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## 109. Yoshinobu Nakai and Yoshio Kubo*2 : Studies on Powdered Preparations. IV. Studies on Disintegration of Magnesium Oxide Granules and Tablets by Thermal Analysis.

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In the preceding work,[1] tablet disintegration process was examined with basic magnesium carbonate by thermal analysis. Change in surface area of tablet in disintegration was measured and fine processes of tablet disintegration was elucidated.

Granule disintegration was studied by Münzel, *et al*,[2,3] who measured the period required for dispersion or solution of granules in an Erlenmeyer flask containing 50 cc. of water and gave this as the disintegration time in their papers. However, the fine process of disintegration cannot be measured by this method.

In the present series of work, disintegration properties of magnesium oxide granules and tablets were studied in pH 4.2 buffer solution of 1*M* acetate. The effect of particle size, and quantities of binder and disintegrator on granule disintegration was examined and the results were compared with those of tablets. The effect of compressional force, binder, and disintegrator was also examined in tablet disintegration, and the relationship between thermoanalytical values and the one obtained by U.S.P. method is discussed in the present paper. A typical result on thermal analysis of tablet disintegration was given in the preceding paper,[1] in which the result of measurement was given as $t_2$ and $t_3$, where $t_2$ and $t_3$ represented the time when maximum surface area was reached and all particles dissolved in tablet disintegration. In addition to these characteristics, the disintegration properties of granules and tablets are discussed in this paper by the surface area enclosed by *S*–*t* curve and time axis on the graph as shown in Fig. 1.

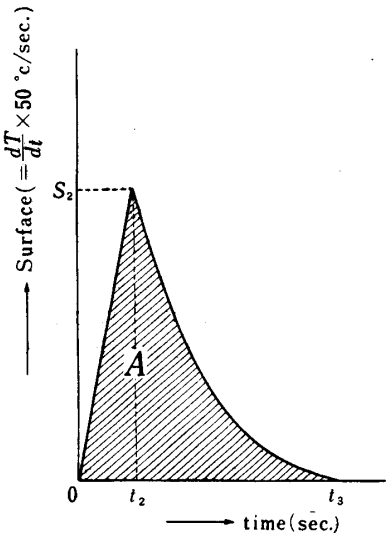


Fig. 1. Typical Result of Change in Surface Area of Tablet and Integral Surface Area, *A*, by Thermal Analysis

This area on the graph is designated as the integral surface area and symbolized by *A*, which is calculated by following scale of 5 seconds expressed by 1 mm. for time axis and 0.1°C/sec. expressed by 10 mm. for surface axis.[4]

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1) Part III. This Bulletin, **7**, 337(1959).
2) K. Münzel, K. Akay : Pharm. Acta Helv., **26**, 271(1951).
3) *Idem* : *Ibid.*, **29**, 277(1954).
4) Part II. This Bulletin, **7**, 331(1959).

## Experimental

**Material**—Magnesium Oxide : Reagent class MgO was dried over $P_2O_5$ at 120° for 72 hr. and kept over $CaCl_2$ in a desiccator. About 0.3 g. of powder passed through 100-mesh sieve was weighed and used for thermal analysis.
Granule : Five kinds of granules were prepared and components are shown in Table I.

Table I. Kinds of Granules and Tablets used

| Granule No. | Disintegrator[a] (%) | Binder[b] (%) | Tablet No. |
|---|---|---|---|
| 1 | 5 | 3 | 1 |
| 2 | 5 | 1.5 | 2 |
| 3 | 5 | 1 | 3 |
| 4 | 10 | 1 | 4 |
| 5 | 10 | 0 | 5 |
| Powder | ··Direct compression | | 0 |

*a*) Percentage of potato starch (J. P.) in granule.
*b*) Percentage of starch paste in granule on dried weight basis.

These granules were prepared as follows : Potato starch and starch paste were used as disintegrator and binder. Each component shown in Table I was weighed, mixed, and granulated with 18-mesh sieve, dried in warm air stream of 50° for 12 hr., and kept in a desiccator.
Tablets : Tablets were made from corresponding granules shown in Table I by an oil press machine at 0.5, 1.0, and 2.0 ton compressional force, using a flat-faced punch of 13 mm. in diameter.

**Apparatus**—Same as described in the preceding paper[1] except for following two points : (1) Two small windows were set at the opposite sides of a Dewar vessel and (2) a sinchronous motor was used and rotating speed of the stirrer was kept constant at 500 r.p.m. The thermal characteristics of this apparatus are shown in Table II.

Table II. Thermal Characteristics of Apparatus

Cooling constant : $4.2\times10^{-3}$°C/min.
Water equivalent : 128 cal. for 1 mole of acetate buffer, 131 cal. for distilled water.
Water equivalent of 100 cc. water at 30° : 99.6 cal.
Water equivalent of vehicle : 131−99.6=31.4 cal.
Water equivalent of 100 cc. acetate buffer : 128−31.4=96.6 cal.

**Procedure**—Same as described in the previous paper.[1]

## Results and Discussion

### Disintegration of Granules

Disintegration properties of granules are shown in Table III.

Table III. Effect of Binder and Disintegrator on Granule Disintegration
(Mesh size : 10/20)

| Granule No. | 1 | | 2 | | 3 | | 4 | | 5 | |
|---|---|---|---|---|---|---|---|---|---|---|
| Disintegrator (%) | 5 | | 5 | | 5 | | 10 | | 10 | |
| Binder (%) | 3 | | 1.5 | | 1 | | 1 | | 0 | |
| | $t_2$ | $t_3$ | $t_2$ | $t_3$ | $t_2$ | $t_3$ | $t_2$ | $t_3$ | $t_2$ | $t_3$ |
| Max. surface time and zero surface time (sec.) | 10 | 160 | 10 | 240 | 10 | 225 | 10 | 150 | 10 | 145 |
| | 10 | 150 | 10 | 220 | 10 | 270 | 10 | 160 | 10 | 145 |
| | 10 | 140 | 10 | 190 | 10 | 255 | 10 | 170 | 10 | 195 |
| | 10 | 170 | 10 | 250 | 10 | 305 | 10 | 150 | 10 | 155 |
| | 10 | 200 | 10 | 270 | 10 | 255 | 10 | 210 | 10 | 230 |
| | 10 | 180 | 10 | 200 | 10 | 230 | 10 | 170 | 10 | 155 |
| Mean | 10 | 170 | 10 | 230 | 10 | 260 | 10 | 170 | 10 | 170 |

Granule No. 4 disintegrated more rapidly than No. 3 as compared by the values of $t_3$, and it could be seen that No. 4 were dispersed in smaller particles. From this result the effect of disintegrator was recognized in the granules as in the tablet.

The effect of binder on disintegration was examined in the granule Nos. 1, 2, and 3. A negative correlation coefficient, $r=-0.81$, was found between $t_3$ and binder quantity. It seems that a greater amount of the binder results in smaller $t_3$ values and, therefore, granules containing larger quantity of binder disintegrate more easily into smaller particle. This result on the quantity of binder does not agree with the common belief that a binder inhibits disintegration. The starch paste was observed under microscope, since starch grains remaining in it may affect disintegration but no starch grain was observed. Therefore, there seems to have been no adverse effect of starch grains in this case. The same effect with binder quantity on disintegration was recognized later in tablets made of these granules, as shown in Table VII.

The effect of granule size is shown in Table IV in which granule No. 2 was divided into three groups by passing through Tailor sieves of 10/18, 18/20, and 20 mesh.

Table IV. Effect of Mesh Size of Granules on Granule Disintegration
(Granule used : Granule No. 2)

| Mesh size (passage) | 10/18 | | 18/20 | | 20 | |
|---|---|---|---|---|---|---|
| | $t_2$ | $t_3$ | $t_2$ | $t_3$ | $t_2$ | $t_3$ |
| Max. surface time and zero surface time (sec.) | 10 | 280 | 10 | 185 | 10 | 140 |
| | 10 | 290 | 10 | 190 | 10 | 130 |
| | 10 | 265 | 10 | 200 | 10 | 120 |
| | 10 | 325 | 10 | 220 | 10 | 135 |
| | 10 | 300 | 10 | 200 | 10 | 120 |

It can be seen that values of $t_3$ decrease for smaller granules having greater specific surface area and they disintegrate more rapidly in fine particles and dissolved in a short period. This result agrees with Münzel's experiment.[2)]

From above experiments with MgO granules, it can be seen that granules disintegrate and reach the maximum surface area rapidly. Particle size in disintegration is affected by the presence of a disintegrator and binder, and by particle size of a granule. Disintegration of granules is different from that of tablets in the fact that irregularity of $S$–$t$ curve can be scarcely seen in disintegration of granules.

The time at which the surface of disintegrating particle reaches the maximum is equal to constant value of 10 seconds, but more accurate measurement by thermister with automatic recorder is desirable, since the time lag of Beckmann thermometer cannot be neglect in rapid reaction. This point will be reported in the near future.

**Disintegration of Tablets**

Disintegration values by thermal analysis and U.S.P. method with tablet No. 1 compressed by 0.5, 1.0, or 2.0 tons are shown in Table V and Table VI, respectively.

It can be seen that in these tablets, higher compressional force results in larger values of $t_3$ and smaller values of $S_2$. This result of $t_3$ and $S_2$ seems to be reasonable, since larger value of $t_3$ means that correspondingly larger particle is present in the process of tablet disintegration and the maximum surface of dispersed particles would be decreased. The product of $S_2$ snd $t_3$ for each tablet is 377 in mean value. Variance, $\sigma$, and coefficient of variance, $CV$, are 78% and 21%. Effect of compressional force on $S_2 \times t_3$ was not significant since value of $F$ was 0.2 in Table V.

The relationship between $S_2$ and $t_3$ is shown in Fig. 2 and each point is almost parallel to the curve of $S_2 \times t_3 = 377$. This result shows that value of $S_2$ decreases with increase of $t_3$.

The integral surface area, $A$, was $24 \pm 0.38\ cm^2$ in mean and variance, and coefficient of variance, $CV$, was 1.6%. This result means that values of integral surface area are constant and independent of disintegration properties of these tablets. These interesting

Table V. Effect of Compressional Force on Disintegration Properties of Tablet No. 1

| Compressional force (ton) | Weight (mg.) | Apparent density | Max. surface time $t_2$ (sec.) | Zero surface time $t_3$ (sec.) | Max. surface* $S_2$/g. (°C/sec.) | Integral surface area $A$/g. (cm.²) | $S_2 \times t_3$ |
|---|---|---|---|---|---|---|---|
| 0.5 | 253 | 1.44 | 30 | 305 | 1.8 | 24.4 | 549 |
| | 313 | 1.45 | 50 | 255 | 1.0 | 23.8 | 255 |
| | 309 | 1.40 | 35 | 280 | 1.3 | 24.0 | 364 |
| | 301 | 1.52 | 45 | 325 | 1.1 | 23.5 | 358 |
| | 262 | 1.45 | 35 | 300 | 1.2 | 24.2 | 360 |
| | 269 | 1.49 | 35 | 325 | 1.5 | 23.7 | 488 |
| 1.0 | 310 | 1.66 | 40 | 375 | 1.3 | 23.8 | 488 |
| | 287 | 1.69 | 40 | 455 | 1.0 | 24.0 | 455 |
| | 309 | 1.70 | 45 | 345 | 1.0 | 23.8 | 345 |
| | 276 | 1.58 | 65 | 400 | 0.8 | 24.0 | 320 |
| | 301 | 1.77 | 95 | 340 | 0.9 | 24.3 | 306 |
| | 300 | 1.66 | 45 | 355 | 1.0 | 24.9 | 355 |
| | 268 | 1.63 | 170 | 470 | 0.6 | 24.0 | 282 |
| 2.0 | 282 | 1.85 | 100 | 670 | 0.6 | 24.6 | 402 |
| | 270 | 1.91 | 75 | 500 | 0.65 | 23.8 | 325 |
| | 285 | 1.87 | 220 | 1500 | 0.3 | 24.2 | 450 |
| | 275 | 1.87 | 110 | 950 | 0.3 | 23.5 | 285 |
| | 328 | 1.93 | 70 | 480 | 0.7 | 24.0 | 336 |
| | 335 | 1.97 | 205 | 450 | 0.7 | 24.0 | 315 |
| | 306 | 1.86 | 195 | 1340 | 0.4 | 24.9 | 536 |
| | 327 | 2.00 | 170 | 1140 | 0.3 | 24.4 | 342 |
| | | | | | Mean | 24.0 | 377 |

* Surface area is represented by $dT/dt$ and each value of $S_2$ was calculated by $dT/dt \times 50$ (°C/sec.).

Table VI. Effect of Compressional Force on Tablet Disintegration Time by U. S. P. Method
(Tablet used : Tablet No. 1)

| Compressional force (ton) | Weight (mg.) | Apparent density | Disintegration time (sec.) |
|---|---|---|---|
| 0.5 | 299 | 1.47 | 135 |
| | 273 | 1.51 | 108 |
| | 293 | 1.48 | 114 |
| 1.0 | 293 | 1.73 | 325 |
| | 301 | 1.72 | 330 |
| | 276 | 1.68 | 305 |
| 2.0 | 315 | 1.86 | 1643 |
| | 246 | 1.89 | 1600 |
| | 312 | 1.97 | 2083 |
| | 305 | 1.90 | 1030 |

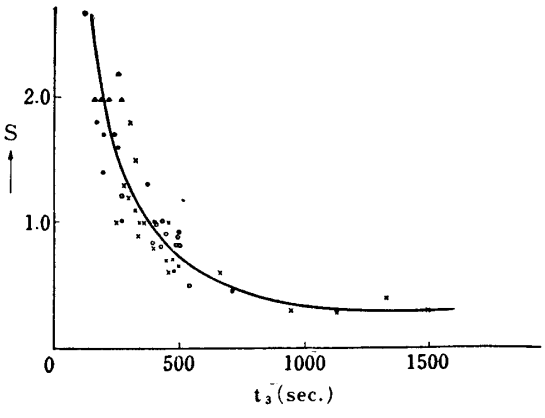


Fig. 2. Relationship between $t_3$ and $S$
Solid line : $S \times t_3 = 377$
Tablet
• : No. 0
× : No. 1
○ : No. 2
▲ : No. 3

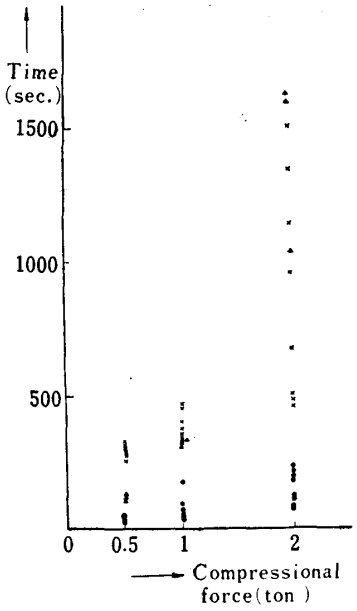


Fig. 3. Effect of Compressional Force on Disintegration Time by Thermal Analysis and U.S.P. Method

×: $t_3$
•: $t_2$
▲: U.S.P. method

phenomena are now being examined. The relationship between compressional force and each value of $t_2$, $t_3$, and U.S.P. method is shown in Fig. 3.

In Fig. 3, it can be seen that values and deviations for $t_3$ and U.S.P. method are markedly increased by larger compressional force, and relationship between compressional force and logarithmic values of $t_3$ and U.S.P. method is linear as shown in Fig. 4.

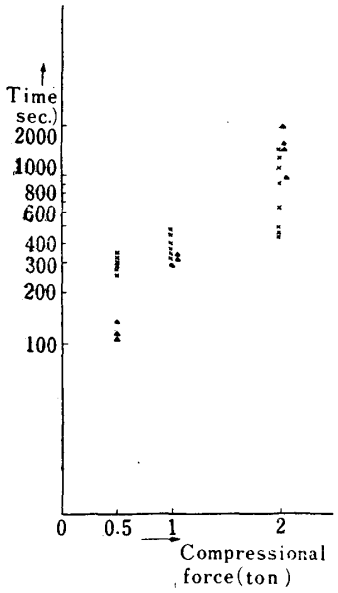


Fig. 4. Relation between Compressional Force and log Time of $t_3$ and U.S.P. Method

×: $t_3$
▲: U.S.P. method

These results are the same as those obtained with $MgCO_3$ tablets reported in the preceding paper.[1] In contrast to these results, values of $t_2$ increased slowly and linearly with larger compressional forces. Taking granule as tablet of zero compressional force, regression coefficient between $t_2$ and compressional force, $P$, was calculated for granules in Table III and tablets in Table V. The values calculated were $t_2=84P+7.6$ and $r=0.85$. This equation is of high significance since $F_0$ was 139 by the test of linearity with this equation. Expressing the regression equation in population for these samples by $\mu_{t,p}=\alpha+\beta(P-P)$, the confidence intervals of $\alpha$ and $\beta$ were calculated as $27<\alpha<60$ and $57<\beta<112$. These results indicated that granules may be considered as

tablets of zero compressional force, and $t_2$ values increased linearly from granule to tablet of high compressional force.

The relationship between apparent density of tablets, and values for $t_2$ and $t_3$ time are shown in Fig. 5.

Values for $t_3$ are markedly increased with larger apparent density and deviation

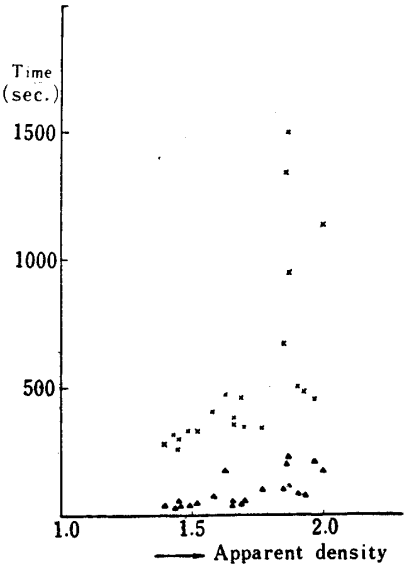


Fig. 5. Relation between Apparent Density of Tablet and $t_2$, $t_3$

×: $t_3$
▲: $t_2$

Table VII. Effect of Binder and Disintegrator on Tablet Disintegration
(Compressional force : 0.5 ton)

| Tablet No. | Disintegrator (%) | Binder (%) | $t_2$ (sec.) | $t_3$ (sec.) |
|---|---|---|---|---|
| 0 | 3 | 0 | 20 | 125 |
| | 3 | 0 | 25 | 185 |
| | 3 | 0 | 20 | 190 |
| | 3 | 0 | 20 | 135 |
| | 3 | 0 | 40 | 235 |
| | 3 | 0 | 25 | 260 |
| 1 | 5 | 3 | 30 | 305 |
| | 5 | 3 | 50 | 255 |
| | 5 | 3 | 35 | 280 |
| | 5 | 3 | 45 | 325 |
| | 5 | 3 | 35 | 300 |
| | 5 | 3 | 35 | 325 |
| 2 | 5 | 1.5 | 55 | 540 |
| | 5 | 1.5 | 40 | 435 |
| | 5 | 1.5 | 45 | 540 |
| | 5 | 1.5 | 45 | 400 |
| | 5 | 1.5 | 45 | 475 |
| 3 | 5 | 1 | 40 | 720 |
| | 5 | 1 | 40 | 555 |
| | 5 | 1 | 70 | 515 |
| | 5 | 1 | 50 | 435 |
| 4 | 10 | 1 | 20 | 250 |
| | 10 | 1 | 25 | 200 |
| | 10 | 1 | 25 | 200 |
| | 10 | 1 | 25 | 260 |
| 5 | 10 | 0 | 25 | 175 |
| | 10 | 0 | 20 | 170 |
| | 10 | 0 | 25 | 220 |
| | 10 | 0 | 25 | 180 |

also increases but linear relationship with smaller deviation is shown for relationship between $t_2$ and apparent tablet density. It seems that a larger compressional force results in correspondingly larger friction between particles or between particle and wall in a compressional process and, therefore, irregular distribution of compressional forces may arise in tablets. Due to this irregularity of compressional force, various sizes of particles were produced in the process of tablet disintegration and deviations of $t_3$ and U.S.P. values were observed. It may be said from these results that the localized properties in tablet, the deviation of binding force between particles in tablet, may be given by $t_3$ and U.S.P. values. However, values of $t_2$ may be scarecely affected by the irregularity of compressional force, because the value of $t_2$ depends upon the average binding force between particles in tablet and the deviation of binding force only affects the surface area, $S_2$, at the time $t_2$. Therefore, the values of $t_2$ may depend upon the difference between destruction and binding force, and it seems that $t_2$ is rational value in examining tablet disintegration.

Disintegration time of tablets compressed at 0.5 ton is shown as Table Ⅶ.

The general conclusion that a disintegration is disturbed by a larger quantity of binder is not consistent with the result on comparison of tablet Nos. 1, 2, and 3 for the effect of binder on disintegration. However, values of $t_2$ and $t_3$ for tablet No. 0 are smaller than those for tablet Nos. 1, 2, and 3, and disturbing effect of binder on a tablet disintegration can be observed. Disintegration time for tablets Nos. 4 and 5 was smaller than that of tablets Nos. 1, 2, and 3, and no difference was recognized between No. 4 and No. 5. It is seen that 10% of a disintegrator is enough to disintegrate a tablet.

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## Summary

Disintegration of magnesium oxide granules and tablets was studied by thermal analysis.

Disintegration was affected by the quantity of binder and disintegrator, and by granule size. The time at which surface area of disintegrated granule reached the maximum was constant, independent of size and quantity of binder and disintegrator. The effect of compressional force on tablet disintegration was examined and the values and deviations of U.S.P. method and the time, $t_3$, at which all tablet dissolves increased exponentially with larger compressional force. In contrast with this, values of $t_2$ increased linearly with larger compressional force and deviation was smaller than that of U.S.P. method and $t_3$. The values of $t_2$ seemed of value in examining disintegration and it was estimated that U.S.P. and $t_3$ represent localized properties of tablet in disintegration.

Integral surface area and the product of maximum surface area and $t_3$ were both independent of compressional force and the former gave smaller deviation than the latter. It could be seen from this result that when values of $t_3$ increased, the maximum surface area decreased conversely.

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