Dosage Variation in Compressed Tablets

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A study was undertaken to evaluate the intertablet dosage variation in a number of different products by the use of automated instrumentation. Representative samples of actual production runs were used; an analysis of the data is presented.

ALTHOUGH PRODUCT DOSAGE is expressed on an individual compressed tablet basis, potency testing utilizes an analytical sample which is a composite of many tablets. An assay procedure will often read: "Weigh and finely powder not less than 20 ——— tablets. Weigh accurately a portion of the powder, equivalent to about . . ." (1). Such procedures give information on the average tablet assay; however, they give no information on the individual tablets. For example, if half of the tablets were 50% high in potency and half 50% low, the composite sample would still assay satisfactorily.

Considerable interest has recently been shown in studying this topic as exemplified in reports by Moskalyk, *et al.* (2), Garrett (3), and Evers (4). Suggestions have been made to modify the presently accepted practice of assaying a composite sample and to assay individual tablets (5, 6). Because of the difficulty of performing large numbers of assays, these studies have been limited to a relatively small sample, usually less than 100, which may not be representative of modern large scale production lots. For this reason, the nature of the distribution of individual tablet assays has not been established. Such information is necessary before the need for a change in existing procedures can be established and corrective action devised.

Recent work in this laboratory has made available automated chemical instrumentation (7–9) capable of automatically analyzing 20 tablets per hour. This facilitates the collection of a large number of assays. This paper presents assay and weight variation data on round, discoid, individual tablets—selected to be representative of different production batches of several products—in an attempt to define the nature of the distribution of dosage variation in commercially available compressed tablets.

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TABLE I.—VARIATION RANGE OF INDIVIDUAL TABLET ASSAYS

Product	Lot	Tablets Assayed, No.	% Tablets Outside 90–110%	% Tablets Outside 85–115%
7	N	314	0.64	0.00
	O	282	0.36	0.00
4	D	277	0.72	0.00
	E	311	0.32	0.00
6	C	252	0.00	0.00
	D	375	0.27	0.00
3	C	267	0.00	0.00
	D	273	0.73	0.00
8	A	264	0.00	0.00
	B	303	0.66	0.00
		2918	Av. 0.37	0.00

EXPERIMENTAL

Chemical assays were performed with modified AutoAnalyzer[1] as described by Michaels and Sinotte (7) and Holl and Walton (8). Individual tablets, taken at approximately uniform intervals throughout the compression of a lot, were assayed automatically. The assay procedures employed were colorimetric as described by Wrightman and Holl (9). The individual tablet weights were obtained by standard analytical balances or the Mettler automatic tablet weigher.[2] All curves in the figures are fitted by eye.

RESULTS AND DISCUSSION

Variation Range of Individual Tablet Assays.—Table I summarizes the assay results obtained on two batches of each of five different products. These data are typical of other products and batches studied over a 1-year period. These results were tested for conformance with the presently accepted composite limits of ±10% (1) and against somewhat wider limits of ±15%, as recently suggested (5). Over 99% of the tablets conform to presently accepted composite limits; only a few minor deviations were found. All tablets conform to the wider limits.

Distribution of Individual Tablet Assay.—To define the distribution of individual tablet assays

[1] T. M. Technicon Controls, Inc., Chauncey, N. Y.
[2] Mettler Instrument Corp., Princeton, N. J.

TABLE II.—DISTRIBUTION OF INDIVIDUAL TABLET ASSAYS

Product	Lot	Active Ingredient, %	Tablets Assayed, No.	$\bar{X}$ in % Label Claim	σ in % Label Claim	α_3[a]	α_4[a]	Curve, Type
1	A	23.8	116	101	2.8	−0.12	3.86	Normal
	B		58	103	3.8	0.05	4.14	Normal
	C		74	98	2.6	−0.42	4.04	Normal
2	A	23.3	88	101	3.4	0.13	3.05	Normal
	B		90	101	2.9	0.09	2.86	Normal
3	A	23.3	104	102	2.7	0.19	2.53	Normal
	B		95	102	2.4	−0.06	3.42	Normal
4	A	23.3	93	102	3.9	0.36	3.16	Normal
	B		108	102	3.4	0.21	2.30	Normal
	C		100	102	3.8	[−0.58]	2.74	Skewed—low side
5	A	68.5	102	98	2.3	[−0.73]	3.34	Skewed—low side
	B		100	100	2.0	0.10	3.75	Normal
	C		95	102	2.8	−0.17	3.81	Normal
6	A	88.5	101	101	2.8	0.29	[4.40]	Leptokurtic
	B		91	100	1.7	−0.46	4.01	Normal
7	A	90.7	105	101	2.1	0.47	3.30	Normal
	B		181	99	1.4	[−0.39]	2.94	Skewed—low side
	C		49	100	4.5	[−1.00]	3.42	Skewed—low side
	D		100	99	1.7	−0.14	3.02	Normal

[a] Tested for significance by student "t" test at 0.05 level; significant values indicated by brackets.

further lots were studied. The curves are described numerically by $\bar{X}$ (average assay), σ (standard deviation), α_3 (a measure of skewness), and α_4 (a measure of kurtosis).

The expected value for α_3 is zero for a normal distribution. A negative value indicates distribution skewed to the left; a positive value indicates a distribution skewed to the right. The expected value for α_4 is 3 for a normal distribution. A value greater than 3 indicates a leptokurtic distribution (more peaked than normal); a value less than 3 indicates a platykurtic distribution (flatter than normal)(10).

It is obvious from the data in Table II that the average assays are very close to label claims. The standard deviations are small which confirms the information reported in Table I and, with few exceptions, the curves are essentially normal. The significance of the α_3 and α_4 values were determined (11), and the type of curve is indicated.

Examination of the data indicates a relationship between standard deviation and per cent of active ingredient in the tablet. Figure 1 shows that as the per cent of active ingredient increases, the variation in individual assays decreases.

The standard deviation of 4.5 (Product 7, Lot C) is an aberrant value and may be due to experimental errors. To confirm that this is not a normal situation, nine more lots of Product 7 were investigated (see Table III). The average standard deviation of these nine lots is 1.7, which lies very close to the estimated line.

Distribution of Individual Tablet Weights.—To define the distribution of individual tablet weights 13 lots representing six different products were studied. The data in Table IV are typical of many other products and lots studied.

Examination indicates that the data are essentially normal as discussed above. The average weights are close to the target weight and the standard deviations are small. These standard deviations in milligrams vary directly with tablet weight as shown in Fig. 2. However, when the relative per cent error ($\sigma/\bar{X} \times 100$) is plotted against average weight (Fig. 3) it is evident that the relative per cent error remains constant at about 1.4 for tablets weighing more than 300 mg. Further work is indicated to study the rise in relative per cent error for tablets weighing less than 300 mg.

Correlation Between Individual Tablet Weight and Assay.—To study the relationship between the two variables, individual tablets from 12 lots representing six different products were weighed and then assayed. The distribution of these two variables have been previously shown in Tables II and IV. The relationship of these two variables is expressed as correlation coefficients. There is no relationship when the value is zero, whereas perfect

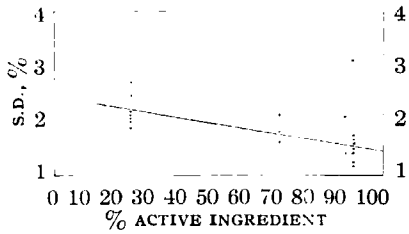

Fig. 1.—Standard deviation (assays) *vs.* per cent active ingredient.

TABLE III.—INDIVIDUAL TABLET ASSAY STANDARD DEVIATION ON ADDITIONAL LOTS OF PRODUCT 7

Lot	Tablets Assayed, No.	$\bar{X}$ in % Label Claim	σ in % Label Claim	Relative Error $\sigma/\bar{X} \times 100$
E	234	100.3	2.2	2.2
F	180	100.5	1.8	1.8
G	91	100.7	2.0	2.0
H	51	101.1	2.0	2.0
I	75	99.3	2.1	2.1
J	79	99.5	1.7	1.7
K	75	99.6	1.3	1.3
L	55	100	1.3	1.3
M	88	100	2.0	2.0
			Av. 1.7	1.7

TABLE IV.—DISTRIBUTION OF INDIVIDUAL TABLET WEIGHTS

Product	Lot	Tablets Weighed, No.	Target Wt.	$\bar{X}$ mg.	σ mg.	$\sigma/\bar{X} \times 100$	α_3[a]	α_4[a]	Curve, Type
1	A	116	105.0	105	2.1	2.0	−0.14	2.51	Normal
	C	74		105	3.3	3.1	−0.06	[4.93]	Leptokurtic
2	A	88	107.5	101	3.4	3.4	0.41	[6.31]	Leptokurtic
	B	90		107	2.2	2.1	0.12	[5.16]	Leptokurtic
3	A	104	215.0	213	2.9	1.4	0.07	3.11	Normal
	B	95		215	3.8	1.8	−0.48	[4.07]	Leptokurtic
5	A	102	365.0	361	6.1	1.7	[−1.24]	[5.84]	Leptokurtic and skewed —low side
	B	100		362	4.5	1.2	[−0.67]	[4.36]	Leptokurtic and skewed —low side
	C	95		372	5.9	1.6	0.02	3.69	Normal
6	A	101	565.0	563	8.6	1.5	−0.10	2.29	Normal
	B	91		564	7.1	1.3	0.09	2.80	Normal
7	A	105	551.0	560	5.8	1.0	0.10	2.54	Normal
	D	100		552	6.4	1.2	0.29	2.12	Normal
9	A	100	713.0	718	9.1	1.3	0.05	2.32	Normal
	B	100		706	7.2	1.0	0.16	2.48	Normal
	C	100		706	7.7	1.1	0.14	2.93	Normal
	D	300		713	10.2	1.4	0.09	[2.31]	Platykurtic
10	A	1001	648.0	656	9.6	1.5	0.15	2.83	Normal
	B	255		646	5.9	0.9	0.03	2.89	Normal
	C	273		648	7.0	1.1	[0.40]	[3.44]	Leptokurtic and skewed —high side
	D	293		648	9.6	1.5	0.24	2.73	Normal

[a] Tested for significance by student "t" test at 0.05 level; significant values indicated by brackets.

positive correlation exists when the value is one. The results in Table V show a significant correlation in 10 out of 12 lots at a low level, in the range studied. In the range studied there seems to be no relationship between weight-assay correlations and per cent of active ingredient in the tablet.

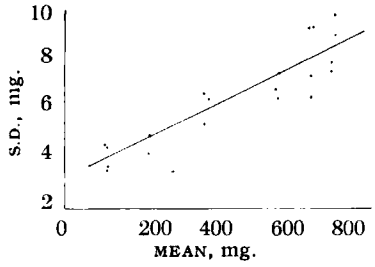

Fig. 2.—Standard deviation (weights) *vs.* mean.

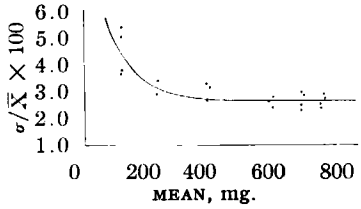

Fig. 3.—Relative error (weights) *vs.* mean.

CONCLUSIONS

It was found from the sample studied in our laboratories that (*a*) the spread of dosage variation in individual compressed tablets was very small, (*b*) the distribution of individual tablet weights and assays was essentially normal; and (*c*) a correlation existed between tablet weight and assay, at a low level, in the range studied.

In this type of situation where extensive research.

TABLE V.—CORRELATION BETWEEN INDIVIDUAL TABLET WEIGHT AND ASSAY

Product	Lot	Tablets, No. (Wt. and Assay)	Correlation Coefficient	Correlation Significance	% Active Ingredient by Wt.
1	A	116	−0.16	$p > 0.05$ N.S.	23.8
	C	74	0.35	$p < 0.01$ S	23.8
2	A	88	0.46	$p < 0.001$ S	23.3
	B	90	0.22	$p < 0.05$ S	23.3
3	A	104	0.40	$p < 0.001$ S	23.3
	B	95	0.24	$p < 0.05$ S	23.3
5	A	102	0.55	$p < 0.001$ S	68.5
	B	100	0.18	$p > 0.05$ N.S.	68.5
	C	95	0.44	$p < 0.001$ S	68.5
7	A	105	0.27	$p < 0.01$ S	90.7
	D	100	0.47	$p < 0.001$ S	90.7
6	B	91	0.34	$p < 0.001$ S	88.5

considerable production experience, and sufficient in-process controls exist, low dosage variation in individual compressed tablets may be achieved. Modern quality control concepts emphasize that quality should be built into the product rather than tested in. The results of this study indicate what can be achieved by following this concept.

It should be noted that the tablets studied were round, discoid shape, containing more than 20% active ingredient, and the assay procedures involved have a high degree of reliability. Further studies should be performed with tablets of irregular shapes and lower percentage of active ingredient. It would also be interesting to examine the effects of assay procedures of greater variability on this type of study.

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Notes

Synthesis of Selected Amides of Mono- and Bis(carboxypiperidino)alkanes

By RONALD P. QUINTANA and WAYNE A. SHRADER

The synthesis of selected amides of mono- and bis(carboxypiperidino)alkanes is reported.

THE SYNTHESIS of selected amides of mono- and bis(carboxypiperidino)alkanes has been undertaken to expand significantly those series of compounds previously reported (1–4). The compounds described in this communication were chosen on the basis of enzymodynamic studies, wherein particularly interesting variations in biochemical response relative to modifications in chemical constitution were noted and parallel effects upon surface and interfacial tension were observed. The fact that in some instances, among the monomethyl-, dimethyl-, monoethyl-, and diethylcarboxamido derivatives, the latter was the only one effecting appreciable or even significant inhibition in isolated human plasma "pseudo"-cholinesterase systems (5), prompted us to explore variations in the amide group in terms of steric factors and the electrophilic character of the carbonyl carbon. Since the mono- and bis[3-(N,N-diethylcarboxamido)piperidino]-ethanes and decanes reflected perhaps the most interesting relationships between molecular constitution, cholinesterase inhibition (5), and surface and interfacial tension (6), these four analogs were selected as model molecules for this study.

In general, the synthetic procedures employed in this investigation were those utilized by Lassio and co-workers (1, 2, 4). The compounds 1-ethyl-3-(N,N-diethylcarboxamido)-1,2,5,6-tetrahydropyridine hydrochloride (XVIII) and 1-decyl-3-(N,N-diethylcarboxamido)-1,2,5,6-tetrahydropyridine hydrochloride (XIX) were synthesized by sodium borohydride reduction of the appropriate pyridinium salts, a method employed by Lyle and co-workers (7) in the preparation of arecoline (methyl 1-methyl-1,2,5,6-tetrahydronicotinate) and methyl 1-methyl-1,2 5,6-tetrahydroisonicotinate.

The position of the double bond in compounds XVIII and XIX was confirmed by a comparison of the ultraviolet and infrared spectra of these compounds with the corresponding spectra of 1-methyl-3-(N,N-diethylcarboxamido)-1,2,5,6-tetrahydropyridine hydrochloride (XX) (1), prepared from arecoline (see Table I). Lyle's recent interpretation (8) of the mechanism involved in the sodium borohydride reduction of pyridinium ions provides further substantiation in this regard.

EXPERIMENTAL

4-(N,N-Diethylcarboxamido)pyridine (I).—This

TABLE I.—ULTRAVIOLET AND INFRARED SPECTRA

Compd. No.	Infrared Spectra, μ[a]	Ultraviolet Spectra[b] $\lambda_{max.}$ mμ	ϵ
XVIII	5.99 (m),[c] 6.20 (s)[d,e]	206	7800
XIX	5.99 (m),[c] 6.20 (s)[d,e]	206	8100
XX[f]	5.99 (m),[c] 6.20 (s)[d,e]	206	7880

[a] Infrared spectra were run in chloroform. [b] Ultraviolet spectra were run in ethanol by Huffman Microanalytical Laboratories, Wheatridge, Colo. [c] Attributed to the double bond. [d] Attributed to the conjugated amide carbonyl function. [e] Band is broad. [f] Lasslo, *et al.* (1).

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