# Dosage Variation in Tablets

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**Tablet granulations of phenobarbital and reserpine were prepared on a routine manufacturing basis and compressed on a single-punch tablet press. The tablets were collected in small groups in the order of compression, weighed, and analyzed individually. Statistical quality control charts were prepared for weight variation and per cent composition, the main variables affecting the dosage variation. Inspection of the control charts and results obtained by application of the *F*-test indicated that some disruption of uniformity occurred during the compression of the tablets.**

THE TOLERANCE LIMITS in the "United States Pharmacopeia" and "National Formulary" are established in such a way as to make allowance for a number of unavoidable variables, including the assay error, the sampling error, and a certain amount of deterioration of the active ingredient (1, 2). In an effort to reduce the sampling error for tablets, the official compendia specify that not less than a stated number of tablets be taken as the sample. Although this number frequently may be as low as 10 or 20, it may run as high as 200 for tablets of certain potent drugs. The result of the assay expresses the average content of active ingredient per tablet in the sample but tells nothing about the uniformity of dosage. There are two obvious sources of variability affecting the drug dosage in tablets—namely, the variation in weight and the variation in per cent composition. The variation in weight has been extensively studied by many investigators (3–5) and can be determined and controlled by the official method or, better, by a method based on the standard deviation. The control chart is a useful tool for controlling the weight variation during production. Composition variation is not as easily determined. Studies carried out in several laboratories have indicated that this variation often is the largest of the two.

Variation in per cent composition is associated with the problems of mixing. Although there is now an appreciable literature on the mixing of solids in general, it is only in recent years that the pharmaceutical aspects of mixing have been studied and their effects on the uniformity of drug dosage and drug standardization have been recognized. In the production of tablets, a perfect mixture represented by a random distribution of the particles can never be attained. Proper equipment and sufficient time of mixing are certainly important considerations, but the mixing process is also affected by the size, shape, proportion, and density of the particles and by various surface-active forces (6, 7). Even if a fairly uniform particle distribution has been achieved, this condition is unstable and is easily disturbed by vibration or bumping (7). In the preparation of uniform tablet granulations, the solubility of the drug in the granulating solvent, and the conditions of drying also play important roles (8).

The various problems associated with the mixing of solids together with the minimum sample required for analysis of tablets have led Train (7) to predict that, although the official specifications may be met under the conditions of the assay, the dosage variation can be over twice the official limits in a few cases, over four times the official assay limits in most cases, and eight or more times the official limits with one or two formulations. This is especially true if the active ingredient is less than half the tablet weight and is added as a powder or a batch of concentrated granules which are mixed with other granular materials.

The effect of the particle size and the proportion of active ingredient on the uniformity of powder mixtures, granulations, and compressed tablets have been studied by Fryklöf (9) and Banker, Christian, and DeKay (8). Commercial samples of various tablet preparations analyzed by the Food and Drug Administration showed a wide range of dosage apparently not related to the weight variation (10). Moskalyk, *et al.* (11), reporting on the uniformity of drug dosage in commercial tablets, have also found

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variations in potency which have been greater than those indicated by the weight variation.

Raff, *et al.* (12), have shown that internal flow and segregation of granulation take place during compression, causing a change in the weight and the hardness of the tablets. It is of interest to know to what extent such segregation affects the composition of the tablets. The present investigation was undertaken with this in mind and also for the purpose of studying the relationships between dosage variation and composition variation for tablets containing various concentrations of active ingredient.

## EXPERIMENTAL

**Tablet Preparations.**—Phenobarbital tablets were prepared in three different strengths—16 mg., 65 mg., and 100 mg. per tablet—the drug constituting approx. 10, 33, and 44% of the tablet weight, respectively. A batch of 0.25 mg. reserpine tablets was also included in which reserpine amounted to about 0.175% of the tablet weight. The tablet granulations were prepared according to standard manufacturing procedures by wet granulation of mixtures of the drug and the diluents with aqueous granulating agents. The tablet press was a Colton model 2B single-punch machine operated at a speed of 90–100 tablets per minute. It had been in operation for many years and was worn to the extent of having a somewhat rough action. The batches which ranged in size from 60,000–300,000 tablets were produced on a routine basis in the Pharmaceutical Technology Laboratory for the University Hospital Pharmacy.

**Sample Collection.**—The hopper was filled, the machine adjusted for correct weight and pressure, and allowed to run for about 0.5 hour. From then on, samples of five tablets each were collected at 30-minute intervals; the tablets were weighed and assayed individually. This was done independently of the checking for weight variation and the normal adjustments made by the manufacturing personnel.

To study the uniformity of the tablet granulations, small samples were collected from the bulk granulation during the course of the tableting process. Amounts approximately equal to the tablet weight were weighed out and analyzed as described below.

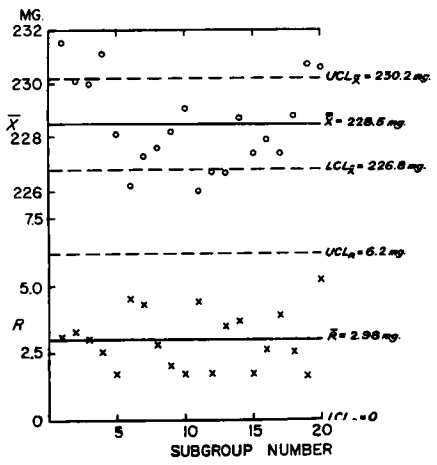


Fig. 1.—Control chart for weight variation of 100-mg. phenobarbital tablets.

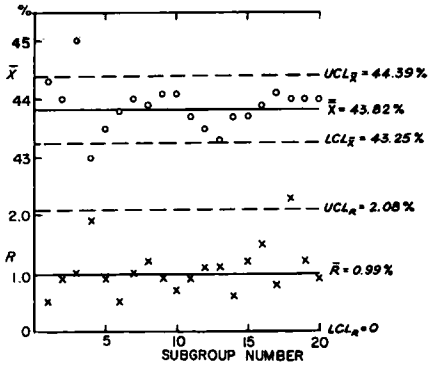


Fig. 2.—Control chart for the variation in per cent composition of 100-mg. phenobarbital tablets.

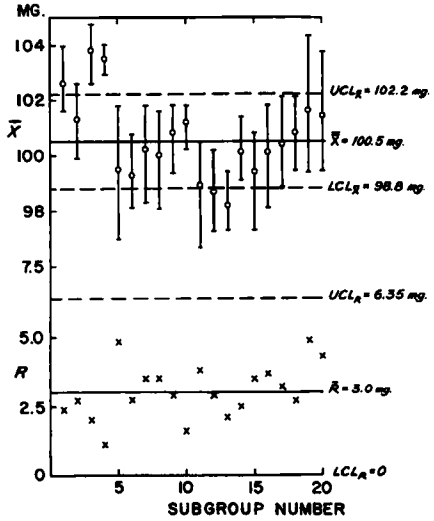


Fig. 3.—Control chart for dosage variation of 100-mg. phenobarbital tablets.

**Assay Procedures.**—Because of the large number of determinations to be made and the low dosage of some of the tablets, it was essential to have assay procedures which were rapid and sensitive and had a high degree of precision. Individual phenobarbital tablets were placed in 100-ml. volumetric flasks containing 25 ml. of water. After disintegration of the tablets, ethanol (95%) was added to volume. When the drug had dissolved, the solution was thoroughly mixed and filtered through a dry filter; the first 25 ml. of the filtrate was discarded. An aliquot portion of the filtrate was mixed with borate buffer of pH 10, diluted with water to an appropriate concentration, and the absorbance was read in a Beckman model DU spectrophotometer against a reagent blank at 240 mμ. Phenobarbital from the same production batch was used as the reference standard.

Reserpine tablets were also assayed by ultraviolet spectrophotometry. One tablet was placed in a 25-ml. volumetric flask, 2 ml. of water was added, and the tablet was allowed to disintegrate. After

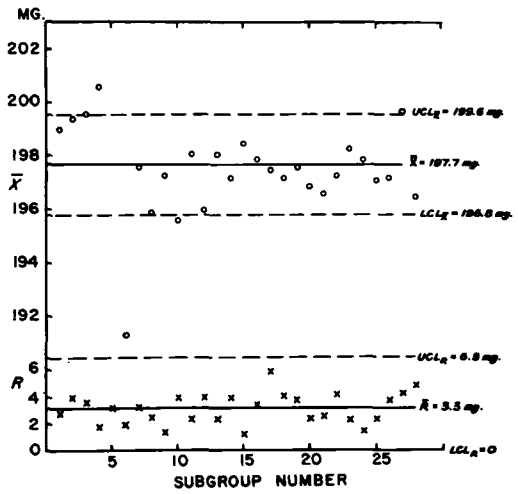


Fig. 4.—Control chart for weight variation of 65-mg. phenobarbital tablets.

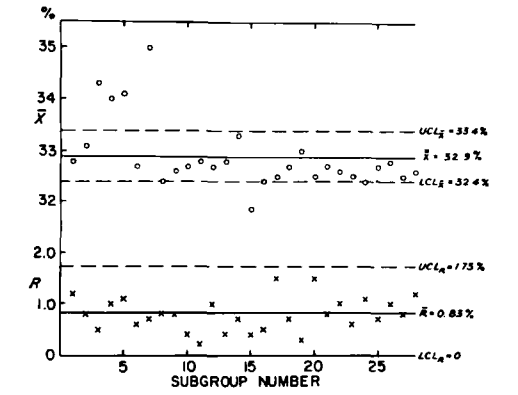


Fig. 5.—Control chart for the per cent composition variation of 65-mg. phenobarbital tablets.

addition of 20 ml. of reagent grade methanol, the mixture was heated gently on a steam bath for 5 minutes and then cooled to room temperature. Methanol was added to volume, the solution mixed well and filtered through a small dry filter; the first 10 ml. of the filtrate was discarded. The absorbance of the filtrate was determined at 268 mμ against a mixture of 2 ml. water and 23 ml. methanol.

**Precision.**—For the determination of precision, accurately weighed amounts of the reference standards were dissolved and treated in the same manner as the tablets. The standard deviation was calculated on the basis of 15 independent determinations. The coefficient of variation was 0.80% for the phenobarbital assay and 2.5% for the reserpine assay.

**Control Charts.**—The control chart designed by Shewhart, a commonly used tool for process control, is based on the two types of variables involved in the manufacturing process. One is the random variability associated with short-term variability in the raw material, handling, measurement, etc. The other is the variability due to real changes in the process level. The random variability is estimated on the basis of the variability within small subgroups collected in short periods of operation during which only random errors, but no real changes in process level, are likely to occur. Three-sigma limits are usually drawn about an established standard level. If there is no shift in the process level, 99.73% of the subgroup averages would be expected to fall within these control limits. The commonly used control charts for variables are the $\bar{X}$ and the $R$ charts, showing shifts in the process average and the dispersion, respectively. The statistical methods for preparation and use of the control charts are given in standard texts (13, 14).

## RESULTS AND DISCUSSION

Figure 1 illustrates the $\bar{X}$ and $R$ charts for weight variation of 100-mg. phenobarbital tablets. The range shows evidence of control during the whole period of production, whereas the process average does not. This is partly due to the rough action of the tablet machine and segregation of the particles in the granulation. The variation in per cent composition for the same tablets is illustrated in Fig. 2. It is apparent that the system is not in control from a statistical point of view. Instead of being randomly distributed around the batch mean, the process average shows a cycling effect. The two sources of variation are combined in Fig. 3 which gives the actual dosage variation in terms of content of phenobarbital per tablet. The vertical lines in the $\bar{X}$ chart indicate the spread of individual tablets about the subgroup means. None of the 100 tablets analyzed during the compression of this batch deviated more than ±4% from the batch average or more than ±4.5% from the labeled amount.

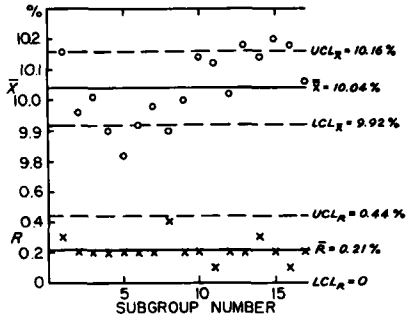


Fig. 6.—Control chart for the per cent composition variation of 16-mg. phenobarbital tablets.

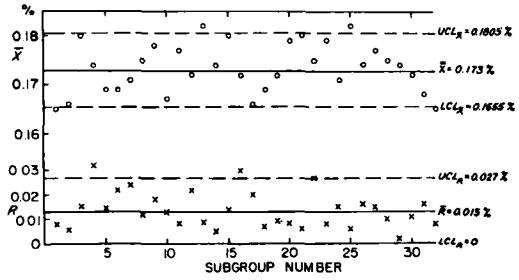


Fig. 7.—Control chart for the per cent composition variation of 0.25-mg. reserpine tablets.

TABLE I.—COEFFICIENTS OF VARIATION FOR TABLET WEIGHT, POTENCY, AND PER CENT COMPOSITION OF FOUR BATCHES OF TABLETS

| Tablet Batch | Coefficient of Variation—Tablet Wt. | Dosage | Composition, % |
|---|---|---|---|
| Phenobarbital, 100 mg. | 0.87 | 1.87 | 1.38 (1.12[a]) |
| Phenobarbital, 65 mg. | 1.21 | 2.84 | 2.32 (2.17[a]) |
| Phenobarbital, 16 mg. | 1.14 | 2.02 | 1.44 (1.20[a]) |
| Reserpine, 0.25 mg. | 2.01 | 4.86 | 4.43 (3.65[a]) |

[a] This value does not include the assay error.

The control charts for 65-mg. phenobarbital tablets are shown in Figs. 4 and 5.

After subgroup 12 had been collected, the hopper was refilled regularly every 30 minutes when it was about half full. This resulted in much better control of the weight variation (Fig. 4). The tablet composition showed considerable lack of uniformity during the early part of the operation. It improved later, but there was an apparent cycling tendency during the production schedule in the same way as shown in Fig. 2. Of the 140 tablets analyzed from this batch, only ten exceeded the limits of 100 ± 6% of the labeled amount, and all ten tablets came from the first 12 subgroups. Beginning with subgroup 13 no tablet deviated from the labeled amount by more than ±5%.

The per cent composition variation of 16-mg. phenobarbital tablets is illustrated in Fig. 6. Although the composition is not in control in a statistical sense, the variability is still relatively minor. A total of 85 tablets were analyzed from this batch, and no tablet deviated from the labeled amount by more than ±5%.

Figure 7 gives the control charts for the composition variation of 0.25-mg. reserpine tablets. A total of 160 tablets were analyzed individually and only six tablets fell slightly outside the limits of 100 ±10% of the batch average.

A comparison of the coefficients of variation for weight, potency, and per cent composition of the four tablet batches is given in Table I. The apparent variabilities calculated on the basis of the experimental results include the errors of measurement along with the actual variability in the tablets. Although the weighing error is very small and may be ignored in this connection, the assay error is appreciable, particularly for reserpine. In Table I the coefficients of variation in parentheses express the actual variability of the per cent composition ($V'$), calculated from

$$V'_{\text{compn.}} = \sqrt{V^2_{\text{compn.}} - V^2_{\text{assay}}}$$

The variation in composition was of approximately the same magnitude as the variation in weight in two of the tablet batches. The composition variation was the greatest in the other two batches. As would be expected, there was a tendency for the mixing error to increase as the percentage of the drug in the granulation decreased. This tendency is not always apparent when commercial tablets are studied because greater care is usually exercised in the mixing process when the drug is in low concentration. Generally speaking, the greatest variability in the tablet composition occurred early in the production schedule, after which the process appeared to settle down to a more or less regular cycle. This is not only due to a lack of homogeneity on the part of the granulation, but probably also due to a change in its composition during the compression of the tablets. Samples of granulation collected from the bulk container during the compression schedule gave a variance which by the $F$-test was significantly smaller than the variance of the tablets ($P = 0.05$). The vibration taking place in the hopper of the tablet press might cause many of the original granules to break up into smaller particles; they would pass through the spaces between the larger particles together with the finely powdered lubricant and disintegrating agents, thus changing the composition.

Banker, Christian, and DeKay (8) have shown that uniformity of a tablet granulation can be improved if a granulating solvent is used in which the drug is soluble. The aqueous granulating agents used for the tablets described in our work are poor solvents for phenobarbital and reserpine. In view of this handicap, the uniformity achieved in the tablet composition appears to be quite satisfactory.

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