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124. **Yoshinobu Nakai**: Studies on Powdered Preparations. VI.[*1] Theoretical Consideration of Tablet Disintegration Process by Thermal Analysis.

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Previous papers[1~4] described the application of thermal analysis for the measurement of tablet disintegration and experimental results were reported. The change in surface area of dispersed particles was measured during the process of tablet disintegration and the time t_1 at which the surface area begins to increase, t_2 at which the surface area reaches the maximum, S_2, and t_3 at which all particles dissolve, were used as the thermoanalytical characteristic values in the processes of disintegration. Apparent particle size distribution was estimated by which the tablet disintegration was evaluated as a powder. From these results, the whole process of disintegration could be continually investigated.

During a series of this work, interesting results were found in the relationship between the compressional force of a tablet and thermoanalytical values for magesium oxide tablets. The integral surface area, A, was almost constant and $S_2 \times t_3$ was also independent of compressional force, as shown in a previous paper.[3]

In the present series of work, these experimental results were studied theoretically and it was ascertained that tablet disintegration could be regarded as powder.

When a powder is measured by thermal analysis, the result will be represented as in Fig. 1. The graphic surface area, α, enclosed between the curve of surface area and the time axis are calculated theoretically in the process of solution as follows:

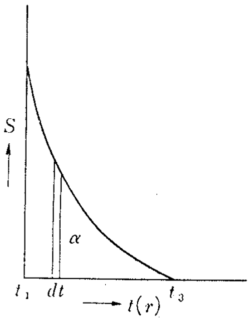

Fig. 1. Integral Surface Area of Powder

The graphic surface area, α, is given by

$$\alpha = \int_{t_1}^{t_3} S(t)\,dt \qquad (1)$$

and the rate of acid-basis reaction is

$$dM/dt = K'S[\mathrm{H}^+] \qquad (2)$$

[*1] Part V : This Bulletin, 8, 642 (1960).

[*2] Hongo, Tokyo (仲井由宣).

1) H. Nogami, J. Hasegawa, Y. Nakai : This Bulletin, 7, 331 (1959).

2) *Idem* : *Ibid.*, 7, 337 (1959).

3) Y. Nakai, Y. Kubo : *Ibid.*, 8, 634 (1960).

4) Y. Nakai : *Ibid.*, 8, 641 (1960).

where K' is the rate constant of the reaction, S the surface of particles, and $[H^+]$ is the hydrogen ion concentration. Integrating equation (2) from the time, t_1, when the reaction begins, to the time, t_3, when the reaction finishes, the following relation is obtained :

$$\int_{t_1}^{t_3}(dM/dt)\,dt=\int_{t_1}^{t_3}K'[H^+]S\,dt \tag{3}$$

where $\int(dM/dt)\,dt$ is zero at t_1 and is M at t_3, M being the total mass of powder. From equations (2) and (3), M and the volume of particles, V, are given as

$$M=\int_{t_1}^{t_3}(dM/dt)\,dt=K'[H^+]\int_{t_1}^{t_3}S\,dt=K'[H^+]\alpha \tag{4}$$

$$V\rho=K'[H^+]\alpha$$

$$V=(K'[H^+]/\rho)\,\alpha=K\alpha \tag{5}$$

where ρ is the density of the particles and K is given by $K'[H^+]/\rho$. From equation (5), it can be seen that the graphic surface area, α, is related to the true volume of all particles and that α is constant for a powder in a fixed condition.

An examination may be necessary to apply this theory of powder to a tablet, because the surface area of a tablet increases to the maximum and then decreases to zero in the disintegration process. As described above, the change in surface area is used to measure disintegration process by thermal analysis. The increase of surface area in the disintegration may be due to new particles produced into a solution. This phenomenon for a tablet may be considered the same as the addition of powders in a powder system. From equation (5), α is constant to the same total volume, V, even if the volume is divided and measured separately.

$$V=\sum V_i=K\sum\alpha_i=K\alpha \tag{6}$$

It can be seen that the graphic surface area of a tablet is identical with that of an equal amount of componental powder. In a series of this work, dT/dt expressed the surface area of total particles in a solution according to the following relationship :

$$dT/dt=(Q/W)(dM/dt)=K'[H^+](Q/W)S \tag{7}$$

where Q is the heat of reaction and W is the water equivalent of the reaction systems. It can be seen from equation (7) that integral surface area, A, becomes constant, same as graphic surface area. The integral surface area has linear relationship with the total temperature change in the reaction system and the consideration described above is rational.

Experimental

Material——Magnesium Oxide : Reagent class MgO passed through 100-mesh sieve was dried over P_2O_5 at 120° for 72 hr. and kept over $CaCl_2$ in a desiccator.

Reaction Liquid——100 cc. of Walpole's buffer solution of pH 4.2 was prepared by mixing 1*M* solution of AcOH and AcONa.

Apparatus——Same as those described in the previous paper.[3)]

Calculation of Integral Surface Area——This area was calculated by following the scale of 5 sec. expressed by 1 mm. for time axis and 0.1°/sec. expressed by 10 mm. for surface axis.

Result and Discussion

The experimental results of powder addition are shown in Figs. 2 and 3. In the experiment of Fig. 3, 0.3 g. of magnesium oxide powder was divided into 0.2 g. and 0.1 g. Each powder group was studied independently and the results were figured on a graph, where t_1 from the result of 0.1 g. was placed at the result of 40 sec. in the case of 0.2 g. In Fig. 3, 0.1 g. of powder was added into a solution after 40 sec. in measurement of 0.2 g. of powder. These results showed good agreement with each other and their integral surface was 24 cm²/g. Equation (6) may be proved experimentally from these results. As the tablet disintegration can be considered as the increase of particles produced by disintegration, the disintegration process can be shown by the increased number of particles. The surface area curve of disintegration can be expressed by the surface area curves of powder groups, P_1, P_2, P_3, etc., as shown in Fig. 4, where the total weight of all powder groups is equal to that of the tablet. The apparent particle size distribution of a tablet can be given by the particle size distribution d_1, d_2, d_3, etc., of each particle groups P_1, P_2, P_3, etc. Rapid disintegration corresponds to the rapid addition of fine powder that has large specific surface area, and slow disintegration means the slow addition of a large particle size powder. The apparent particle size distribution in rapid disintegration must be the small mean diameter and narrow distribution as reported in the previous paper.[2]

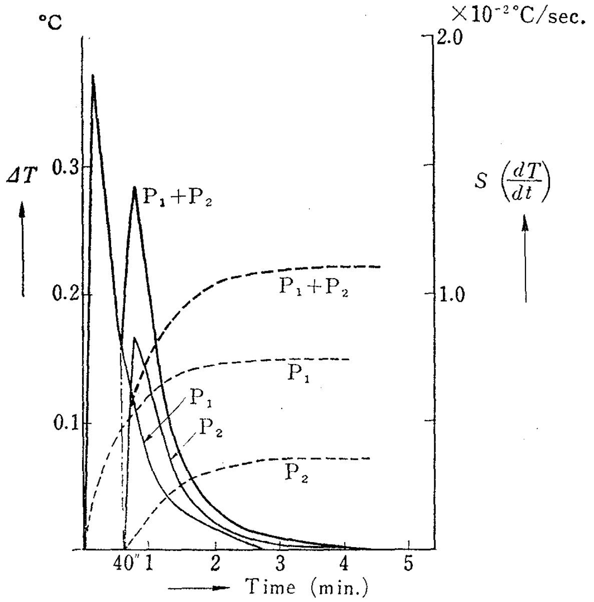

Fig. 2. Surface Area Curve synthesized by the Result of P_1 and P_2

P_1: 0.2 g. P_2: 0.1 g.
----- (T-t) Curve
—— (S-t) Curve

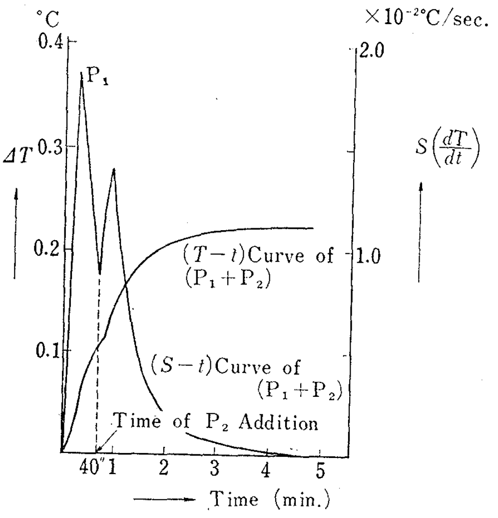

Fig. 3. Surface Area Curve of P_1 and P_2

P_2 was added into solution 40 sec. after P_1
P_1: 0.2 g. P_2: 0.1 g.

Tablet disintegration process could be elucidated by the values of t_2, S_2, and t_3 in which the values of $S_2 \times t_3$ were found to be independent of the compressional force, as stated in a previous paper.[3] This result is explained by the relationship between $S_2 \times t_3$ and integral surface area as

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5) E. Suito, *et al.*: Nippon Kagaku Zasshi, **72**, 713 (1951).

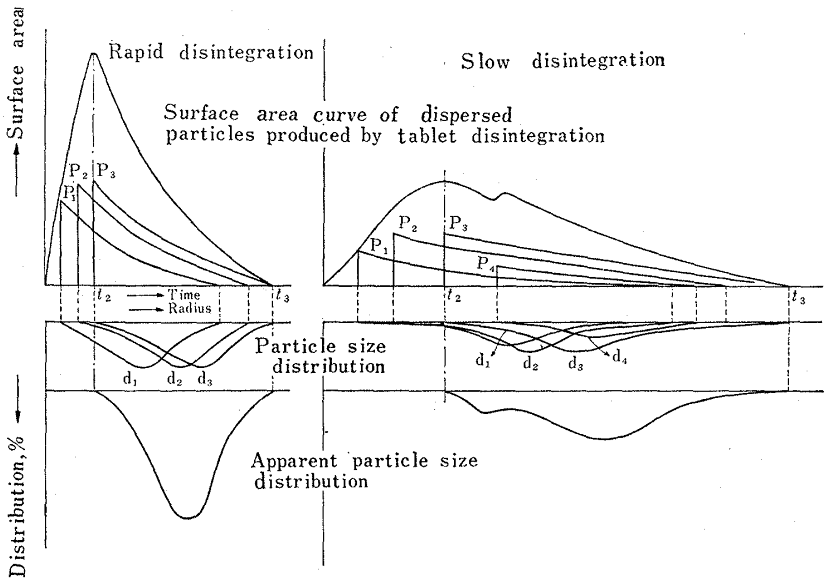

Fig. 4. Tablet Disintegration evaluated as Powder

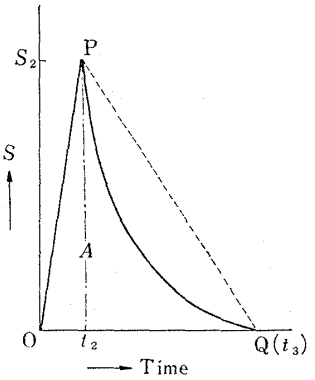

Fig. 5. Relationship between Integral Surface Area, A, and $S_2 \times t_3$ in Tablet Disintegration

shown in Fig. 5. The value of $S_2 \times t_3/2$ is equal to the surface area $\varDelta$OPQ, which is similar to the constant value of the integral surface area. The surface area of $\varDelta$OPQ was equal to $377 \times 1/2 \times 1/0.1 \times 1/50 = 37.7\,\text{cm}^2$ for the mean value of 377 of $S_2 \times t_3$ and nearly equal to $24\,\text{cm}^2$ of integral surface area.

The effect of compressional force on the values of t_3 was highly significant but not on $S_2 \times t_3$ by the analysis of variance shown in the previous paper[3] since the value of F was 10.4 and 0.2, respectively. The physical meaning of this result may be interpreted as follows. The particles produced by tablet disintegration are taken as spherical, the mean volume surface diameter, the largest diameter, and the total surface area in this dispersion system being expressed by $\bar{r}_s$, $r_{\max}$, and S_2, respectively.

$$2 = 6/\rho \bar{r}_s S_2$$
$$S_2 = 3/\rho \bar{r}_s \tag{8}$$

where ρ is the true density of a particle. $r_{\max}$ is given by the following equation:

$$r_{\max} = Kt_3 \tag{9}$$

From equations (8) and (9), equation (10) is obtained,

$$\begin{aligned} S_2 \times t_3 &= (3/\rho \bar{r}_s)(r_{\max}/K) \\ &= (3/\rho K)(r_{\max}/\bar{r}_s) \end{aligned}$$
$$S_2 \times t_3 = C(r_{\max}/\bar{r}_s) \tag{10}$$

where C is $3/\rho K$. This result shows that the value of $S_2 \times t_3$ may become constant at the ideal disintegration in which the largest particle size measured in experiment relates to the mean volume-surface diameter in the dispersion system of each tablet. The observed values of $S_2 \times t_3$ were experimentally nearly constant, though some deviation was found. Therefore it can be said from equation (10) that the mean particle size may increase in this case when the largest particle size increases.

In the previous papers,[2,3] it was shown that the value obtained by U.S.P. method was similar to the t_3 value from thermal analysis. This result may be rational since the largest particle in the dispersion system is measured by both methods. The value of U.S.P. method depends upon only the largest particle size and not on the whole process of tablet disintegration. The measured value in U.S.P. method has no physical meaning if few particles were observed for a long time. U.S.P. XV specifies that a tablet is disintegrated if any residue remains in a soft mass having no palpably firm core. This description may show the consideration described above.

The U.S.P. method of tablet disintegration may be available for a quality control of tablet manufacturing but may not be sufficient to estimate the dissolution process of a tablet.

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Summary

The characteristic values of tablet disintegration by thermal analysis were considered theoretically and their physical meaning was examined.

The graphic surface area, α, enclosed by the curve of surface area in solution and time axis, was calculated for a powder system and it was proved that the value of α was constant for the same substance and experimental conditions. Moreover it was proved theoretically and experimentally that the graphic surface area of the same weight of powder was constant in total amount when the powder was divided and measured. This result of a powder could be applied to a tablet and the integral surface area of a tablet was constant for the same weight. The experimental results agreed with this theory, and it was proved that the meaning of $S_2 \times t_3$ was similar to the integral surface area. The mean volume surface diameter is related to the largest particle size evaluated in tablet disintegration.

From these theoretical considerations, the physical meaning of the value of U.S.P. method was discussed and elucidated.

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