast, both categories III and IV indicate the presence of a slope, in the latter case not demonstrably different from β_1, and hence suggest a situation in which the uniformity of weight test may possibly be used as an indicator of content uniformity. A typical example of a sample falling into each category is illustrated in Fig. 1.

Table II gives the number of samples in each category by drug and range of per cent active ingredient. The samples have been divided into a low group and a high group on the basis of per cent active ingredient, with the division occurring at 33%. This classification is an arbitrary one and is simply that suggested by the observed frequencies. Table II suggests that a relationship exists between the proportion of active ingredient and the category of response. Promazine tablets, having the smallest proportion of active ingredient, gave only category I and II responses, suggesting that the uniformity of weight test would be unsatisfactory as an indicator of content uniformity. Tolbutamide tablets, having the highest proportion of active ingredient, gave only category III and IV responses, suggesting that the uniformity of weight test may be usefully employed in such situations.

Since the drugs which gave the extreme responses were also those at the extremes in per cent active ingredient, it is impossible to state whether the observed relationship with category is a property of per cent active ingredient or a property of the drug examined. Only two drugs, phenylbutazone and

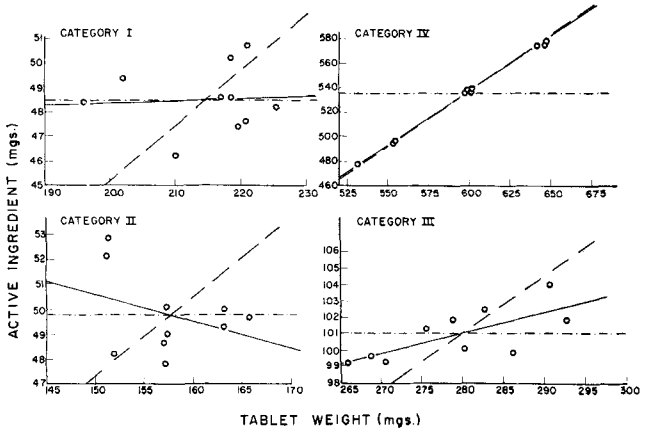

Fig. 1.—Examples of regression relationships. Key: category I, promazine, 23% active ingredient; category II, isoniazid, 32% active ingredient; category III, phenylbutazone, 36% active ingredient; category IV, tolbutamide, 90% active ingredient; · · · · · · · , β_0; — — —, β_1; ————, b.

TABLE II.—NUMBER OF SAMPLES IN EACH CATEGORY[a] INDICATED BY SIGNIFICANCE TESTS OF REGRESSION COEFFICIENTS

Drug	Range of % Active Ingredient		Category					
			I		II		III	IV
	Low	High	Low	High	Low	High	Low	High
Promazine	15–23		2		3		0	0
Isoniazid	20–32		1		3		0	3
Phenylbutazone	23–33	36–43	2		1		0	2
				3		3	1	1
Phenobarbital	26–31	33–60	1		0		0	3
				0		0	2	1
Tolbutamide		73–90						
				0		0	4	18

[a] See text for description of categories.

TABLE III.—NUMBER OF SAMPLES BY PER CENT ACTIVE INGREDIENT AND CATEGORY

Active Ingredient, %	Cagetory	
	I and II	III and IV
Low	13	8
High	6	27

phenobarbital, gave sufficiently varied responses and were represented over a sufficiently wide range of per cent active ingredient to give an indication of the effect of per cent active ingredient free from the effect of drug. Table II illustrates that the results of this examination are inconclusive.

The summary given in Table III illustrates the apparent relationship between per cent active ingredient and category. While some caution is needed in interpreting this table due to the partial confounding of drug with per cent active ingredient described in the preceding paragraph, it may be helpful to note that the interaction chi-square is significant at $P = 0.01$.

The data presented here were examined in the light of the observation of Moskalyk *et al.* (1) that, "Greater deviations," in active ingredient, "were found to occur in lighter weight tablets," within preparations. The variance about the line with slope β_1 was computed for the three largest and the three smallest tablets for all 54 samples. The ratio

$$\frac{\text{variance about the line with slope } \beta_1 \text{ of 3 largest tablets}}{\text{variance about the line with slope } \beta_1 \text{ of 3 smallest tablets}}$$

was formed for each sample. Values of the ratio less than 1 support Moskalyk's statement while those greater than 1 do not. In fact, 28 ratios were less than 1, and 26 were greater. This result is not different from the 1:1 ratio which is expected on the basis of no difference between the two variances. At one point in the paper of Moskalyk *et al.* the observation was restricted to "less uniformly mixed brands," these being the ones with large over-all variation about the line having slope β_1. If this hypothesis were true, the ratio would be expected to be small when the variance about the line for all 10 tablets is large, and tend toward 1 when the variance is small. No relationship between variance and ratio is apparent in these data (Fig. 2).

Since the preceding discussion is based on a model assuming that all points lie about the line passing through the origin and since this is not the best fitting line for all 54 samples, the same techniques

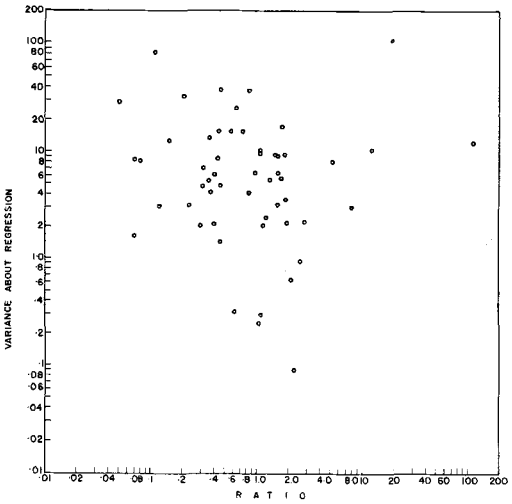

Fig. 2.—Lack of a relationship between variance about regression and ratio:

$$\frac{\text{variance about regression of larger tablets}}{\text{variance about regression of smaller tablets}}$$

were applied to the variation about the least squares line without restriction, *i.e.*, having slope b. A 31:23 ratio of ratios was obtained and the plot was similar to Fig. 2. Not all samples gave exactly similar results, but the conclusions are not different.

The present study fails to confirm the observation of Moskalyk *et al.* that "Greater deviations," in active ingredient," were found to occur in lighter weight tablets." A reason for the apparent contradiction may lie in the fact that no statistical tests were applied to the data bearing on this point in their paper.

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