Compressed Coated Tablets I

Measurement and Factors Influencing Core Centration

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A novel and accurate procedure for measuring the horizontal and vertical centration of tablet core in compressed coated tablets is described. This method of measurement permits the determination of core dislocation along and across the axis of turntable movement. The influence of size distribution of the coating granulation on core expansion and centration was studied. Results are presented for compressed coated tablets processed under similar operating characteristics on the Manesty and Kilian machines. A statistical treatment of the data was performed to permit a more meaningful interpretation and comparison of the results within one machine as well as between machines. This method for measuring core centration permits the determination of the size distribution of granulation necessary to give optimal centration.

THE PAST several years have seen the principle of coating tablets by compression meet with wide acceptance and enthusiasm in the pharmaceutical industry. This is evidenced by the numerous compressed coated tablets on the market today.

Literature reports relative to dry coating also began to appear during this time. Linde (1) and Windheuser and Cooper (2) reported on the physical properties required for core and coating granulations to give suitable compressed coated tablets. Wolff (3) presented coating and core formulations adequate for use in compression coating. Klump, *et al.* (4), have shown that the process of dry coating can be used to hide the bitter taste of active medicaments, to eliminate discoloration, and to improve the stability of active ingredients. Core formulations intended for sustained action dry coated tablets have been described by Cooper and Windheuser (5). Several reports have recently appeared in the literature pertaining to the application of an enteric coating to a core by compression methods (6–9).

It is evident from the above that considerable research has gone into the development of suitable formulas for compression coating. On the other hand, there appears to be little work reported relative to accurate methods for measuring horizontal and vertical centration of cores in compressed coated tablets. Weinstein (10) made an attempt in this direction by employing a roentgenographic technique. This consisted of including a small concentration of elemental iron in the core formulation and subsequently developing a radiographic plate showing the contrast between core and coating. Using this method the author was only able to present a general picture of core dislocation in the horizontal plane and cocking in the vertical plane.

In this report an accurate procedure for measuring horizontal and vertical centration of tablet cores in compressed coated tablets will be described. The method to be illustrated permits the determination of core dislocation in the horizontal plane, both parallel and at right angles to turntable movement, as well as maximum dislocation. In addition, it is possible to determine cocking in the vertical plane along the same three vectors and also core displacement up or down along the vertical axis. The utility of this method for determining the optimal size distribution of a coating granulation to give the most satisfactory core centration is demonstrated. This was done for the Manesty and Kilian dry coating machines using one formula granulation which was fractionated to give four granulations, each having a different size granule as its major component.

EXPERIMENTAL

Core Tablets

The core tablets were prepared according to the following formula and procedure:

Material and Formula.—Lactose U.S.P., 10.000 Kg.; wheat starch, 2.750 Kg.; Aerosil Compositum,[1] 0.750 Kg.; gelatin U.S.P., 0.250 Kg.; stearic acid, spray dried, 0.625 Kg.; charcoal, 0.125 Kg.; talcum U.S.P., 0.500 Kg.; and purified water, *q.s.*

Procedure.—The granulation was prepared according to customary wet granulating techniques using gelatin solution as the granulating agent. The wet granulation was dried at 40° in a circulating

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[1] Aerosil Compositum is composed of 85% colloidal silica and 15% hydrolyzed starch.

air oven to a moisture content of 1.5%. The dried granulation was screened through a No. 12 mesh screen in a Fitzpatrick model D comminuting machine. Into this granulation were mixed the charcoal and stearic acid, which were previously passed through a No. 40 mesh screen.

Table I shows the sieve analysis for a representative sample of this granulation.

TABLE I.—SIEVE ANALYSIS OF CORE GRANULATION

Sieve Number	Per Cent on Screen
8	60.5
12	34.5
20	4.0
30	0.5
50	0.5

Coating Granulation

Material and Formula.—This granulation was prepared according to the procedure described under the core tablets. The following was the formula used: lactose U.S.P., 16.000 Kg.; Aerosil Compositum, 1.500 Kg.; gelatin U.S.P., 0.500 Kg.; wheat starch, 2.500 Kg.; arrowroot starch, 2.500 Kg.; talcum U.S.P., 1.000 Kg.; stearic acid, spray dried, 1.000 Kg.; and purified water, *q.s.*

The granulation was then divided into four parts and each part sieved through different size screens to give granulations of different size distribution. The sieve analysis data for these four batches of granulation are presented in Table II.

TABLE II.—SIEVE ANALYSIS OF THE FOUR COATING GRANULATIONS

Granulation Fraction	Per Cent on Screen No. 8	No. 12	No. 20	No. 30	No. 50	Per Cent Through Screen No. 100
8	8.0	68.5	15.5	2.0	5.0	1.0
35	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

Preparation of Compressed Coated Tablets on Manesty DryCota and Kilian Prescoter.—The core tablets used for both machines were compressed on the core side of the Manesty DryCota model 350 at a rate of 18,000 tablets per hour. They weighed 150 mg., were 7 mm. in diameter (0.276 inch), and had a radius of curvature of 13 mm. The dry coated tablets produced weighed 400 mg., were 10 mm. in diameter (0.394 inch), and had a radius of curvature of 18 mm.

The Manesty machine is a 16-station press, while the Kilian machine has 20 stations. The die table of the Manesty machine traveled at 18.7 r.p.m. to produce 18,000 tablets per hour, while the die table on the Kilian machine traveled at a rate of 15 r.p.m. to produce the same number of tablets per hour.

Influence of Coating Size Distribution on Core Centration.—In order to determine the influence of particle size on the centering of the core in the finished compressed coated tablets, the particle size distribution of the core granulation was kept constant, while that of the coating granulation varied. Compressed coated tablets were prepared on the Manesty and Kilian machines using the four coating granulation fractions previously described. After the machine was regulated with regard to weight uniformity for each coating granulation, samples of 100 tablets were taken initially and then every 10 minutes for an hour without adjusting the machine during the hour's run. From each of these 100 compressed coated tablets, 10 were taken at random for determining horizontal centration and 20 were taken at random for vertical centration measurements. Of these 20 tablets, 10 tablets were cut crosswise to and the other ten tablets were cut along the axis of die table movement.

Core Centration Measurements

Horizontal Centration.—Figure 1 shows a schematic diagram of a die table and gives the direction of rotation of the die table used for compressing the coating granulation around the core for both the Manesty and Kilian machines. As the coated tablet begins to leave the bore of the die it is marked on the outside of the tablet cylinder with a special marking pen attached to the machine. This takes place just before the take-off point. Marking the tablets in this manner identifies the tablet position with regard to the direction of die table movement. It is then possible to measure the core dislocation along and across the axis of die table movement as illustrated in Fig. 1. In addition, by further calculation it is also possible to estimate the maximum dislocation of the core within the tablet.

In order to permit an accurate measure of core dislocation, tablets were cut along the horizontal surface to a definite depth with the device shown in Fig. 2. Then fivefold magnification photographs were taken, an example of which is shown in Fig. 3. Centration measurements were made using these photographs.

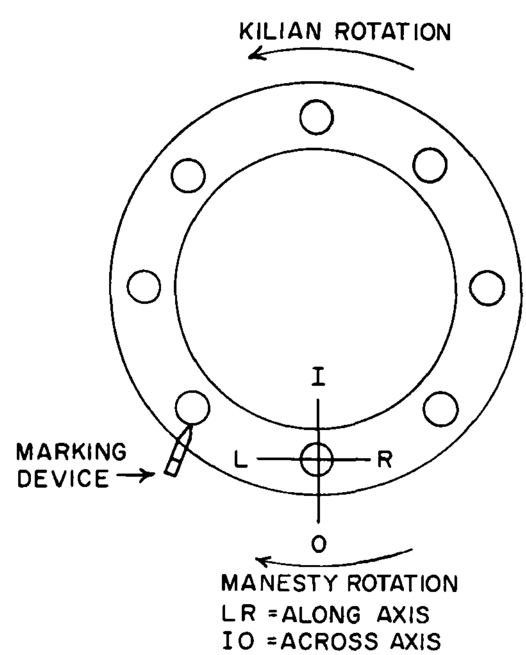


Fig. 1.—Schematic diagram of die table showing marking device attachment and direction of rotation for Manesty and Kilian machines.

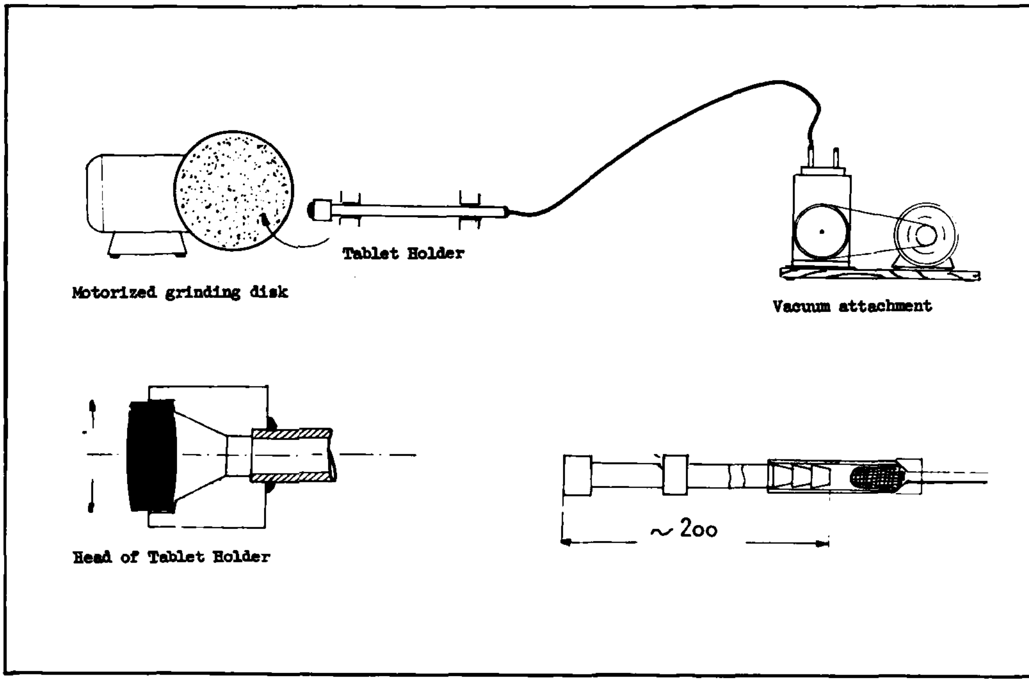


Fig. 2—Tablet cutting device.

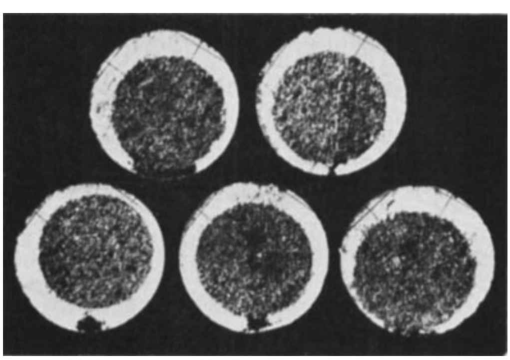


Fig. 3.—A five-fold magnification photograph of horizontal cut tablets.

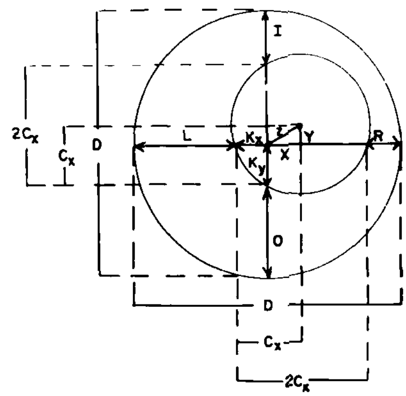
In the past, attempts to measure core centration consisted at best of determining the maximum dislocation of the core in the tablet. Only in the ideal situation, where core dislocation has taken place on the diameter of the tablet along the axis of die table movement, can direct measurements be made of core dislocation by determining the difference between the distance at the left and right between the core and coating along the diameter of the tablet. This ideal situation is seldom observed. Instead, the center of the core is dislocated from the diameter of the tablet along and across the axis of die table movement or in both directions. In this situation if any attempt is made to use the difference between the left and right side of the core edge to the coating edge, incorrect results would be obtained in the estimation of core dislocation. To accurately measure core dislocation along the horizontal plane, the geometry of the tablet was taken into consideration and equations derived to accurately determine centration "along axis" and "across axis" of die table movement and the maximum dislocation. Figure 4 represents a graphic model of the core dislocated from the center of the tablet along and across the horizontal plane. The resulting right triangle having the sides X, Y, and Z, drawn from the center of the tablet to the center of the core, was used to derive the equations needed to measure core dislocation. The equations needed to determine "along axis" dislocation of center of core from center of tablet (X), "across axis" dislocation of center of core from center of tablet (Y), and maximum dislocation of center of core from center of tablet (Z) are as follows:

$$X = \frac{L - R}{2} \qquad Y = \frac{O - I}{2} \qquad Z = \sqrt{X^2 + Y^2}$$

The symbols used in the derivation of the equations from Fig. 4 are defined as follows: D = diameter of tablet; R = distance between core and coating on the right side; L = distance between core and coating on the left side; and R and L are measurements for dislocation along the axis of turntable movement. O = distance between core and coating on the outside; I = distance between core and coating on the inside; and O and I are measurements for dislocation across the axis of turntable movement.

Now if: $X = 0$, the core is not dislocated along axis of turntable movement; $X > 0$, the core is dislocated to the right; $X < 0$, the core is dislocated to the left; $Y = 0$, the core is not dislocated across axis of turntable movement; $Y < 0$, the core is dislocated toward the outside, and if $Y > 0$, the core is dislocated toward the inside.

It is evident from the above equations that it is only necessary to know the values for L, R, I, and O to be able to determine core dislocation in the three directions X, Y, and Z. In order to measure



Derivation of Formulas for x, y and z

x	y	z
Since $x = C_x - K_x$	Since $y = C_y - K_y$	Since $z^2 = x^2 + y^2$
$K_x = \frac{D}{2} - L$	$K_y = \frac{D}{2} - O$	$z = \sqrt{x^2 + y^2}$
$2C_x = D-(R+L)$	$2C_y = D-(O+I)$	
$C_x = \frac{D-(R+L)}{2}$	$C_y = \frac{D-(O+I)}{2}$	
Then	Then	
$x = \frac{D-R-L}{2} - \frac{D}{2} + L$	$y = \frac{D-O-I}{2} - \frac{D}{2} + O$	
$x = -\frac{R}{2} - \frac{L}{2} + L$	$y = \frac{O}{2} - \frac{I}{2} + O$	
$x = \frac{L-R}{2}$	$y = \frac{O-I}{2}$	

Fig. 4.—A graphic illustration of core dislocation along horizontal plane and derivation of equations for "along axis," "across axis," and maximum dislocation of center of core from center of tablet.

these values the exact center of the tablet was determined by drawing two cords along the edge of the coating and taking the intersection of the perpendicular bisectors of these cords as the center.

Horizontal core centration was determined by measuring R, L, I, and O on 70 tablets taken from each of the four coating granulations after compression on both the Manesty and Kilian machines.

Vertical Centration.—Since the tablets were marked as they came out of the die cavity before the takeoff point, it was possible to measure core off-centering "along" and "across" the axis of die table movement by cutting the tablets along L, R, I, or O, respectively, as shown in Fig. 1. This is more adequately illustrated in Fig. 5, where the A portion shows the cutting of the tablet "across" die table movement and the B, "along" the axis of die table movement. Tablets so cut were photographed under fivefold magnification as shown in Fig. 6 and measurements for core centration were made from these photographs.

Off-centering of the core in the vertical plane can take place either by (*a*) tilting or (*b*) displacement of the center of the core up or down along the center axis of the tablet as illustrated by portions B and C, respectively, of Fig. 7. If the distances *AB* and *CD* as shown in portion A of Fig. 7 were measured, incorrect data would result. This is due to the fact that if the core shifted to the left or right of the center axis it would show up by this method of measurement. Since this dislocation is representative of off-centering in the horizontal plane, it was measured earlier. However, by measuring the dislocation along *HG* and *EF* a true indication could be obtained of core off-centering in the vertical plane, thus eliminating the interference in measurement due to horizontal dislocation. Accordingly, this technique of measuring was used to determine tilting, as illustrated by portion *B* of Fig. 7 and up and down displacement, as shown by portion C of Fig. 7.

By measuring the distances L and L' and R and R', O and O', and I and I', as illustrated in portion B of Fig. 7, it is possible to determine tilt "along axis" (T), tilt "across axis" (T_l), maximum tilt (T_m), displacement "along axis" (D), and displacement "across axis" (D_l). The equations used to determine T and T_l are as follows

$$T = \frac{(R - L) + (L' - R')}{2}$$

$$T_l = \frac{(O - I) + (I' - O')}{2}$$

T and T_l could be determined from $R - L$ and $O - I$ alone, but by using the means of $(R - L)$ and $(L' - R')$ or $(O - I)$ and $(I' - O')$ more precise data are obtained by minimizing the error of measurements.

Now if: $T = 0$, no tilt takes place along axis of turntable movement; $T < 0$, the left edge of the core is tilted up; $T > 0$, the right edge of the core is tilted up; $T_l = 0$, no tilt takes place across axis of turntable movement; $T_l < 0$, the inside edge of

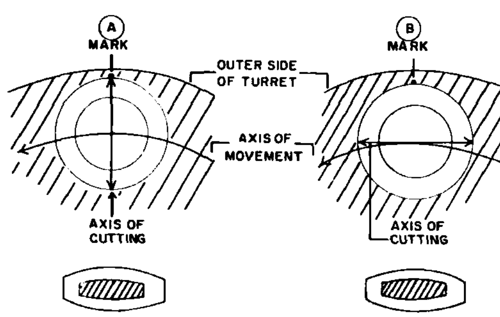


Fig. 5.—A schematic diagram showing the cutting of tablets vertically along and across the axis of die table movement.

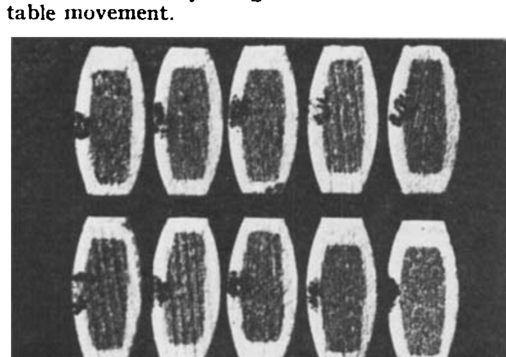


Fig. 6.—A five-fold magnification photograph of tablets cut along vertical plane.

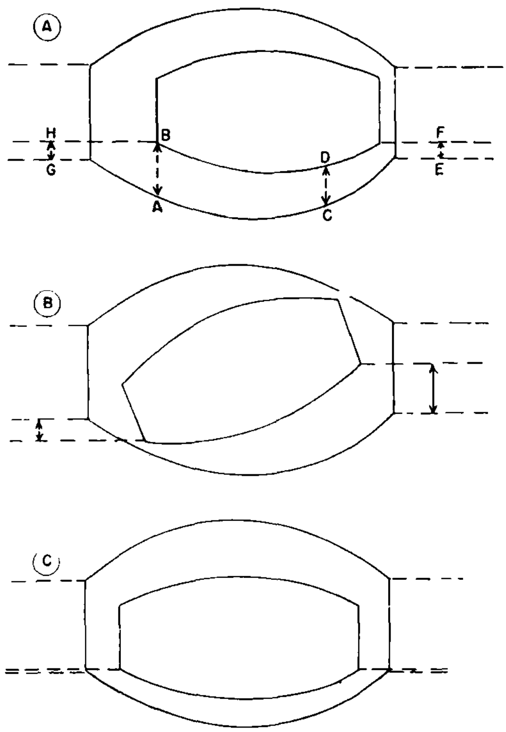


Fig. 7.—A graphical illustration indicating off-centering of core in the vertical plane of the tablet. (A) = horizontal dislocation, B = tilting, C = displacement along vertical plane. Lines AB and CD indicate improper distances to measure, while HG and EF are the correct distances to determine tilt and displacement in vertical plane.

core is tilted up; and if $T_l > 0$, the outside edge of core is tilted up.

To assist in the derivation of Tm, a spatial view of a tilted core is presented in Fig. 8. The solid line shows the tilted core and the dotted line its projection in space. The angle α is between the tilted core and its projection and opposite to T, T_l, and Tm. The triangles are right triangles. The letter ρ is equal to the radius of the core. From this figure it would appear that the values of ρ are different along the various radii, but this is only an optical illusion.

Side views of the right triangles in the spatial diagram give the projection shown by portion A of Fig. 9, and an imaginary top surface view of the tilted core is shown in portion B of Fig. 9.

From the right triangles in portion A of Fig. 9, the following equations can be derived

$$\frac{Tm}{Km} = \frac{T}{K} = \frac{T_l}{K_l} \qquad \text{(Eq. 1)}$$

or

$$TmK = TKm \qquad TmK_l = T_lKm \qquad \text{(Eq. 2)}$$

In portion B of Fig. 9, β is the same angle for both triangles because they are right triangles and the line across axis is perpendicular to the line along axis. Therefore

$$Km = \rho \qquad \text{(Eq. 3)}$$

$$K_l = \rho \cdot \cos \beta \qquad \text{(Eq. 4)}$$

$$K = \rho \cdot \sin \beta \qquad \text{(Eq. 5)}$$

By substituting Eqs. 3, 4, and 5 into Eqs. 1 and 2, we obtain the derivation for the formula to be used to measure maximum tilt (Tm)

$$Tm\ \rho \sin \beta = T\ \rho \qquad Tm\ \rho \cos \beta = T_l\ \rho$$
$$T = Tm \sin \beta \qquad T_l = Tm \cos \beta$$
$$T^2 = Tm^2 \sin^2 \beta \qquad T_l^2 = Tm^2 \cos^2 \beta$$
$$T^2 + T_l^2 = T^2m (\sin^2 \beta + \cos^2 \beta)$$

since $\sin^2 \beta + \cos^2 \beta = 1$, then $T^2 + T_l^2 = Tm^2$ and $Tm = \sqrt{T^2 + T_l^2}$.

In the case where $T \neq 0$ and $T_l \pm 0$, Tm should be determined from the above formula. Such a situation means that the axis of maximum tilt is located somewhere between the "along axis" and the "across axis" of tablet. If the axis of maximum tilt lies on the "along axis" of tablet, then $T = 0$ and $Tm = T_l$. In the case where the maximum tilt lies on the "across axis" of tablet, $T_l = O$ and $Tm = T$.

The equations used to determine core displacement "along axis," D, and core displacement "across axis," D_l, are

$$D = \frac{(R + L) - (R' + L')}{4}$$

$$D_l = \frac{(O + I) - (O' + I')}{4}$$

These equations were derived in the following manner: If the core is displaced by the amount D upward

R is increased by D
L is increased by D
R' is decreased by D
L' is decreased by D

$$(R + L) - (R' + L') = 4D$$

Therefore

$$D = \frac{(R + L) - (R' + L')}{4}$$

The derivation for D_l is analogous to D. Now if: $D = 0$, no displacement takes place along the axis; $D < 0$, downward displacement takes place along the axis; $D > 0$, upward displacement takes place along the axis; $D_l = 0$, no displacement takes place across the axis; $D_l < 0$, downward displacement takes place across the axis; and if $D_l > 0$, upward displacement takes place across the axis.

In measuring core tilting and displacement in the

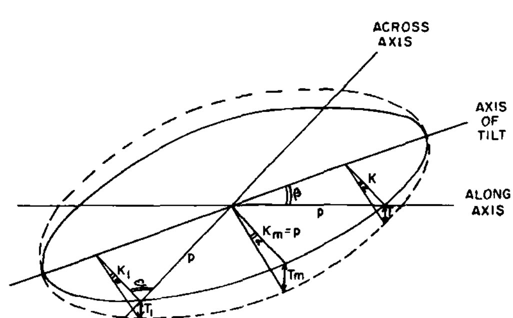


Fig. 8.—A spatial view of tilted core.

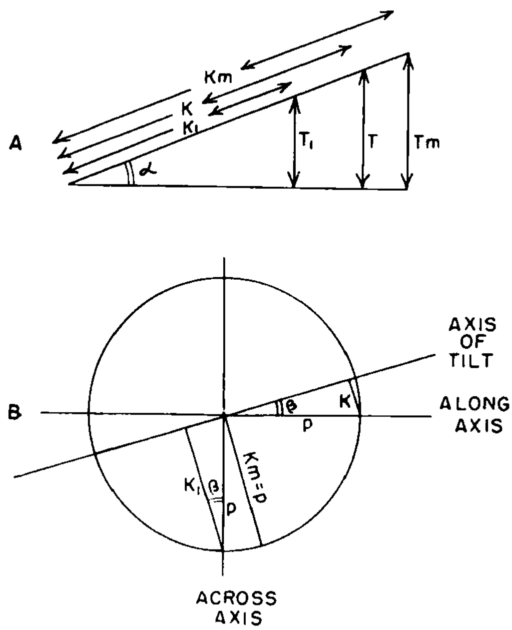


Fig. 9.—Side views of triangles of the spatial diagram A and top view of core shown in spatial diagram B.

vertical plane, measurements for R, R', L, L', O, O', and I, I' were taken for each of the four coating granulations on 70 tablets (10 tablets per each of seven time intervals) for both the Manesty and Kilian machines.

Core Expansion.—Since experience has indicated that the core tablet undergoes expansion in the lateral direction when compressed a second time in the bed of coating granulation, measurements were made of core diameter for tablets produced with the four coating granulations on each machine. The center of the core was obtained in the same manner as was described for determining the center of the tablet. Once the center of the core was obtained, the diameter measurements were readily made. These were done on the fivefold magnification photographs of the horizontally cut tablets.

Statistical Analysis of Data.—The Manesty and Kilian machines were analyzed separately and then compared for each of the following nine parameters for core centration: *1.* dislocation along axis (X), *2.* dislocation across axis (Y), *3.* maximum dislocation (Z), *4.* tilt along axis (T), *5.* tilt across axis (T_l), *6.* maximum tilt (Tm), *7.* displacement along axis (D), *8.* displacement across axis (D_l); and *9.* core expansion (E).

The purpose of this analysis was to determine whether the dislocations, tilts, and displacements were significant (comparison with the theoretical value of zero) and if they differed significantly among themselves. Additional evaluations were performed to determine if there were significant differences between the "along axis" and "across axis" dislocations and tilts.

As methods of analysis, the F test and analysis of variance were employed. In order to specify which of the means are significantly different from one another and from the theoretical zero value, a test suggested by Professor A. P. Dempster of Harvard University (11) was employed. This test is an alternative to the D. B. Duncan multiple range test (12) and is based on tables of F distribution and on the so-called 95% simultaneous confidence statement about true (unknown) means.

For the evaluation of maximum dislocation (Z) and maximum tilt (Tm) it was necessary to estimate and subtract the variance due to bias of measurement because the formulas for Z and Tm contain squared units of measurement. This bias correction was done for each granulation on each of the parameters Tm and Z.

RESULTS AND DISCUSSION

Horizontal Centration

The results obtained from the analysis of core dislocation of tablets prepared on the Manesty and Kilian machines are summarized in Tables III and

Table III.—Measurements of Core Dislocations on Horizontal Cuts for Tablets Prepared on the Manesty Machine[a]

	Dislocation Along Axis (X)				
Granulation fraction	50	35	8	100	
Means of X	0.0685	0.0814	0.1338	0.2478	
Level of significance with theoretical 0	5%	1%	0.1%	0.1%	
Comparison between granulations	———	———	———	———	1% level
	Dislocation Across Axis (Y)				
Granulation fraction	8	35	50	100	
Means of Y	−0.1505	−0.1564	−0.1957	−0.2441	
Level of significance with theoretical 0	0.1%	0.1%	0.1%	0.1%	
Comparison between granulations	———	———	———	———	5% level
	Maximum Dislocation (Z)				
Granulation fraction	35	50	8	100	
Means of Z	0.2283	0.2502	0.2542	0.4122	
Level of significance with theoretical 0	Not	1%	1%	0.1%	
Comparison between granulations	———	———	———	———	0.1% level
	Difference Between Absolute Values of Y and X				
Granulation fraction	100	8	35	50	
$\|Y\| - \|X\|$	0.0036	0.0167	0.0750	0.1272	
Level of significant difference	Not	Not	Not	0.1%	

[a] Any two means not underscored by the same line are significantly different while those underscored by the same line do not differ significantly.

TABLE IV.—MEASUREMENTS OF CORE DISLOCATIONS ON HORIZONTAL CUTS FOR TABLETS PREPARED ON THE KILIAN MACHINE[a]

	Dislocation Along Axis (X)				
Granulation fraction	8	100	35	50	
Means of X	−0.0994	−0.1078	−0.1550	−0.3071	
Level of significance with theoretical 0	Not	Not	1%	0.1%	
Comparison between granulations					5% level
	Dislocation Across Axis (Y)				
Granulation fraction	8	100	35	50	
Means of Y	0.0080	0.0192	−0.2314	−0.2757	
Level of significance with theoretical 0	Not	Not	0.1%	0.1%	
Comparison between granulations					1% level
	Maximum Dislocation (Z)				
Granulation fraction	100	8	35	50	
Means of Z	0.1676	0.3795	0.4890	0.5255	
Level of significance with theoretical 0	Not	0.1%	0.1%	0.1%	
Comparison between granulations					0.1% level 1% level
	Difference Between Absolute Values of Y and X				
Granulation fraction	8	50	35	100	
$\|Y\| - \|X\|$	0.0039	0.0314	0.0735	0.0871	
Level of significant difference	Not	Not	Not	Not	

[a] Any two means not underscored by the same line are significantly different while those underscored by the same line do not differ significantly.

IV, respectively. The significant dislocations shown in both tables are graphically illustrated in Fig. 10.

Manesty Machine.—The tablets prepared with all four different size distribution granulations show the core to be significantly dislocated toward the right ($+X$) and to the outside ($-Y$) of the compressed coated tablet. The tablets prepared with granulation fraction 100 exhibit cores that are significantly more dislocated than the cores in the tablets prepared from the other three granulation fractions, which do not differ in dislocation among themselves.

Kilian Machine.—For this machine only the tablets prepared with granulation fractions 35 and 50 show cores that are dislocated toward the left ($-X$) and to the outside ($-Y$) of the compressed coated tablets and these dislocations differ significantly from the tablets prepared with the other two granulation fractions.

The difference between the absolute mean values for "across axis" and "along axis" core dislocations

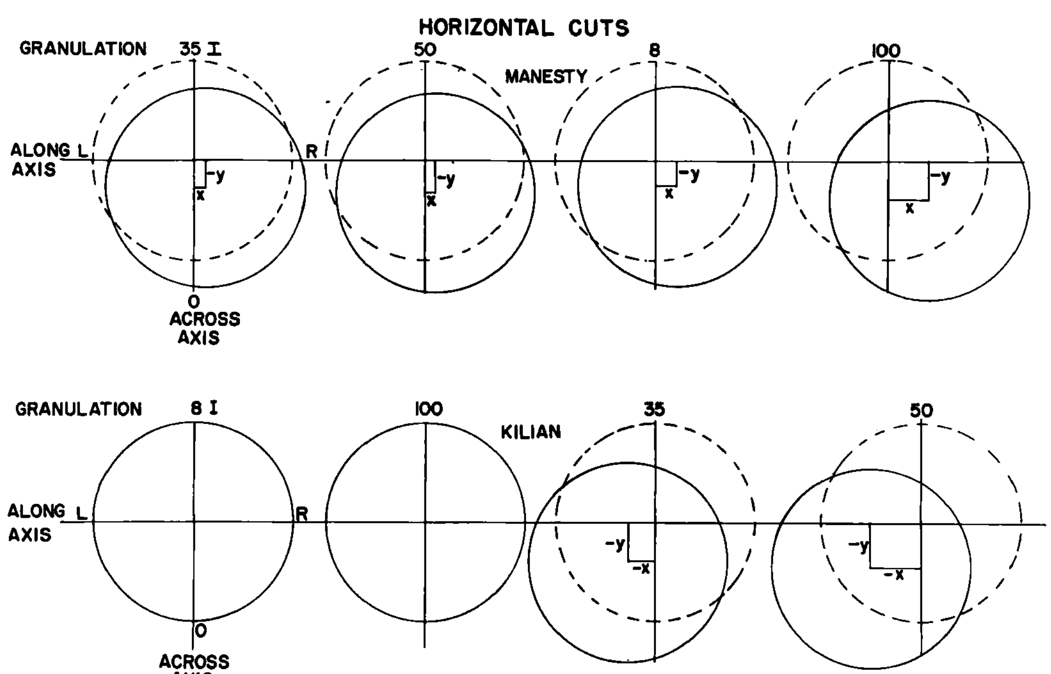


Fig. 10.—A graphic illustration of the influence of coating granulation size on core dislocation along the horizontal plane for tablets produced on the Manesty and Kilian machines. Only statistically significant dislocations are shown.

TABLE V.—CORE EXPANSION FOR MANESTY AND KILIAN MACHINES[a]

	Manesty				
Granulation fraction	100	50	35	8	
Means of expansion	7.44	7.62	7.73	7.78	
Comparison between granulations	———	———	———	———	
	———	———		———	1% level
	Kilian				
Granulation fraction	100	50	8	35	
Means of expansion	7.42	7.63	7.61	7.82	
Comparison between granulations	———	———	———	———	
	———	———	———	———	0.1% level

[a] Any two means not underscored by the same line are significantly different while those underscored by the same line do not differ significantly.

was proved significant only for the tablets prepared with granulation fraction 50 for the Manesty machine. This would mean that the cores are more dislocated toward the outside than toward the right position in the compressed coated tablet.

In analyzing the core dislocations of tablets prepared on the Manesty and Kilian machines, it was found that no conclusions could be drawn simultaneously for both machines. Consequently, the results for each machine must be reported separately.

Core Expansion

The results obtained for the Manesty and Kilian machines are presented in Table V. For both machines the core expansion in the tablets prepared with granulation fraction 100 is significantly smaller than that obtained with the other three granulation fractions.

Since the data for both machines, when analyzed simultaneously, showed significant interaction between machine and granulation fraction, the conclusions concerning core expansion for the granulation fractions must be drawn independently for each machine.

Vertical Centration

The data obtained from the analysis of tilt and displacement of core for the tablets prepared on the Manesty machine are summarized in Tables VI and VII and those for the Kilian machine in Tables VIII and IX. In Figs. 11 and 12 the tilt and displacement data found to be statistically significant are graphically presented for the Manesty and Kilian machines, respectively.

Manesty Machine.—From the mean values of tilt in the three directions, it seems that the tablets prepared with coating granulation fraction 8 show a consistent tendency for least tilting of core. On the other hand, the mean values of core displacement "along" and "across axis" show that the tablets prepared with granulation fraction 100 give the least displacement "along axis" and those prepared with granulation fraction 35 give the least displacement "across axis." But in each case, granulation fraction 8 results in tablets having cores exhibiting the most significant displacement. Where the displacement is significant, it is always in the upward direction for both "along" and "across axis."

Kilian Machine.—It is apparent from the data that the tilting of core has the tendency to take place in the upward direction at the left side of the tablet for the "along axis" and in the upward direction at the inside of the tablet for the "across axis" cuts. From the mean values of tilt in the three directions it is evident that the tablets prepared with granulation fractions 8 and 100 show the least tilting of core. However, for core displacement, "along" and "across" die table movement, the mean values obtained indicate that the tablets

TABLE VI.—MEASUREMENT OF CORE TILT ON VERTICAL CUTS FOR TABLETS PRODUCED ON THE MANESTY MACHINE[a]

	Tilt Along Axis (T)				
Granulations	8	35	50	100	
Means of tilt	0.0207	0.0395	0.0750	0.1135	
Level of significance of tilt	Not	Not	Not	1%	
Comparison between granulations	———	———	———	———	Not signif.
	Tilt Across Axis (T_l)				
Granulations	8	35	50	100	
Means of tilt	−0.0001	0.0330	−0.0367	−0.1613	
Level of significance of tilt	Not	Not	Not	0.1%	
Comparison between granulations	———	———		———	1% level
	Maximum Tilt (T_m)				
Granulations	8	35	50	100	
Means of tilt	0.0718	0.0907	0.1157	0.2353	
Level of significance of tilt	Not	Not	Not	0.1%	
Comparison between granulations	———	———		———	5% level
	Difference Between Tilt Across Axis and Along Axis				
Granulations	50	35	8	100	
$\|T_l\| - \|T\|$	−0.0692	−0.0123	0.0011	0.0563	
Level of significance	Not	Not	Not	Not	

[a] Any two means not underscored by the same line are significantly different while those underscored by the same line do not differ significantly.

TABLE VII.—MEASUREMENT OF CORE DISPLACEMENT ON VERTICAL CUTS FOR TABLETS PRODUCED ON THE MANESTY MACHINE[a]

	Displacement Along Axis (D)				
Granulations	35	100	50	8	
Means of displacement	−0.0620	0.0586	0.0717	0.1417	
Level of significance of displacement	Not	Not	Not	1%	
Comparison between granulations	———			———	1% level
	Displacement Across Axis (D_t)				
Granulations	35	100	50	8	
Means of displacement	0.0014	0.0775	0.1113	0.2480	
Level of significance of displacement	Not	1%	0.1%	0.1%	
Comparison between granulations	———	———		———	1% level
	———		———		5% level

[a] Any two means not underscored by the same line are significantly different while those underscored by the same line do not differ significantly.

TABLE VIII.—MEASUREMENT OF CORE TILT ON VERTICAL CUTS FOR TABLETS PRODUCED ON THE KILIAN MACHINE[a]

	Tilt Along Axis (T)				
Granulations	100	8	35	50	
Means of tilt	−0.0042	−0.0282	−0.0317	−0.0450	
Level of significance of tilt	Not	Not	Not	Not	
Comparison between granulations	———	———	———	———	Not signif.
	Tilt Across Axis (T_t)				
Granulations	100	8	35	50	
Means of tilt	0.0326	−0.0015	−0.0564	−0.0842	
Level of significance of tilt	Not	Not	5%	0.1%	
Comparison between granulations	———		———	———	1% level
		———		———	5% level
	Maximum Tilt (Tm)				
Granulations	100	8	50	35	
Means of tilt	0	0	0.0890	0.1029	
Level of significance of tilt	Not	Not	Not	5%	
Comparison between granulations	———	———	———	———	Not signif.
	Difference Between Tilt Across Axis and Along Axis				
Granulations	100	8	35	50	
$\|T_t\| - \|T\|$	0.0155	0.0093	0.0047	0.0412	
Level of significance	Not	Not	Not	Not	

[a] Any two means not underscored by the same line are significantly different while those underscored by the same line do not differ significantly.

TABLE IX.—MEASUREMENT OF CORE DISPLACEMENT ON VERTICAL CUTS FOR TABLETS PRODUCED ON THE KILIAN MACHINE[a]

	Displacement Along Axis (D)				
Granulations	35	50	100	8	
Means of displacement	−0.0400	−0.0771	−0.0800	−0.1082	
Level of significance of displacement	Not	0.1%	0.1%	0.1%	
Comparison between granulations	———			———	5% level
	Displacement Across Axis (D_t)				
Granulations	100	35	8	50	
Means of displacement	0.1121	0.0617	0.0318	−0.0957	
Level of significance of displacement	0.1%	5%	Not	0.1%	
Comparison between granulations	———	———	———	———	0.1% level
	———		———		5% level

[a] Any two means not underscored by the same line are significantly different while those underscored by the same line do not differ significantly.

prepared with granulation fraction 35 exhibit the best overall results.

A statistical evaluation of the difference between the absolute mean values of core tilt "across" and "along axis" of die table movement for each tablet press indicated no significant difference of tilt for "along" or "across axis."

Since the results obtained for tilt and displacement of core in the tablets produced on the Manesty and Kilian were so different, it was unreasonable to attempt a pooled analysis of the data for both machines.

GENERAL DISCUSSION

From the data presented under horizontal and

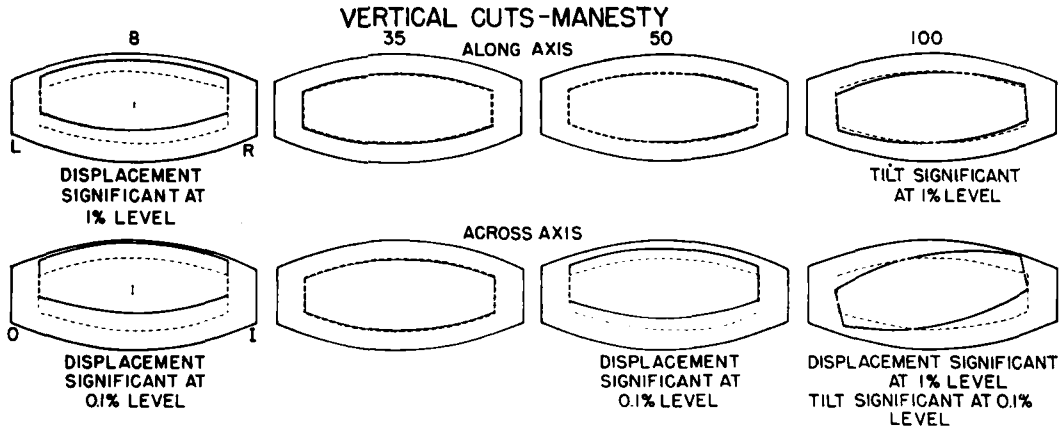


Fig. 11.—A graphic illustration indicating the influence of coating granulation size on core tilt and displacement "along" and "across" axis of die table movement for vertical cuts of tablets produced on the Manesty machine.

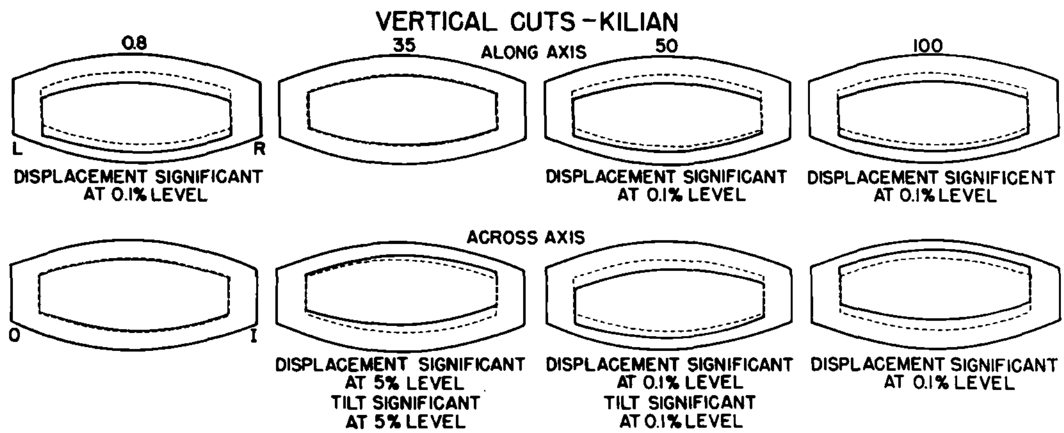


Fig. 12.—A graphic illustration indicating the influence of coating granulation size on core tilt and displacement "along" and "across" axis of die table movements for vertical cuts of tablets produced on the Kilian machine.

vertical core off-centering, it became evident that the cause for core dislocation in the horizontal cuts and core tilting and displacement in the vertical cuts could be explained by certain basic laws of physics. It seems that there are two major forces which are responsible for core dislocation, and these will be discussed in the subsequent paragraphs of this section.

As a result of the die table rotation, two forces are exerted on the tablets, one being centrifugal and the other tangential. Since the density of the core is greater than that of the coating granulation in the die, these two forces will tend to displace the core in the coating bed before the final compression step in the formation of the compressed coated tablets. The centrifugal force will tend to displace the core in the radial direction while the other force, which is tangential to the movement of the die table, will cause core displacement in the direction opposite to the rotation of die table. This effect is graphically illustrated in Fig. 13. The tangential force is dependent upon the direction of die table movement, while the centrifugal force is in the same direction for both machines. This effect is illustrated in Fig. 10, where the core is dislocated to the right and outside for the Manesty and toward the left and outside for the Kilian machine.

In the vertical plane, "across the axis" of die table movement, centrifugal force is active in causing the core to tilt toward the more stable vertical position. Because of the constraining properties of the coating granulation bed on the core, the only possible movement toward the vertical position is the lifting of the inside edge of the core in the upward direction. The core is also displaced in the upward direction along the vertical axis of the tablet. This is illustrated in Fig. 11.

For the vertical "along axis" core centration measurements, the tablets produced on the Manesty machine showed lifting of the right edge of the core and for those produced on the Kilian machine lifting of the left edge. This tilting of the core can be caused if the bottom bed of coating granulation onto which the core is deposited lies at a slant, instead of in a flat position in the die. The rotational movement of the die table would be expected to cause the bottom bed of coating granulation in the die to accumulate to a larger amount at the rear edge of the die wall which is on the right for the Manesty and on the left for the Kilian. This larger amount of coating granulation at edge of the die would cause the coating bed to take on a tilted position in the die cavity. Subsequently, when the core tablet is deposited, it will take the tilted position of the coating bed. In the Kilian machine, where the core is imbedded into the coating bed by the free fall of the upper punch before the upper layer of coating granulation is added, the "along axis" tilt would be expected to be less due to the overall flattening out of the coating bed by the free fall of the upper punch. This was found to be the case and can be seen from the drawings in Figs. 11 and 12.

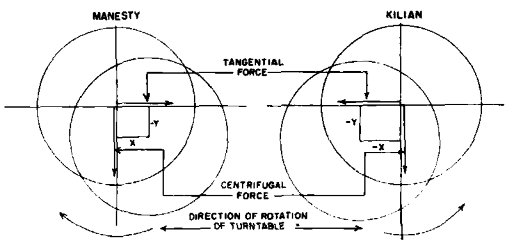


Fig. 13.—A graphic illustration showing the direction of tangential and centrifugal force acting to displace core along horizontal plane for Manesty and Kilian machines.

It is apparent from the vertical cut data in Table VII that the displacement of core along the vertical axis takes place in the upward direction for tablets prepared on the Manesty machine. In this tablet press, the core is transferred to the bottom bed of coating granulation by a transfer arm and deposited into the coating bed by a transfer pin, causing the tablet to fall into the bed center. Coating granulation is then added and the upper punch comes down to compress the tablet. Here it would be expected that the displacement of the core would be in the upward direction along the vertical plane.

For the tablets produced on the Kilian machine, the core shows a downward displacement when measured "along axis" and an upward displacement when measured "across axis" as shown by the data in Table IX. The vertical core displacement in the Kilian machine may be caused by the free fall action of the upper punch to imbed the core in the bottom bed of coating granulation before the upper layer of coating granulation is added. Since there is core displacement in both directions for this machine, the responsible factors are rather complex and will not be considered at this time.

As is apparent by comparing the data for the horizontal cuts, Tables III and IV with those of the vertical cuts, Tables VI to IX, the effect of the centrifugal and tangential forces are more pronounced on the dislocations of core on the horizontal cuts than the tilts of core on the vertical cuts.

From the data obtained for core dislocation along horizontal cuts and tilt and displacement along vertical cuts, there seems to be a definite relationship between degree of core off-centering and the size distribution of coating granulation. In addition, the machine design (Kilian and Manesty) appears to influence this effect.

On the basis of all the data for the Kilian and Manesty machines it is evident that coating granulations 100 and 50 yield tablets exhibiting the poorest core centration for the Manesty and Kilian machines, respectively. On the other hand, it appears that optimal core centration is obtained with coating granulation fraction 35 for the Manesty machine and with coating granulation fractions 8 or 100 for the Kilian machine. This relationship also holds when only the data from horizontal cuts are compared. However, a comparison of the data from the vertical cuts shows that for both the Manesty and Kilian machines, coating granulation fraction 35 gives the smallest displacement of core and coating granulation fraction 8 gives the least tilt of core. It becomes evident from these off-centering data that the dislocations of core from the horizontally determined cuts exert the predominant effect on the overall centration of core in tablet.

From the core expansion data reported in Table V, it is evident that the core expansion is smallest when coating granulation 100 is used. This has been found to hold for tablets produced on both the Manesty and Kilian machines. Since the sieve analysis on granulation 100 has shown it to have the smallest size distribution granules of the four coating granulations studied, it would be expected to cause the least core expansion. This may be explained on the basis that the smaller the particles, the less void space there is between particles and consequently, less space for the core to expand during the final compression step in the bed of coating granulation.

SUMMARY

The information obtained from this investigation may be summarized as follows:

1. A procedure has been developed for the determination of core dislocation in compressed coated tablets.

2. These factors appear to be responsible for core dislocation: (*a*) Two major forces which are acting tangentially and radially. (*b*) The bottom bed of coating granulation taking on a slanted shape due to die table rotation.

3. The data obtained in this study show that the core dislocation measured along the horizontal cuts have a more pronounced effect on the overall off-centering than the core tilt measured along the vertical cuts.

4. The results obtained indicate that the coating granulation size distribution influences core centration. In addition, this influence is not the same for the Manesty and Kilian machines.

5. Core expansion was observed to take place for each coating granulation, the least being with the coating granulation containing the smallest granules.

6. Using this procedure for determining core dislocation it should be readily possible to determine the optimal granule size distribution for a

particular coating granulation required to give optimal core centration.

7. Optimal core centration is desired for several reasons, the major ones being (*a*) Uniformity of dose, *i.e.*, if the tablets were to be broken along a center bisection, unequal doses would be obtained if the core is not in the center of the tablet. (*b*) Protective action of coating, *i.e.*, if the coating is used to improve the stability of the core ingredients, conceal the bitter taste of medicaments used in the core, and the like, the coating must completely cover the core tablet, otherwise the effectiveness of the coating is reduced. (*c*) Physical appearance, *i.e.*, if the core was to protrude out of the coating, either due to tilting or displacement in the vertical plane or horizontal dislocation, it would give an unsatisfactory aesthetic appearance.

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Study of the Thermistor Bridge for the Measurement of Colligative Properties

By FRANK M. GOYAN and RICHARD D. JOHNSON

Further refinement of the apparatus described by Goyan and Reck has been studied, using thermistors. One variation described involves the use of intermittent power with simultaneous recording. Another variation treats the problem of using relatively high battery voltages in order to increase the sensitivity of the bridge without the use of amplifiers. The paper discusses the determination of molecular weights, as well as osmometry and isotonicity measurements. Results indicate that significant measurements can be made without minimizing the heating produced by the bridge current.

THERMISTORS may be used as resistance thermometers with high negative temperature coefficients. Because of their small size and low cost as compared to platinum resistance thermometers and their high coefficient; they seem to be ideally suited to the determination of temperature changes associated with freezing-point lowering and boiling-point elevation. One of the authors (1) has described an isotonicity meter based upon freezing-point measurements which includes a single thermistor in a Wheatstone bridge. The off-balance condition of the bridge is read on a vacuum-tube voltmeter. Ballard and Goyan (2) have shown that isotonicity in terms of per cent sodium chloride is a linear function of the usual colligative properties within the range of concentration and accuracy normally required.

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It is quite proper to generalize that any osmometer, within the special limitations of each instrument, measures some approximately linear function of the colligative properties of solutions. The Hill-Baldes thermoelectric osmometer is no exception. In its original form it consisted of a thermocouple arranged in a constant temperature humidified air chamber (3). By placing a drop of solvent on one junction of the thermocouple and a drop of solution on the other, a temperature increase of the drop of solution relative to the drop of solvent develops measurable thermal E.M.F. This temperature difference and the resulting E.M.F. is proportional to the isotonicity or osmolal concentration of the solution.

With the advent of thermistors, many investigators (4–6) have modernized the Hill-Baldes osmometer by placing two thermistors in the chamber and connecting them as two arms of a Wheatstone bridge. This change has the advantage that the electric circuits are easier to