Nevertheless, on acid hydrolysis the compound gave herniarin. The formation of herniarin may be accounted for by the transformation of the liberated 2-hydroxy-4-methoxy-*trans*-cinnamic acid (IV, Scheme II) to the *cis*-form in presence of hydrogen ions. However, enzymatic hydrolysis did not give herniarin but gave 2-hydroxy-4-methoxyethyl *trans*-cinnamate (IV) which was found to be less mobile on paper than herniarin. The structure of the glucoside (I) was also ascertained through its de-ethylation to the free-acid glucoside (III) which was identical in every respect with authentic material prepared synthetically (7).

SUMMARY

2-Glucosyloxy-4-methoxyethyl *trans*-cinnamate was isolated in a crystalline form from the alcoholic extract of *Prunus mahaleb* L. fruit kernels. The structure of this compound was proved by IR, NMR, and mass spectra. It was further ascertained by de-ethylation of the compound to the free-acid glucoside which was identical with authentic material. On acetylation, it afforded a tetraacetate, the spectral studies of which (IR, NMR, and mass spectra) assured the suggested structure. On acid and enzymatic hydrolysis, it afforded glucose which was identified by chromatographic techniques.

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Tablet-to-Tablet Variation of Drug Content of Sugar-Coated Tablets Containing Drug in the Sugar Coat

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Abstract □ In dosage forms where active drug is added to a sugar coat, it may be shown that the distribution of assays should be normal and the standard deviation should be proportional to the square root of the number of coats. Although, in a series of batches, the standard deviation was found linearly related to the square root of the number of coats, the plot failed to intersect at the origin and did not have the required slope, presumably due to secondary contributions to the variation such as pan build-up.

Keyphrases □ Drug content variation—sugar coating, tablets □ Tablet coatings—drug content variation □ Core size, tablets—coating drug content variation □ Coatings, tablet—drug content relationship

In recent years, several publications have dealt with tablet-to-tablet variation of uncoated tablets or compression coated tablets. Garrett (1) and Garrett and Olson (2) have studied the problem from the point of view of content of drug; Brochmann-Hanssen and Medina (3), Smith *et al.* (4), Lazarus and Lachman (5), and Airth *et al.* (6) analyzed the situation from the point of view of weight variation. Some publications, *e.g.*, those of Lachman *et al.* (7) and Kaplan (8), conclude that statistical variation may be used as a means of evaluating processes; whereas others, *e.g.*, those by Grundman and Ecanow (9) and French *et al.* (10), have been concerned with the problem of statistical sampling.

The inherent variations in sugar-coated tablets have been touched upon by Bhatia (11), but this paper aims not at the statistical variation to be expected but rather on the effect of incompatibilities. Anderson and Sakr (12), in a comprehensive treatment of the statistics of sugar coating, studied the mean line average as a parameter, since smoothness of the tablet was their main point of discussion. Since some coated tablets contain the active component in the sugar coat, it would appear important to know whether expected statistical variations might apply in such a situation. Mattocks (13) has pointed out the problem associated with uniformity of coating, and Butensky (14) has found that, weightwise, the coefficient of variation rises to a maximum of 7% at a stage prior to the final subcoating. The work by Anderson and Sakr (12) also implies that the coefficient of variation of the mean line average appears to level off at a certain stage of the coating operation,

Table I—Tablet-to-Tablet Variation of Sugar-Coated Tablets, Showing Standard Deviation as a Function of Number of Coats, *n*

Number of Coats (*n*)	$\sqrt{n}$	$10^2 \times SD$ (Σ), mg.	Average Drug Content per Tablet ($n\mu$), mg.	$\sqrt{n\mu}$
1	1.00	1.6	0.120	0.347
2	1.41	3.0	0.244	0.494
6	2.45	12.5	0.693	0.835
11	3.32	19.3	1.214	1.102
13	3.61	23.6	1.456	1.208
16	4.00	22.5	1.790	1.340

Table II—Results of Applying an Active Drug in Sugar Coating, Showing Distribution of Assays after the First Coats

Range, mg.	Actual Assays, mg.[a]	Number of Occurrences	Fraction of Total	Fraction Expected if Normally Distributed
<0.087		0	0	0.001
0.087–0.103	0.099, 0.100, 0.096, 0.101, 0.102	5	0.25	0.34
0.104–0.119	0.118, 0.107, 0.113 0.117, 0.116, 0.109	6	0.55	0.50
0.119–0.135	0.123, 0.132, 0.123 0.128, 0.125	5	0.80	0.84
0.135–0.154	0.149, 0.135, 0.143 0.152	4	1.00	0.999
>0.154		0	1.00	1.00

[a] Average assay 0.119 mg., *SD* 0.016 mg.

and, thereafter, the coefficient of variation remains fairly constant with increasing weight.

In studying the drug content uniformity in the coating of tablets, it has been the experience of the authors that the size of the tablet affects the final tablet-to-tablet variation. The aim of the investigation reported here is an analysis of this point and of the statistical assumptions which can and cannot be made.

EXPERIMENTAL

Deep concave placebo tablet cores were enteric coated, and subcoats were added in conventional fashion in an 81.31-cm. (32-in.) tablet-coating pan. The drug, which had an exceedingly low water solubility, was micronized and then added in form of a suspension in a gelatin–acacia syrup. Sixteen applications of equal weight were used to accomplish a total addition of 1.79 mg. of drug per tablet.

Twenty tablets were removed and assayed individually after the first and 16th applications, and 10 tablets were removed and assayed after the 2nd, 6th, 11th, and 13th applications. The average drug content and the standard deviations were calculated for each sample. The standard deviations obtained after the various coats are listed in Table I. The results are shown graphically in Fig. 1. The individual results from the sample taken after the first coat are listed in Table II.

Four additional batches were made, using the same coating procedure and tablet core (120 mg.), but assays were only performed on the final tablet (20 individual tablets). One batch was made with a 100-mg. core, two batches were made with a 160-mg. core, and three batches were made with a 175-mg. core, again employing the same manufacturing procedure but only assaying 20 individual tablets of the final product. Seven batches of tablets of four other active compounds were produced and assayed in a similar fashion, using different core sizes (120, 175, 300, and 390 mg.). The tablet-to-tablet variation of the final tablets appeared normally distributed; the results from all 18 batches are shown in Figs. 2 and 3.

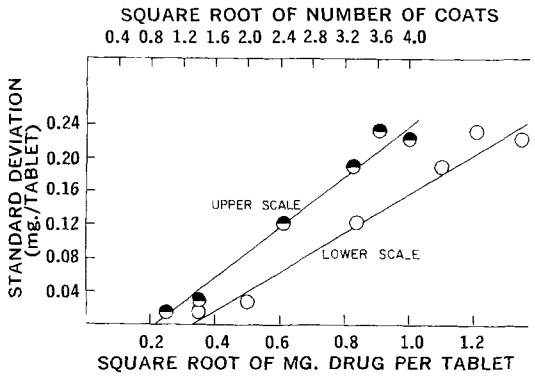

Figure 1—*The standard deviation of assayed drug content of tablets as a function of the square root of the number of coats (upper scale) and the square root of the amount of drug found per tablet (lower scale).*

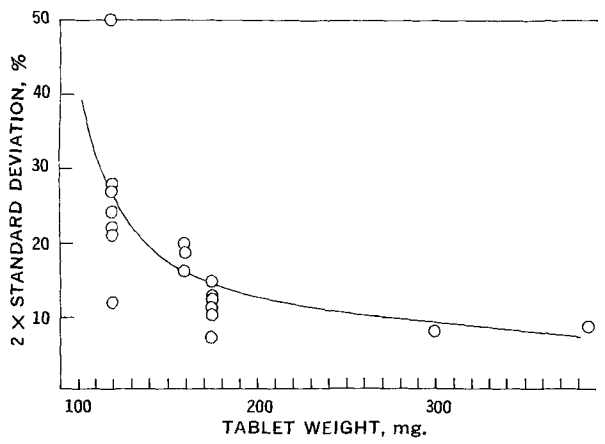

Figure 2—*Sugar-coated tablets with drug in sugar coat: 2 × standard deviation as a function of tablet size.*

RESULTS AND DISCUSSION

The data in Table II and Fig. 4 imply a normal distribution of the assays of the first coat; the variance associated with this will be denoted as σ^2 in the following. The test for normality is not rigorous, but suffices to justify the assumption of normality as a starting point. As shall be shown, this assumption implies a normal distribution of the final tablet assays as well. Other conceivable distributions would be binomial (fraction p coated, $[1-p]$ not coated). This for a large number of applications would lead to a Poisson distribution and eventually, for a very large number of coatings, would approximate a normal distribution. In this light, 16 applications is not a large number. If one assumes that the distribution of the first coat can be described by the normal deviate x_1, the second coat by x_2, and the n^{th} coat by x_n, each with an average μ, and if one assumes $x_1, x_2, \ldots x_{16}$ to be independent variables, then (as shown in the *Appendix*) it is straightforward to show that the variance after n coats (Σ^2) should be given by $n\sigma^2$, where σ is assumed to be identical for each coat, *i.e.*, equal to that of the first coat. A plot of the standard deviation as a function of the square root of the number of coats should, therefore, produce a straight line through the origin with a slope identical to the standard deviation of the first coat: $\Sigma = \sigma \cdot \sqrt{n}$. The coefficient of variation will decrease with increasing number of coats since

$$\frac{\sqrt{n\sigma^2}}{\mu n} = \frac{\sigma}{\mu\sqrt{n}} \qquad \text{(Eq. 1)}$$

It is seen from Fig. 2 that the standard deviation of individual tablet assays from all 18 batches (of varying tablet size) exhibited great scatter. The trend, however, is unmistakably that the standard deviation decreases with increasing tablet size. Although it is difficult to draw conclusions from such data, some speculation may be offered. Figure 3 represents the data of Fig. 2 in logarithmic form, and a line of slope 1 is more compatible with the data than a line of slope $\frac{2}{3}$, so that the standard deviation might be related to the volume (or weight) of the tablet rather than to the surface. If this

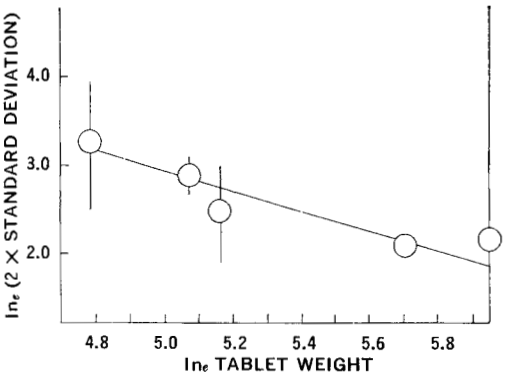

Figure 3—*Variation of drug content as a function of tablet size on a natural logarithmic scale. The standard deviation is on a percentage basis, the tablet weight is in milligrams.*

indeed is the case, then the assumption that σ is the same for all 16 applications may not be true.

The volume increase during the 16 coats is small; however, it would appear from Fig. 1 that the size increase during the application of the active coat does not play an important role, since linearity seems to prevail. On the other hand, it is obvious that the line neither passes through the origin nor has a slope equal to the standard deviation of the first application. It is possible, since there is always build-up on the pan, that in the earlier stages some drug is deposited on the build-up on the pan and that in later coats some drug is applied back to the tablets by attrition, and thus a second contribution to the standard deviation occurs.

The findings have significance in the sense that the tablet-to-tablet variation will be smaller the larger the number of coats, *i.e.*, the application of a given amount of drug is best accomplished with a larger number of coatings of more dilute coating mixture than with a smaller number of coatings with a more concentrated mixture. The data also imply that a large tablet core yields a better drug distribution in the active coat than a small core. It is obvious that other factors (*e.g.*, viscosity and surface activity of the syrup-suspension containing the active ingredient, as well as core shape) are of significance. These have not been a subject of this study and have been kept constant in order to evaluate the statistical, rather than the physicochemical, aspect of sugar coating.

APPENDIX

Suppose n coats of active material are applied to a panload of tablets. Let the distribution of the first coat be designated by the normal deviate x_1, the second x_2, and the n^{th} x_n, and, assuming $x_1, x_2, \ldots x_n$ to be independent variables with identical variances, then the moment-generating function for the distribution of $x_1 + x_2 + \cdots + x_n$ is (15)

$$M_{x_1+x_2+\cdots+x_n}(\theta) = M_{(x_1)}M_{(x_2)}\ldots M_{(x_n)} =$$

$$\prod_{i=1}^{n} \frac{1}{\sigma\sqrt{2\pi}} \int_{-\infty}^{\infty} \exp[x_i\theta] \cdot \exp\left[-\frac{[x_i-\mu]^2}{2\sigma^2}\right] dx_i = e^{\theta n\mu} \cdot e^{n\sigma^2\theta^2/2} \quad \text{(Eq. 2)}$$

where μ is the amount of drug applied. The first moment about $\theta = 0$ is the mean $n\mu$ and is given by:

$$\left[\frac{\partial M}{\partial \theta}\right]_{\theta=0} = n \cdot \mu \quad \text{(Eq. 3)}$$

The second moment is

$$\left[\frac{\partial^2 M}{\partial \theta^2}\right]_{\theta=0} = [n\mu]^2 + n \cdot \sigma^2 \quad \text{(Eq. 4)}$$

The variance is the second moment minus the square of the first moment, both at $\theta = 0$, *i.e.*:

$$\Sigma^2 = [n\mu]^2 + n\sigma^2 - [n\mu]^2 = n\sigma^2 \quad \text{(Eq. 5)}$$

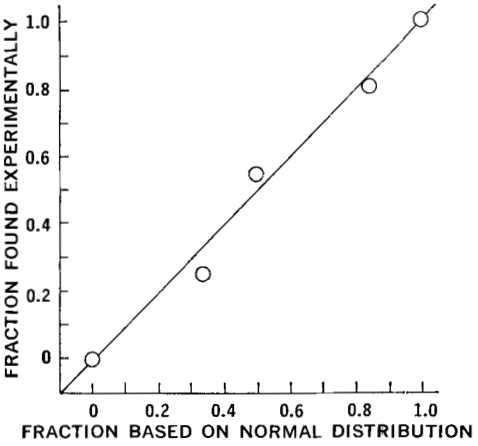

Figure 4—*Results from the last two columns of Table II. The ordinate is the cumulative fraction larger than a certain figure, and the abscissa is the fraction expected if the distribution were normal with average content 0.119 mg. and* SD *0.016 mg.*

If one takes the square root:

$$\Sigma = \sigma \cdot \sqrt{n} \quad \text{(Eq. 6)}$$

i.e., the standard deviation after n coats (Σ) is proportional to the square root of the number of coats with σ, the standard deviation of the first coat, as the proportionality factor. Furthermore the distribution after n coats will be normal if it was normal originally. For large n, this may be expected for any type distribution (central limit theorem).

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