Compressed Coated Tablets II

Influence of Size Distribution of Coating Granulation on Weight Uniformity of Tablets

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Compressed coated tablets were prepared on a Manesty machine from four granulations of the same formulation, each having a granule of different size as its major component. The effect of granulation size on the weight variability of tablets was determined. The coating granulation sizes which give minimum and maximum weight variability are illustrated and are shown to be reproducible. The relationship that exists between weight variation and core centration is discussed.

IT IS EVIDENT from the numerous compressed coated tablets on the market today that the principle of coating tablets by compression has met wide acceptance in the pharmaceutical industry.

Literature reports (1–9) appearing on the subject of dry coating are concerned with (*a*) the physical properties required for core and coating granulation to give suitable compressed coated tablets, (*b*) coating and core formulations adequate for use in compression coating, (*c*) formulations concerned with disguising a bitter taste, eliminating discoloration, and improving the stability of an active ingredient, (*d*) formulations for imparting sustained-action properties to a drug, and (*e*) forming enteric-coated tablets. However, studies relative to the factors influencing the quality of the compressed coated tablets appear to be lacking. Accordingly, investigations along these lines were initiated in our laboratories. An initial report (10) from these studies was concerned with the factors influencing core centration and methods of evaluating same.

In this report, it will be shown that coating granulation size influences the weight variability of compressed coated tablets prepared on the Manesty Dry Cota machine. The relationship that exists between the weight variation results and the core centration data presented in an earlier report is discussed. The utility of these evaluation techniques to determine the coating granulation size for a particular formula compressed coated tablet to give optimal centration and weight uniformity is illustrated.

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EXPERIMENTAL

The Manesty Dry Cota shown in Fig. 1 basically consists of two rotary tablet presses coupled by a single drive shaft and a special transfer device in such a manner that core tablets can be compressed and coated in one continuous cycle.

Core Granulation.—The formula and procedure of preparation of this core granulation have been described in a previous study (10). The formula is as follows:

Material and Formula	
Lactose U.S.P.	10.000 Kg.
Wheat starch	2.750
Aerosil compositum[1]	0.750
Gelatin U.S.P.	0.250
Stearic acid, spray dried	0.625
Charcoal	0.125
Talcum U.S.P.	0.500
Purified water	*q.s.*

The sieve analysis for a representative sample of this formulation is given in Table I.

Coating Granulation.—The formula and procedure of preparation of this coating granulation have been described in an earlier report (10). The formula is as follows:

Material and Formula	
Lactose U.S.P.	16.000 Kg.
Aerosil compositum	1.500
Gelatin U.S.P.	0.500
Wheat starch	2.500
Arrowroot starch	2.500
Talcum U.S.P.	1.000
Stearic acid, spray dried	1.000
Purified water	*q.s.*

The above granulation was fractionated through screens to give four granulations of different size

[1] Composed of 85% colloidal silica and 15% hydrolyzed starch.

Fig. 1.—Photograph illustrating the Manesty Dry-Cota machine.

distribution, each one having a different size granule as its major component. The sieve analyses for these four granulations are presented in Table II. In an earlier study concerned with core centration, granulation fraction 12 was numbered 8, and granulation fraction 20 was numbered 35.

Preparation of Compressed Coated Tablets on Manesty Dry Cota.—The compressed coated tablets were prepared on the Manesty Dry Cota model 350 at a rate of 18,000 tablets/hr. The cores weighed 150 mg., were 7 mm. in diameter (0.276 in.), and had a radius of curvature of 13 mm. The coated tablets weighed 400 mg., were 10 mm. in diameter (0.394 in.), and had a radius of curvature of 18 mm.

Influence of Coating Granulation Size Distribution on Weight Uniformity.—By varying the size distribution of the coating granulation and maintaining the size of the core granulation constant, the influence of coating granulation on tablet weight uniformity was investigated. Tablets were compressed for 1 hr. with each of the four granulations. The Manesty machine was regulated for tablet weight uniformity at the start of the hour's run. Then 100 tablets were collected initially and every 10 min. thereafter during the hour without adjusting the machine. This resulted in a collection of seven samples of 100 tablets each for each of the four granulations. This experiment was repeated one-half year later to determine the reproducibility of the data. In the first experiment, 15 tablets were taken at random from each of the seven samples of 100 tablets; and for the second experiment, 10 tablets were taken at random from each of the second set of seven samples of 100 tablets. The tablets in each of these subsamples were weighed individually on an analytical balance and the weights analyzed statistically. Therefore, the set of data from the first experiment consisted of 28 samples of 15 tablets, and the set of data from the second experiment consisted of 28 samples of 10 tablets.

Table I.—Sieve Analysis of Core Granulation

Sieve No.	On Screen, %
8	60.5
12	34.5
20	4.0
30	0.5
50	0.5

Statistical Analysis of Data.—For the samples of tablets taken at the seven time periods for the four granulations in each experiment, the means and standard deviations of tablet weights were computed. The sample means at the various time periods will be hereafter called "time-means."

To permit a comparison of the variabilities "between time-means" and the variabilities "within time-means" of the tablets produced from the four coating granulations, a simple manner of rating these variabilities is provided.

An *Index of Variability* was calculated to describe the variations that exist "between time-means," and an *average variance* for 1 hr. of machine operation was used to describe the variability which exists "within time-means." Both measures of variability are based on an analysis of variance on individual tablet weights of each granulation. The indices are provided by "between time-means" variance components, and the average variances are provided by residual terms of analysis of variance (Table V). The homogeneity of sample variances (seven time samples of two experiments = 14 variances for each granulation) was checked by Bartlett's test (11).

RESULTS AND DISCUSSION

It should be noted that the estimations of tablet weight variability prepared from the four different granulation fractions of the same formulation was based on data obtained from compressed coated tablets. The variance of coated tablets equals the variance of core plus the variance of coating plus twice the covariance of core and coating expressed as follows:

$$V_t = V_c + V_{ct} + 2\,Cov_{c \times ct} \qquad \text{(Eq. 1)}$$

where V_t = variance of coated tablets; V_c = variance of core; V_{ct} = variance of coating; and $Cov_{c \times ct}$ = covariance of core and coating.

A preliminary study on 50 core tablets prepared from the core granulation used for all the compressed coated tablets in the first experiment indicated that

Table II.—Sieve Analysis of the Four Coating Granulations

Granulation Fraction	On Screen, %					Through Screen, %
	No. 8	No. 12	No. 20	No. 30	No. 50	No. 100
12	8.0	(68.5)	15.5	2.0	5.0	1.0
20	0.0	26.0	(43.5)	6.0	18.5	6.0
50	0.0	0.2	13.5	9.0	(56.0)	21.3
100	0.0	0.0	0.0	0.1	15.5	(84.4)

TABLE III.—MEANS OF TABLET WEIGHTS FOR THE SEVEN TIME PERIODS FOR TWO EXPERIMENTS

Granulation	Expt.	Sample Size	Tablet Wt. Means at Time Periods, min. 0	10	20	30	40	50	60
12	I	10	396.6	415.2	422.8	411.6	402.1	421.5	421.5
	II	15	398.8	419.5	427.4	416.8	407.8	421.2	425.6
20	I	10	393.4	404.6	407.5	407.6	406.8	407.3	398.2
	II	15	393.9	408.5	412.4	408.9	412.0	412.6	399.4
50	I	10	410.6	404.1	405.0	403.3	408.2	402.5	409.2
	II	15	414.3	405.1	409.7	407.7	411.2	406.3	411.5
100	I	10	385.3	395.2	396.5	388.9	380.8	393.2	400.1
	II	15	395.2	396.0	401.9	391.2	384.5	395.7	400.7

TABLE IV.—STANDARD DEVIATIONS OF THE MEANS OF TABLET WEIGHTS FOR THE SEVEN TIME PERIODS OF TWO EXPERIMENTS

Granulation	Expt.	Sample Size	S. D. of Tablet Wt. at Time Periods, min. 0	10	20	30	40	50	60
12	I	10	7.89	2.49	5.29	5.10	5.02	4.72	2.42
	II	15	7.47	4.11	4.31	4.25	3.67	4.34	2.43
20	I	10	2.59	2.22	2.64	2.12	2.53	1.95	2.25
	II	15	2.41	2.79	2.31	2.53	2.78	1.91	3.25
50	I	10	2.50	3.63	2.79	4.57	3.82	3.44	1.62
	II	15	1.76	6.02	3.46	4.60	4.68	3.60	3.11
100	I	10	5.52	15.93	5.91	11.34	4.96	1.87	4.53
	II	15	9.38	15.95	10.15	6.10	4.24	7.04	4.16

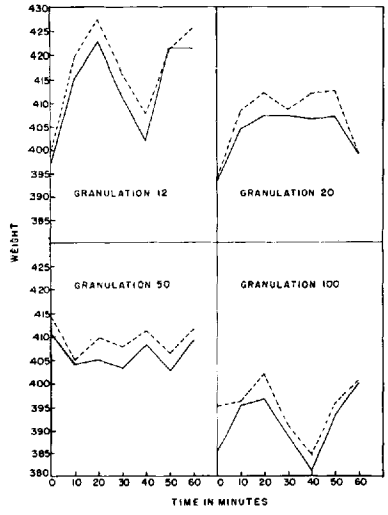

Fig. 2.—Means of tablet weights at 10-min. intervals for 1 hr. tablet press operation. Key: ————, experiment I; ----------, experiment II.

the variance of core (V_c) is very small relative to the variance of coated tablets (V_t). The absolute value of covariance of core and coating ($Cov_{c \times ct}$) is at most the square root of the product of variance of core (V_c) and variance of coating (V_{ct}) (Eq. 2)

$$| Cov_{c \times ct} | \leq \sqrt{V_c}\,\sqrt{V_{ct}} \qquad \text{(Eq. 2)}$$

and is small relative to the variance of the coated tablets (V_t).

From Eq. 1, it can be seen that if V_c and $Cov_{c \times ct}$ are small, the difference, $V_t - V_{ct}$, is necessarily very small.

Therefore, in this study, core variance corrections were not made, and the analysis was performed on the assumption that variance of coating equals variance of coated tablets ($V_{ct} = V_t$). This assumption is further justified by the fact that the authors are more interested in relative values of the four granulations "estimates of variances" than in their absolute values.

The computed means and standard deviations for each sample of 10 or 15 tablets of the two experiments are summarized in Tables III and IV.

To depict more clearly the variability of the tablet weights for the two experiments over the 60-min. time period of the compression operation, the means and standard deviations are plotted in Figs. 2 and 3, respectively. It is interesting to note that each

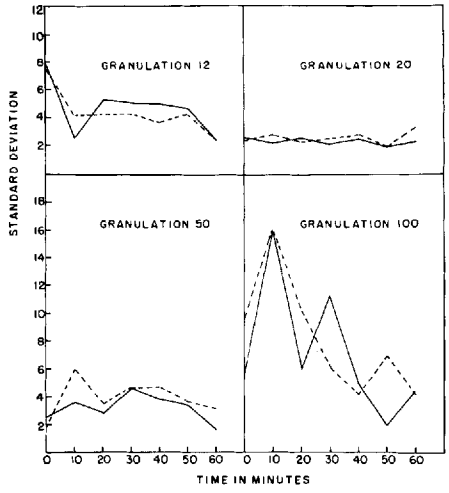

Fig. 3.—Standard deviation of tablet weights sampled at 10-min. intervals for 1 hr. tablet press operation. Key: ————, experiment I; ----------, experiment II.

TABLE V.—ANALYSIS OF VARIANCE ON INDIVIDUAL TABLET WEIGHTS FOR THE FOUR GRANULATIONS

Source of Variation	Granulation 12 S.S.	d.f.	M.S.	20 S.S.	d.f.	M.S.	50 S.S.	d.f.	M.S.	100 S.S.	d.f.	M.S.
Total	9755.48	149		3897.17	149		3490.00	149		16546.47	149	
Between time-means	6749.68	5	1349.94[a]	2443.79	5	488.76[a]	829.88	5	165.98[a]	5304.27	5	1060.85[a]
Between experiments[c]	561.69	1	561.69	479.60	1	479.60	367.35	1	367.35	236.13	1	236.13
Interaction	138.61	5	27.72	107.71	5	21.54[b]	59.07	5	11.81	98.64	5	19.73
Residual	2305.50	138	16.71	866.07	138	6.28	2233.70	138	16.19	10907.43	138	79.04
Indices (The estimates of between time-means variance components)	$I_{12} = \frac{1349.94-27.72}{25} = 53$			$I_{20} = \frac{488.76-21.54}{25} = 19$			$I_{50} = \frac{165.98-11.81}{25} = 6$			$I_{100} = \frac{1060.85-19.73}{25} = 42$		
Average variances[d] (Within time-means provided by residual)	$V_{12} = 17$			$V_{20} = 6$			$V_{50} = 16$			$V_{100} = 79$		

[a] Significant at $p = <0.001$. [b] Significant at $p = 0.01$. [c] "Between experiments" mean squares are not tested for significance since they reflect initial adjustment of tablet press. "Interaction" mean squares are not significant for granulations 12, 50, and 100, indicating that time variation of means does not differ significantly from experiment to experiment, *e.g.*, these time patterns are systematic. "Interaction" mean squares for granulation 20 are significant. However, the "between time-means" mean square is much larger than the "interaction" mean square so that although the time pattern does differ between experiments, the common part of the pattern is much greater than the difference between experiments (Fig. 2, granulation 20). The variances of 12 samples for granulation 100 are not homogeneous across an hour run. However, the samples with heterogeneous variances were included in the analysis of variance so that the variability "within time-means" is measured by the average variance for the whole run of the machine. The ratio of "between time-means" mean square and "residual" mean square is sufficiently large so that the significance of the former is not in doubt.

granulation has a typical pattern of variability for time-means and a different pattern for standard deviations which was similar for both experiments, even though they were performed about 6 months apart. It is evident from the plots in Fig. 2 that granulation 12 shows the greatest scatter of mean tablet weights over the time period of compression and granulation 50 the least. However, the standard deviation of the mean tablet weights is the smallest for granulation 20 and largest for granulation 100 as seen from the plots in Fig. 3.

The results obtained from Bartlett's test showed that for granulation 12 and 50, the zero time variances differ significantly (are heterogeneous) when compared with the remaining 12 samples' variances from 10 to 60 min. Granulation 20 showed homogeneous variances for the mean weights of the 0- to 60-min. samples. Granulation 100, however, showed heterogeneous variances for the mean tablet weights for the 0-, 10-, and 20-min. samples as compared with the other time periods. As a result of these findings, the zero time data were eliminated from further analysis since it was felt that the tablet press was not yet standardized at the zero time sampling. Although the 10- and 20-min. samples of granulation 100 exhibited heterogeneous variances, they were retained for the analysis of variance. The justification for this is given with Table V which shows the analysis of variance and the calculations of indices (I), as well as average variances (V) for each granulation.

It was found that granulation 12 had an $I = 53$, granulation 20 an $I = 19$, granulation 50 an $I = 6$, and granulation 100 an $I = 42$. The higher the index, the larger the variability of the tablet weight time-means during the 1-hr. compression period. The granulations exhibit the following order of increase of variability of time-means over the 1 hr. duration of tablet manufacture: $50 < 20 < 100 < 12$. It is interesting to note that the granulations of the medium particle size range show the smallest indices. The average variances for the four granulations are $V_{12} = 17$, $V_{20} = 6$, $V_{50} = 16$, and $V_{100} = 79$. It is evident from these data that the following increasing order of variability exists within the mean tablet weights for the four granulations: $20 < 50 < 12 < 100$. The average variances for the four granulations demonstrate that granulation 100 exhibits the worst variability.

Comparison of Weight Uniformity and Core Centration Data.—In order to permit this evaluation, the tablets used in this study and in a previous one on core centration (10) were from the same batch. When the results obtained in this study are compared with the core centration data, it is found that the tablets prepared from coating granulation fraction 20 also exhibited optimal core centration.

SUMMARY

The influence of coating granulation size distribution of the same formulation on the weight variability of compressed coated tablets prepared on a Manesty machine was studied, and simple measures of tablet weight variability were presented. The following summarizes the findings.

1. The size distribution of the coating granulation substantially affects the weight uniformity of the compressed coated tablets.

2. For each granulation, there is a pattern of time variation of means which is systematic for the experiments.

3. Granulations 12 and 100 cause the largest variability in tablet weight means during the 1-hr. period of tablet press operation. In addition, granulation 100 has the largest variability of all the granulations when scatter of tablet weight within a sample of 10 or 15 tablets is taken under consideration.

4. Granulations 20 and 50 cause small scatter of means of tablet weights; and in addition, granulation 20 shows particularly low variability of tablet weights within samples of 10 or 15 tablets.

REFERENCES

(1) Linde, S., *Svensk Farm. Tidskr.*, **35**, 875(1955).
(2) Windheuser, J., and Cooper, J., *J. Am. Pharm. Assoc., Sci. Ed.*, **45**, 542(1956).
(3) Wolff, J. E., U. S. pat. 2,757,124 (1956).
(4) Klump, T. G., Wolff, J. E., and Kaplan, L. J., U. S. pat. 3,019,169 (1962).
(5) Cooper, J., and Windheuser, J., U. S. pat. 2,887,438 (1959).
(6) Blubaugh, F. C., Zapapas, J. R., and Sparks, M. C., *J. Am. Pharm. Assoc., Sci. Ed.*, **47**, 857(1958).
(7) James, K. M., Jeffrey, J. C., and MacAuley, W. C., *Can. Pharm. J., Sci. Sect.*, **1958**, 456.
(8) Swintosky, J. V., U. S. pat. 2,971,889 (1961).
(9) Millar, J. F., and Lindner, G., U. S. pat. 3,018,221 (1962).
(10) Lachman, L., Speiser, P. P., and Sylwestrowicz, H. D., *J. Pharm. Sci.*, **52**, 379(1963).
(11) Bennett, C. A., and Franklin, N. L., "Statistical Analysis in Chemistry and Chemical Industry," John Wiley & Sons, Inc., New York, N. Y., 1954, p. 197.

Lined and Unlined Rubber Stoppers for Multiple-Dose Vial Solutions II

Effect of Teflon Lining on Preservative Sorption and Leaching of Extractives

By LEON LACHMAN, WAYNE A. PAULI, PRAVIN B. SHETH, and MIRIAM PAGLIERY

This report demonstrates the protective action of Teflon linings on the sorption and leaching characteristics of polyurethan and natural rubber stoppers. This lining was effective in essentially eliminating extractives from appearing in water, 50 per cent polyethylene glycol 300, 50 per cent *N,N*-dimethylacetamide, 10 per cent ethanol, and 2 per cent benzyl alcohol when these solvents were in contact with the closures for 6 hr. at 115°. Sorption of the preservative, *p*-chloro-β-phenylethyl alcohol, from aqueous solution was effectively retarded by the Teflon lining on the stoppers. Reduced protection against sorption and leaching was found when Teflon lined closures, which previously underwent multiple puncture with a 20-gauge hypodermic needle, were used.

WITHIN recent years, the influence of rubber closures on the contents of multiple-dose vial solutions has received considerable attention (1, 2). It has been shown that both leaching of rubber extractives from rubber closures into solution and sorption of materials from solution by rubber stoppers can be detrimental to multiple-dose injectable preparations. Since many of the materials extracted from closures are reactive chemicals, they could cause stability (3–5) or toxicity and pyrogenicity (6, 7) problems with the vial contents, as well as interfere with assay methods (2), making it difficult or impossible to quantitatively identify active ingredients. The loss of antibacterial preservatives from multiple-dose vials resulting from sorption into rubber closures and/or reaction with rubber extractives is recognized as a serious problem. Since these agents are added to multiple-dose injectable preparations to insure bacteriostasis for the life of the product, any significant loss of the antimicrobial agent from solution can seriously undermine sterility maintenance of the product. Various attempts have been made to retard sorption of materials from vial solutions and to reduce the amount of extractives leached from closures into solutions. Certain rubber stopper manufacturers have attempted to eliminate these incompatibilities between vial solutions and closures by application of a lacquer lining to the inner surface of their closures. This lining appears to be essentially noneffective in retarding both sorption and leaching effects (8). A recent report from these laboratories (9) contains an evaluation of the protective action of an epoxy lining on rubber stoppers of varying composition. Although this lining was found to afford partial protection against leaching, no protective action against sorption was observed.

This study was initiated to determine the extent of protection afforded by Teflon linings, described by Hopkins (10), on polyurethan and natural rubber stoppers against sorption and leaching. The sorption characteristics of the lined and unlined elastomer closures were tested

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