Quantitative Methods.—The chloride content of uracil mustard determined by a sodium peroxide fusion and gravimetric analysis gave an average value of 28.0 ± 0.3%.[2] The colorimetric analysis of uracil mustard using 8-hydroxyquinoline reagent in alkaline solution serves to differentiate uracil mustard and the 5-[bis(2-hydroxyethyl)amino] uracil intermediate. Conformity to Beer's law was observed from 10–40 mg. of uracil mustard per 50 ml. of reaction solution. Analysis of commercial uracil mustard capsules by this method gave an average value of 96.2 ± 4.3%.[2] The colorimetric method of Petering and Van Giessen (3) provides an alternate quantitative procedure and an additional identity test for uracil mustard and related alkylating agents. This method employs the reaction of alkylating agents with 4-(*p*-nitrobenzyl)pyridine (NBP) producing a chromophore with a maximum at about 600 mμ and may be adaptable to the capsule formulation, although limited investigation in this laboratory did not yield quantitative results.

[2] Maximum deviation from the mean value.

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Technical Articles

Experiences with Unit-to-Unit Variations in Tablets

By LEON LACHMAN and HANNA D. SYLWESTROWICZ

The literature reports on the subject of interunit dosage and weight variations of tablets indicate that past studies were mainly concerned with analyzing the finished product to detect gross departures from the desired quality. These studies, however, were cognizant of the several stages of manufacture before the compression step could contribute to the end tablet variability. In this investigation, the variability in several stages of tablet manufacturing (dry mixing, granulating, lubricating, and tableting) was evaluated for a particular tablet formulation. The importance of employing correct sampling procedures to obtain random samples to be used for the accurate estimation of the sources of variability and product uniformity is illustrated. The relationship that exists between tablet weights and drug concentration was determined. Since systematic sampling is commonly employed in the in-process control of tableting operations, the information that can be gained from this type of sampling procedure and random sampling is presented and discussed.

THE TERM "unit-to-unit variation of potency" of solid dosage forms has developed considerable significance in recent years. Several reports have appeared in the literature on this subject (1–5). It has been demonstrated (1, 2) that substantial variations can exist in the potency between individual tablets which would not be detected by test methods devised to determine average drug content.

Realizing the importance of this situation, the Quality Control Section of the Pharmaceutical Manufacturers Association initiated an extensive study of this problem. As a result of this study, recommendations have been submitted to the United States Pharmacopeia and National Formulary revision committees that these compendia include a two-limit attribute statistical test in their specifications for tablet composition-uniformity to measure intertablet dosage uniformity (6).

Tablets have received the most attention and study with regard to interunit dosage variation (1–5) because they are the most acceptable dosage form on the U. S. market for the administration of orally effective therapeutic agents and account for a major part of the pharmaceutical sales.

Although these studies were cognizant of the several stages of manufacture before the compression step could contribute to the over-all end variability of the drug concentration in the tablets, none of these investigators studied in detail the variability of each of these steps; instead, they sampled the finished product to detect gross departures from the desired quality. However, to insure acceptable quality of the finished product, the successive phases of the manufacturing process must be evaluated to

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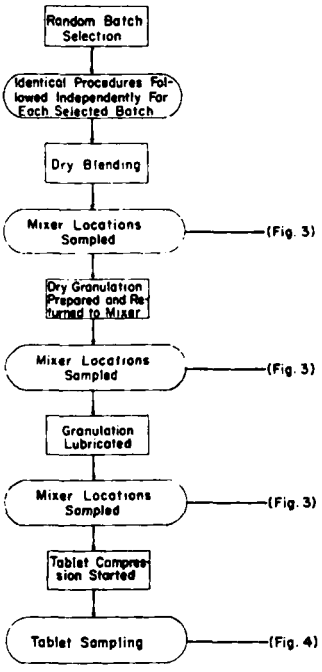

Fig. 1.—Sequence of production sampling.

pinpoint the sources of variability. Only in this way can they be minimized, with resultant optimal quality levels for each stage of the manufacturing process.

The causes for variability of drug content in the final product can be broken down into two major factors: (*a*) variations in tablet weight and (*b*) heterogeneous drug distribution in the tablets. If a homogeneous drug distribution is found, the problem lies at the compression step; where a heterogeneous drug distribution is found, the problem most likely is at the stages of granulation manufacture.

In practice, several situations could arise which involve variations in tablet weight or heterogenous drug distribution in the tablets or both. A brief description follows.

(*a*) For a tablet preparation which exhibits a large variability in tablet weight and homogeneity of drug distribution in the tablets, a high correlation coefficient between tablet weight and drug content which approaches unity results. The large tablet weight variability in turn causes a large variability in drug content. To improve such a process, the factors that can contribute to this large tablet weight variability must be evaluated. Factors such as hopper load, machine settings and adjustments, size distribution of the granulation, segregation of the granulation, and flow properties of the granulation can influence the weight variability of the tablets. Since there is homogeneity in drug distribution, it should be possible to predict the drug content in the tablets from the weight data.

(*b*) In the case where the tablets exhibit small weight variability and homogeneous drug distribution, again the correlation coefficient is high approaching unity. However, such a situation indicates that the production operation is satisfactory, and no further study is required. Here, as for (*a*) it should be possible to predict the drug content in the tablets from the weight data.

(*c*) For a tablet formulation which exhibits large variations in tablet weight and a heterogeneous drug distribution in the tablets, the correlation coefficient would be small and not significant. To improve such an operation, it is necessary to investigate the factors responsible for heterogeneous drug distribution—completeness of the mixing at the several stages of granulation manufacture, whether separation or segregation of the granulation occurs during compression—and the factors responsible for large variations in tablet weight presented earlier.

(*d*) In the situation where a tablet preparation exhibits small variability in tablet weight and heterogeneous drug content in the tablets, a correlation coefficient approaching zero is obtained. Here it is necessary to study the factors that can contribute to this heterogeneity of drug content.

In the remainder of this report, information will be presented that was obtained from an evaluation of several of the critical steps concerned with the manufacture of a tablet formulation which exhibited low tablet weight variability but high drug content variability in the tablets. The methods developed to estimate the variability at the end of the mixing, granulating, lubricating, and tableting procedures will be described, and the importance of the sampling plan will be illustrated. It will be shown that by pinpointing the stage of manufacture responsible for intertablet dosage variation, studies then can be undertaken readily to determine the cause of this variation, and corrective measures can be instituted.

EXPERIMENTAL

The tablet formula chosen for investigation contained about 5% drug and weighed approximately 1.0 Gm. The tablets were prepared in the production department with production personnel and in accordance with the established manufacturing procedure. The granulations for these tablets were prepared by the customary wet granulation tech-

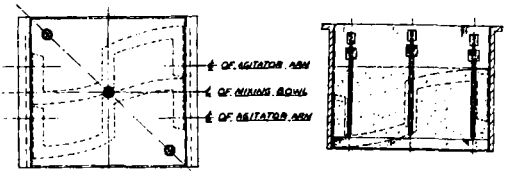

Fig. 2.—Right, plan view; left, section view of Readco mixing bowl with theft sampler positions.

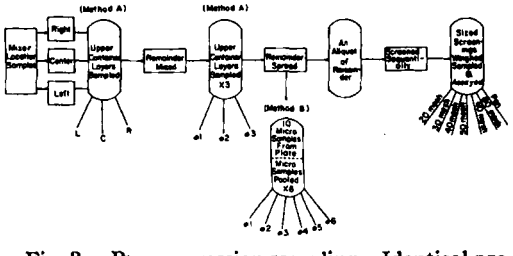

Fig. 3.—Precompression sampling. Identical procedures were followed independently for the dry mix, dry granulation, and lubricated granulation.

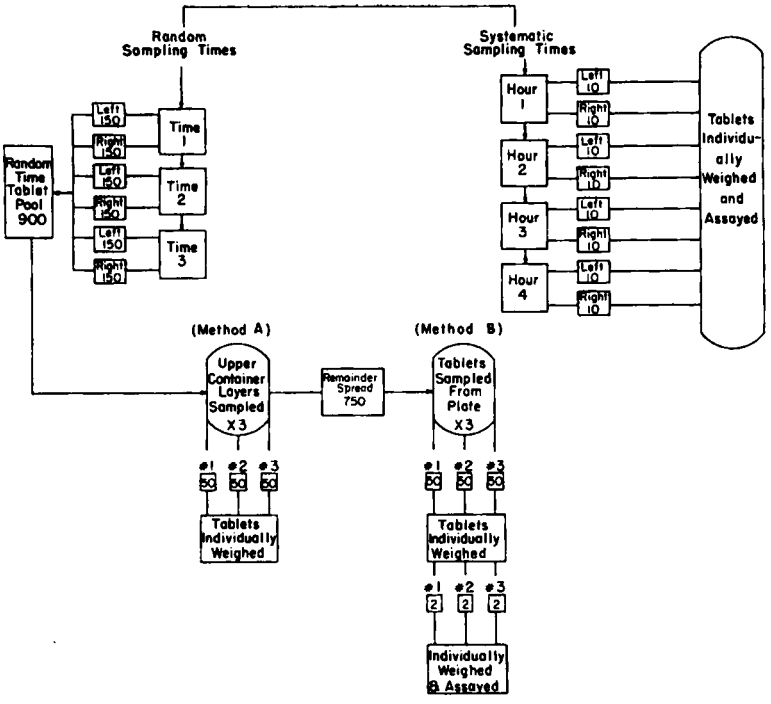

Fig. 4.—Tablet sampling.

niques. The entire batch of lubricated granulation was placed in a master hopper which fed two hoppers on a Stokes model 540 double rotary tablet press, and tablets were produced at a rate of 1200 per minute. Normal machine adjustments were made by the tablet operator to keep the weights of the tablets under control.

Sampling Plans

Since the production order for the tablet formulation under study consisted of eight individual batches of 240,000 tablets per batch, three batches were selected at random for study which will be known subsequently as batches K_4, K_6, and K_8. Each batch was processed individually and controlled accordingly. A schematic illustration of the sampling performed during the several stages in the manufacture of the tablet preparation is presented in Fig. 1. In the subsequent sections of this report, each stage will be treated in detail.

Method A.—*Sampling of Dry Mix, Dry Granulation, and Lubricated Granulation.*—In studying the variability at the end of the mixing, granulating, and lubricating stages of the manufacturing process for each of the three batches, three location samples of 300 Gm. were taken from the mixer with a sample thief at (*a*) the end of the dry blending period, (*b*) when the dried screened granulation was returned to the mixer for lubrication, and (*c*) after lubrication. The samples were taken along the diagonal of the mixer at three locations illustrated by Fig. 2. The location points were designated left (L), center (C), and right (R).

From each location sample one analysis sample equivalent to the weight of one tablet was taken at random by *Method A*, weighed on a semimicro analytical balance, and assayed. The remaining material in the three location samples was blended. Three random samples, each equivalent to the weight of one tablet, were taken by *Method A;* six random samples, each equivalent to the weight of one tablet, were taken by *Method B* and assayed. Figure 3 summarizes these sampling plans.

Method A consisted of removing samples for analysis equivalent to the weight of one tablet from the top portion of the samples in glass bottles. *Method B* consisted of spreading the sample from the glass bottle on a rectangular surface, 8 × 10 in., then taking approximately 10 small quantities from different locations on the spread material with a microspatula which made up an analysis sample equal to the weight of one tablet.

In addition, 100-Gm. aliquots were taken by *Method B* from the blended samples and screened sequentially. The distribution of the 100 Gm. of material on the particular size screens was determined and will be presented as per cent of the initial aliquot. The material on each size screen was sampled and analyzed for drug concentration.

Method B.—*Random and Systematic Sampling of Tablets.*—The same three random batches used to study the several stages of granulation manufacture were also used to study the variability of the compression operation. As illustrated in Fig. 4, the random sampling plan employed was to take three samples of 300 tablets in sequence (150 from the left side and 150 from the right side of the press) during the compression of each batch of tablets on the Stokes model 540 tablet press at three random times.

The three samples of 300 tablets were mixed together for each batch to form a composite sample of 900 tablets. Then three random laboratory samples of 50 tablets each were taken by two methods. *Method A* consisted of taking the three samples of 50 tablets each from a bottle holding the 900 composite sample of tablets. *Method B* consisted of placing the remaining tablets from the 900 in the bottle onto a circular disk of such diameter that the tablets formed a single layer on the disk.

TABLE I.—VARIATIONS IN DRUG CONCENTRATION FOR SAMPLES TAKEN AT THE VARIOUS STAGES OF GRANULATION PREPARATION[a]

	Dry Mix			Dry Granulation			Lubricated Granulation		
	K_4	K_6	K_8	K_4	K_6	K_8	K_4	K_6	K_8
Location samples, *Method A*									
L	37.3	47.4	54.1	32.5	40.4	35.9	36.9	37.7	40.7
C	54.1	52.2	52.3	37.3	38.4	35.0	40.4	40.7	38.5
R	53.2	52.0	39.9	52.2	38.5	32.1	39.9	38.0	33.3
Random samples, *Method A*									
1	55.2	51.9	56.1	41.9	35.0	53.9	34.1	39.5	39.1
2	55.6	53.4	56.7	37.6	37.5	47.6	36.1	37.4	37.4
3	54.8	53.5	57.3	39.0	36.2	50.4	32.2	36.6	35.7
Random samples, *Method B*									
1	49.1	51.6	49.0	48.3	46.3	52.1	43.7	45.4	46.4
2	48.2	53.2	47.1	53.3	47.0	50.8	45.6	45.9	53.6
3	47.3	51.4	47.7	52.3	44.2	47.6	44.9	43.3	46.1
4	47.5	52.5	47.4	47.7	45.9	54.2	44.3	44.1	49.9
5	49.6	55.1	46.6	48.1	43.4	58.3	45.6	45.1	47.0
6	47.6	51.1	46.3	44.8	47.7	52.3	46.7	46.4	47.4
Means	48.2	52.5	47.4	49.1	45.8	52.6	45.1	45.0	48.4

[a] Milligrams per tablet weight.

Subsequently, 50 tablets were taken three times at random from this disk. Each of the 50 tablets in the random laboratory samples was weighed on a semimicro analytical balance individually. From the second set of three samples of 50 tablets, two analysis samples composed of two individual tablets were taken from each of the three samples of 50 tablets by a random method, weighed, and assayed. Subsequently, it will be illustrated that the sampling method is important in insuring that the samples selected are, in fact, random.

Method C.—*Systematic Sampling.*—This is commonly employed in the in-process control of tableting operations. This sampling plan is also outlined in Fig. 4. It consisted of taking 10 tablets from the left and right compression sides of the Stokes model 540 tablet press at 1, 2, 3, and 4 hours for the same batches of tablets previously described. Individual weights and assays were performed on all tablets. The 4-hour period was chosen since this is approximately the time required for the compression of a batch of tablets. During this 4-hour period, normal machine adjustments were made by production personnel in their weight control of the tableting operation. This could involve a different number of adjustments to the right and left compression sides of the press and can be made at different times during the compression of a batch of tablets.

RESULTS AND DISCUSSION

Dry Mix, Dry Granulation, and Lubricated Granulation

The drug content of location and random samples taken by *Methods A* and *B* for the three production batches are presented in Table I.

It is evident from the data in Table I that the method of taking samples is extremely important. For the dry mix, the random samples taken by *Method A* are generally substantially higher in drug content than those taken by *Method B*. However, the reverse is true for the dry granulation and lubricated granulation. If one were to use the results obtained by *Method A*, a completely different interpretation would have been given to the situation which prevailed in the production of this granulation.

Consequently, unless correct sampling techniques are employed, the data obtained can be very misleading concerning the prevailing conditions of drug concentration and uniformity at the several stages in the production of the tablet granulation.

The reason for this phenomenon becomes clear after observing the size distribution of this granulation and the corresponding drug content for the different sized granules as shown in Table II.

It would appear that the drug seems to be more concentrated at the larger granules for this particular tablet preparation. The reason for this occurrence possibly can be explained as follows.

Since the drug is poorly water soluble, it would be expected to be found at the granule, if it was adhered to the granule surface by the gum used in the granulating liquid or if it was encapsulated in the granule. Because the large granules exhibit a smaller surface area than the small granules, there is less chance for the drug to dislodge with further processing if it were adhered to the surface of the granule. In addition, the large granules can more readily encapsulate the drug particles fully, thus further insuring its presence in these size granules.

It is clear that unless this granulation is well mixed, so that the various size granules are randomly distributed in the blend, problems can arise when samples are taken. Furthermore, due to the substantial difference in drug concentration for the

TABLE II.—DRUG CONCENTRATION IN DIFFERENT SIZED GRANULES FROM SIZE DISTRIBUTION OF LUBRICATED GRANULATION

Screen Size	% on Screen	Drug Concn.,[a] mg./0.5 Gm.
20	1	56.4
30	13	46.0
40	24	36.5
50	25	20.0
60	13	11.2
80	15	6.7
Pan	10	4.8

[a] Theoretical concentration = 23.3 mg. per 0.5 Gm

various size granules, if unmixing were to take place when transferring the granulation from the sample thief into the glass bottle, the results presented in Table I under *Method A* could occur.

Although it is realized that the location samples which were taken by *Method A* are most likely incorrect indications of the drug distribution in the granulation, the data will be used on a hypothetical basis to illustrate the information that can be gained through an analysis of the various stages of the tablet manufacture. However, the three random samples taken by *Method A* were not used again in this study, but only the six taken by *Method B*, for which it is fairly certain that sampling was done correctly.

The variability of the drug concentration in the mixer load after the several stages of granulation manufacture was determined from an analysis of the random and location samples. Since the per cent active ingredient present in the formulation is small, statistical analysis was performed on the assay values which were transformed into logarithms as suggested in the statistical literature (7).

The analysis of variance for the location samples is summarized in Table III. There were significant interactions between batches and locations for all three stages of production. This would indicate that the mixes in the mixer were not uniform for the three batches. For the dry mix and dry granulation it was not possible to state which location of the mixer would always be low or high, since the results differed from one batch to another. However, in the analysis of the lubricated granulation, differences between locations were significant when the interaction between batches and locations was used as an error term. These location differences indicated that the samples taken from the center of the mixer had a tendency to be consistently higher in drug content when compared with the samples taken from the right side of the mixer. This held true for the three batches as shown in Table I and could be extended further to hold for the eight batches of the production order.

The results can possibly be explained in two ways: (*a*) the mixes were heterogeneous or (*b*) the samples were not taken properly, making it appear as if the drug distribution were heterogeneous. As illustrated earlier, improper selection of location samples is definitely a factor, but it is also felt that heterogeneity of the mixes is a contributing factor. To show that this is the case, analysis of variance was computed for the data at each stage of the operation on the six random samples from each of three batches. These results are summarized in Table IV.

From this analysis, it was proved that there existed significant differences between the means of drug content of each batch for the three stages of production. However, since the procedures of manufacture and the formulas for the three batches were the same, there was no reason to believe that the mean drug content per batch should differ. It is anticipated that if the random samples were taken for analysis from many locations (*e.g.*, 15 or 20) the mean drug content from batch to batch for each stage of the granulation manufacture would not differ significantly from one another.

Table V presents the standard deviations for the six random samples of each stage in the production of each batch.

Table III.—Analysis of Variance on Random Samples and Location Samples of Three Stages of Granulation Manufacture

Source of Variation	D.F.[e]	Dry Mix			Dry Granulation			Lubricated Granulation		
		Sum of Squares	Mean Square	F Test	Sum of Squares	Mean Square	F Test	Sum of Squares	Mean Square	F Test
Total	26	0.03765707	...	...	0.12979881	...	...	0.04908239	...	...
B (Batches)	2	0.00711237	0.00355618	0.9428	0.00286934	0.00143467	0.2222	0.00107681	0.00053840	0.4751
L (Location differences)/	3	0.00630858	0.00210286	0.5575	0.07876028	0.02625342	4.0655	0.03687527	0.01229175	10.8472[b]
B × L	6	0.02262974	0.00377162 = S_2^2	35.2192[b]	0.03874539	0.00645756 = S_2^2	10.2786[b]	0.00679904	0.00113317 = S_2^2	3.9245[a]
B × Random error	15	0.00160638	0.00010709 = S_1^2	...	0.00942380	0.00062825 = S_1^2	...	0.00433118	0.00028874 = S_1^2	...
Random	...	...	...	...	...	...	...	...	...	...

[a] Significant at 5% level. [b] Significant at 0.1% level. [c] S_1^2 was used to test B × L interaction. [d] S_2^2 was used to test B and L. [e] D.F. = degrees of freedom. [f] +, includes contrasts between L, C, R, and random.

Table IV.—Analysis of Variance on Six Random Samples per Batch of Three Stages of Granulation Manufacture

Source of Variation	D.F.[d]	Dry Mix			Dry Granulation			Lubricated Granulation		
		Sum of Squares	Mean Square	F Test	Sum of Squares	Mean Square	F Test	Sum of Squares	Mean Square	F Test
Total	17	0.00814692	...	...	0.02007812	...	...	0.00799471	...	...
Between batches	2	0.00654054	0.00327027	30.5375[c]	0.01065432	0.00532716	8.4793[b]	0.00366344	0.00183172	6.3436[a]
Within batches	15	0.00160638	0.00010709 = S^2	...	0.00942380	0.00062825 = S^2	...	0.00433127	0.00028875 = S^2	...

[a] Significant at 5% level. [b] Significant at 1% level. [c] Significant at <0.1% level. [d] D.F. = Degrees of freedom.

TABLE V.—STANDARD DEVIATIONS OF DRUG CONTENT FROM RANDOM SAMPLES TAKEN AT THE VARIOUS STAGES OF GRANULATION MANUFACTURE

Batch	Dry Mix	Dry Granulation	Lubricated Granulation
K_4	0.93	3.16	1.07
K_6	1.50	1.65	1.15
K_8	0.98	3.57	2.88

The nine standard deviations shown in Table V do not differ significantly. However, if a greater number of samples were taken from the mixer at more than three locations for each batch, significant differences between batches could possibly be obtained. This would suggest that the degree of mixing was insufficient and also different for the three batches.

It would be expected that the standard deviation for consecutive stages in the granulation manufacture should decrease since the mix is being exposed to further mixing. However, as the data in this table illustrate, the standard deviation *increases* as we go from dry mix to dry granulation. This indicates that there are certain factors acting which interfere with the improvement of the drug uniformity. On the other hand, as we proceed from dry granulation to lubricated granulation, the standard deviation *decreases* as is expected.

Tablets

Before performing analysis of variance on the data, studies were undertaken to investigate the homogeneity of variances and the types of distribution exhibited by the tablet weights and tablet drug content. This was done on the original data and on the logarithms transformation. It is necessary to determine the above two factors, since for a valid application of analysis of variance, homogeneity of variances and normality of distributions are the necessary prerequisites. The logarithms transformation of data was investigated since it was anticipated that it would facilitate bivariate analysis of variance (simultaneous analysis of tablet weight, tablet drug content, and per cent drug concentration in the tablets).

The weight variances of the tablet samples from the random and systematic sampling plans were investigated, and no departures from homogeneity were observed. Tests of skewness (assymetry) and kurtosis (steepness of peak) were performed (7) on the data from each batch and on a composite of all batches for each sampling plan; no gross departures from normality were observed. There was, however, a tendency toward leptokurtosis for the pooled data. This is not a surprising result when a mixture of distributions is analyzed (8). The same tests performed on the data transformed to logarithms showed no significant departure from normality, but a tendency toward negative skewness.

Tests for normality performed on the distributions of tablet drug content and on their logarithms for each batch and for a pool of the three batches showed that both distributions exhibited no departures from normality.

Random Time Samples.—*Weights.*—In this analysis the three sets of 50 tablets taken by *Method A* and the three sets of 50 tablets taken by *Method B* were compared to determine whether the sampling

TABLE VI.—ANALYSIS OF VARIANCE OF TABLET WEIGHTS OF RANDOM TIME SAMPLES TAKEN BY METHODS *A* AND *B*

Source of Variation	*Method A and Method B*			*Method A*			*Method B*		
	D.F.	Sum of Squares	Mean Square	F Test	D.F.	Sum of Squares	Mean Square	F Test	Sum of Squares	Mean Square	F Test
Total	899	0.12155779	...	...	449	0.01893859	...	...	0.10190115	...	...
Batches (B)	2	0.00440295	0.00220147	41.0416[c]	2	0.00247227	0.00123648	15.0186[b]	0.00194845	0.00097422	24.6139[c]
Methods (M)	1	0.00071705	0.00071705	13.3678[c]	...	...	...	...	...	...	...
B × M	2	0.00001948	0.00000974	...	...	...	...	...	...	...	...
Samples within batches (pool)	12	0.00073149	0.00006095	...	6	0.00049400	0.00008233 = S_2^2[a]	2.2731[a]	0.00023749	0.00003958 = S_2^2	0.1750
Within samples of 50	882	0.11568682	0.00013116	...	441	0.01597162	0.00003622 = S_1^2[d]	...	0.09971521	0.00022611 = S_1^2	...
Pool (B × M samples within batch)	14	0.00075097	0.00005364 = S^2	...	...	...	...	...	...	...	...

[a] Significant at 5% level. [b] Significant at 1% level. [c] Significant at <0.1% level. [d] S_1^2 was used to test samples within batches. [e] S_2^2 was used to test batches.

method has a bearing on the randomness of the sample.

By analysis of variance, it was shown that there was a significant difference between sampling *Methods A* and *B*. These data are summarized in Table VI. The samples taken by *Method A* resulted in a significant difference between samples within batches, indicating that the samples were *not random*. This would suggest that the composite sample of 900 tablets was not adequately mixed to give random samples by *Method A*. However, the samples taken by *Method B* were *proved random*. Here again, as illustrated earlier for the sampling of the various stages in granulation manufacture, the sampling technique is extremely important in the collection of data for evaluation.

The analysis of variance has also shown highly significant differences between the tablet weight means of batches. There appear to be no valid reasons to believe that these differences really exist, but are probably due to time-to-time or adjustment-to-adjustment variability during the whole production of an order. It is believed that if a greater number of random tablet samples (which could be smaller in size than 50) would be taken per batch, these differences that were found, probably would not exist.

Random Time Samples.—*Weights, Assays, and Per Cent Drug Concentration.*—To determine whether a relationship existed between the weights and drug content of the individual tablets, analysis of variance was performed on the logarithms of the weight and drug content data, and analysis of variance was performed on the logarithm of the per cent drug concentration data.

The analysis was performed on 18 tablets, six from each of the three batches. There were no significant differences between batches for tablet weights, drug content, and per cent drug concentration. In addition, the samples within the batches were not significantly different from one another, indicating proper random sampling.

The correlation coefficient between tablet weight and drug content was not significant. This means that from the data available, it was not possible to trace dependence of drug content on tablet weight.

Systematic Samples.—*Weights, Assays, and Per Cent Drug Concentration.*—The analysis was performed on 240 tablets (three batches, two sides of the tablet press, four intervals, 10 tablets per sample) and analyzed by analysis of variance for the *Random Time Samples*.

When the data were analyzed as a nested classification, the differences between samples within batches were highly significant for tablet weight, assay, and per cent drug concentration.

Since the eight samples of 10 tablets each per batch were not selected at random but at four time intervals from each compression side of the tablet press, analysis of variance was performed on the basis of a factorial experiment to determine the sources of between-samples–within-batches variability.

The results summarized in Table VII indicate significant interaction between batches and hours for the tablet weights. When each batch was analyzed separately, no significant differences were found between hours.

The data in Table VIII summarize the mean

TABLE VII.—ANALYSIS OF VARIANCE OF SYSTEMATIC SAMPLING DATA[c]

Source of Variation	D.F.	y = Log Tablet Wt.		x = Log Drum Amt.		z = Log % concn.	
		SS_y	MS_y	F Test	SS_x	MS_x	F Test	SS_z	MS_z	F Test
Total	239	0.0011599	0.0000048	...	0.0393486	0.0001646	...	0.0436741	0.0001827	...
Batch (B)	2	0.0000429	0.0000214	1.6461	0.0005922	0.0002961	1.0020	0.0008667	0.0004333	0.8943
Hr (H)	3	0.0000245	0.0000122	0.9384	0.0028231	0.0009410	3.1855	0.0030132	0.0010044	2.0730
Side (S)	1	0.0000247	0.0000247	1.9000	0.0005682	0.0005682	1.9234	0.0003557	0.0003557	0.7341
B × H	6	0.0003359	0.0000559	4.3000[a]	0.0037760	0.0006293	2.1303	0.0060295	0.0010049	2.0740
B × S	2	0.0000203	0.0000102	0.7846	0.0119128	0.0059564	20.1638[b]	0.0125549	0.0062774	12.9564[b]
H × S	3	0.0000255	0.0000085	0.6538	0.0007453	0.0002484	0.8408	0.0011264	0.0003754	0.7748
B × H × S	6	0.0000783	0.0000130 = S^2	...	0.0017727	0.0002954 = S^2	...	0.0029072	0.0004845 = S^2	...
Within samples of 10	216	0.0006078	0.0000028	...	0.0171583	0.0000794	...	0.0168205	0.0000779	...

[a] Significant difference at 5% level. [b] Significant difference at 1% level. [c] Correlation coefficient between y and x = $r_{y,x}$ = 0.1464 D.F. 216.

tablet weights for the four time intervals for the three batches of tablets. It is evident from the data in this table that there exists no consistency in batches concerning the time of low or high weight tablets.

TABLE VIII.—INFLUENCE OF TIME ON MEAN TABLET WEIGHT

Batch	Time, Hr. 1	2	3	4
K_4	1.0698	1.0630	1.0461	1.0620
K_6	1.0678	1.0621	1.0700	1.0661
K_8	1.0653	1.0699	1.0590	1.0655

As indicated by the data in Table VII, analysis of the drug content results showed highly significant interaction between batches and compression sides of the tablet machine. This significant interaction indicates that from batch to batch the difference between sample means from each compression side of the tablet press is not consistent for the three batches. When each batch was analyzed separately, the results obtained showed that batch K_4 gave tablets on the left side of the machine which were significantly higher in concentration compared to those obtained from the right side of the machine. The data in Table IX summarize the mean drug content values for the tablets from the left and right sides of the double rotary press.

TABLE IX.—MEAN DRUG CONTENT RESULTS SHOWING BATCH-BY-SIDE INTERACTION OF TABLETS

Batches	Tablet Press, Left Side	Tablet Press, Right Side
K_4	49.5	47.38
K_6	48.13	49.08
K_8	48.70	49.29

The results of the analysis of variance on per cent drug concentration are shown in Table VII; they indicate that the conclusions here are the same as from the analysis of variance of drug content. The highly significant interaction between batches and compression sides indicates that factors taking place during the compression operation are influencing the per cent drug concentration differently on each side of the tablet press.

The correlation coefficients between tablet weights and drug content were computed from within sample variances and covariance and were not significant. The values are given in Table VII. This is not surprising when we compare the "within samples variances" for weights and drug content in Table VII. It is obvious that the variability of the drug content data is comparatively large compared to the weight data. This is clearly illustrated by the results in Table X, which show that the coefficient of variation for drug content is about five times that of the coefficient of variation for tablet weights.

From the bivariate analysis of variance data, we find that about 50% of the variability for weights, drug content, and per cent drug concentration can be attributed to such factors as compression sides, hours, batches, and their interactions. This tends to point to the fact that the tableting operation can be improved to some extent, but will not alter the fact that the major problem lies in the heterogeneity of drug distribution in tablets.

Precision of Assays

For this study the assay precision was estimated by analysis of variance on 80 assays performed in replicate and had a standard deviation of 0.061 mg., which is about 0.1%.

Tablet Quality

According to the intertablet potency test recommended to the U.S.P. and N.F. by the Quality Control Section of the Pharmaceutical Manufacturers Association (6), the assays of 10 individual tablets are to fall within 85–115% of the mean value of the official purity rubric to meet the standards for tablet potency variability. From Table X, it is seen that batch K_4 exhibits the greatest potency variability. By taking three standard deviations around the mean drug concentration, 99% of the population should be covered. Three standard deviations around the mean drug concentration of the tablets for batch K_4 give a range of 43.6–53.7 mg. The ±15% around the theoretical drug concentration of 50 mg. for these tablets gives a permissible range for intertablet dosage variation of 42.5–57.5 mg. Consequently, the results obtained for the three batches of tablets studied indicate that they meet the tolerances of intertablet dose variations as recommended by the Quality Control Section of the Pharmaceutical Manufacturers Association. However, the range obtained for batch K_4 is rather broad, indicating that it would be desirable to correct the sources of variability that exist in the stages of granulation manufacture to insure minimum intertablet dosage variations.

SUMMARY AND CONCLUSIONS

This report has been concerned mainly with a description of certain methodology and sampling plans appropriate for obtaining the components of variation in the manufacture of tablet dosage forms. To illustrate clearly the effectiveness or ineffectiveness of the methodology and sampling plans, the production manufacture of a tablet formulation was followed from the dry blending operation to the final compression of the granulation into tablets.

The precompression stages studied were the dry blending, granulating, and lubricating. Each stage

TABLE X.—COMPARISON OF MEANS, STANDARD DEVIATIONS, AND COEFFICIENT OF VARIATION OF THE WEIGHTS AND DRUG CONTENT FOR SYSTEMATIC SAMPLED TABLETS

Batches	Wt., Gm. Mean ± S.D.	Coeff. of Variation, %	Drug Content, mg. Mean ± S.D.	Coeff. of Variation, %
K_4	1.0647 ± 0.0066	0.62	48.67 ± 1.68	3.46
K_6	1.0664 ± 0.0063	0.59	48.60 ± 1.33	2.74
K_8	1.0649 ± 0.0068	0.64	49.00 ± 1.24	2.53

was analyzed to estimate its variability. The following findings are briefly summarized.

1. By performing a size analysis on the granulation and then determining the corresponding drug content of each sized fraction, it was possible to ascertain whether the drug is uniformly distributed throughout the different granules.
2. If the drug is not uniformly distributed, the technique of sampling is extremely important in obtaining a true representation of the drug distribution in the mix. Misleading estimates of variance were produced by the samples taken by *Method A*.
3. To determine the uniformity of drug content at different locations in the mixer, location samples were compared with random samples. Through the computation of standard deviations, it is possible to estimate the homogeneity of drug content in the mixer and to compare the same stage of manufacture for different batches.
4. In determining the standard deviation of the drug content at the different stages of granulation manufacture, it is possible to pinpoint the stage which is interfering with good mixing.

To evaluate weight and drug content variability of the tablets, random and systematic sampling plans were employed. The systematic sampling plan gave more information about the tablet compression operation than the random sampling plan. The following information was gained from this study.

1. The sampling technique is important for obtaining random samples.
2. The influence of compression time and compression sides of a double rotary press on tablet weight and drug content can be determined by analysis of variance.
3. The relationship between tablet weight and drug content was determined by computing the correlation coefficient and was not significant. This was because for each of the three batches of tablets studied, the coefficient of variation for drug content was about fivefold that of the tablet weight.

Although this report described certain methodology and sampling plans, it should be realized that similar and possibly more extensive information could be obtained through the use of other sampling plans. However, before any sampling plan is decided upon, careful consideration must be given to the factors that are to be evaluated. Only then is it possible to design the correct methodology and sampling plans which would result in the accumulation of sufficient random samples to evaluate adequately each factor and eliminate the possibility of taking samples from materials which may have undergone unmixing.

Additional studies presently are underway on different dosage forms using modified sampling plans to obtain maximum information regarding the relationship that may exist between drug heterogeneity in the several stages of granulation manufacture and the final tablets.

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Notes

Titrimetric Assay of Sulfonamides by Diazotization Using Ferrocyphen as Indicator

By W. M. BANICK, Jr., and J. R. VALENTINE

A study has been made concerning the use of ferrocyphen [dicyano-bis-(1,10-phenanthroline)-iron(II) complex] as an internal, reversible indicator for the diazotization titration of sulfonamides. Many of the sulfonamides of pharmaceutical interest can be determined using the ferrocyphen visual end point. The titration procedure is simple and rapid.

Most of the sulfonamides of pharmaceutical interest have the general formula $H_2NC_6H_4SO_2NHR$, in which the amino group and the sulfonamide group are in a *para* position to each other. Many different methods have been described (9) for the analysis of these sulfonamides. Diazotization of the primary amino group appears to be the preferred method, probably because it is applicable to nearly all sulfonamides and employs a titrant which is stable, readily available, and easily standardized.

The end point in the diazotization titration may

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