Summary

4-Cyano-5-methoxymethylquinoline was prepared from quinoline-5-carboxylic acid through several steps. This quinoline compound was found to easily form a δ-lactone compound on boiling with conc. hydrochloric acid.

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64. Hisashi Nogami, Jun Hasegawa, and Yoshinobu Nakai*: Studies on Powdered Preparations. II. Studies on Tablet Disintegration of Calcium Carbonate by Thermal Analysis.

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Disintegration time of a tablet is the most important characteristic by which the quality of a tablet is evaluated. The pharmacopoeiae of several countries contain the method of testing this value. The Japanease Pharmacopoeia VI specifies time of disintegration of a tablet in water at 37° under specific conditions; a test tablet is placed in a 100-cc. Erlenmeyer flask, 50 cc. of water is added and shaken occasionally, and the end of disintegration is recognized when the original form of the tablet disappears completely. A testing apparatus is specified in U.S.P. XV and the time necessary for all particles of the tested tablet to pass through a 10-mesh sieve attached to the bottom of a basket assembly is measured.

The end-point of disintegration is not clear by the method of J. P. VI, the deviation may increase by the difference of shaking, the determination is subjective, and moreover, the deviation is not small. The determination of disintegration is more clear and objective by the U.S.P. method, but true determination may not be known exactly.

These methods are very simple in finding the outline of tablet disintegration, but the values are not related directly to physical phenomena such as the increase of surface area and the solution of crystalline medicine contained in a tablet during its disintegration, and details of the phenomena cannot be elucidated.

The process of solution, absorption through the gastric tissues, and the effect on blood concentration were examined by Nelson[2] on theophylline salts and derivatives and he concluded that the rate of solution was determinant. Edward[3] discussed the solution rate of Aspirin crystal after disintegration of the tablet and referred to the effect of absorption.

As can be seen from these reports, disintegration of a tablet is directly responsible for the appearance of medicinal effect. Since the most widely used method is to compress granules into a tablet, the tablet has a secondary structure and is not a simple assembly of microcrystals. Therefore, it is considered that examination of tablet disintegration and its physical process is very important and is required for the elucidation of mechanism of disintegration.

A new method using thermal analysis for the detailed investigation of tablet disintegration is proposed. By this means continuous variation in the surface area of solid medicine can be studied and each stage of disintegration and physical process are easily and distinctly recognized. This method was applied to the tablet of calcium

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1) Part I: Yakuzai-gaku, **18**, 167(1958).
2) E. Nelson: J. Am. Pharm. Assoc., **46**, 607(1957).
3) L. J. Edward: Proc. Roy. Soc., **47**, 1191(1951).

carbonate and it became evident that the method was satisfactory for the purposes described above. Some reports on chemical kinetic studies[4] and particle size distribution of powder[5] by thermal analysis have been published. According to these papers, the reaction rate of a solid particle is represented as follows :

$$-\frac{dM}{dt}=kS[H^+] \tag{1}$$

where $\frac{dM}{dt}$ is the rate of reaction, k the rate constant, S the surface area of a solid, and $[H^+]$ the concentration of hydrogen ion. The reaction rate is given by thermal determination as,

$$\frac{Q}{W}\cdot\frac{dM}{dt}=\frac{dT}{dt}+K\Delta\theta \tag{2}$$

where $\frac{dT}{dt}$ is the rate of temperature change, K the cooling constant, $\Delta\theta$ the temperature difference between the reaction system and the environment, W the water equivalent of reaction system, and Q the heat of reaction per gram of solid. Combining Eqs. (1) and (2), (3) is obtained.

$$\frac{Q}{W}\cdot\frac{dM}{dt}=\frac{dT}{dt}+K\Delta\theta=-\frac{Q}{W}kS[H^+] \tag{3}$$

When a buffer solution is used, the concentration of hydrogen ion is kept constant, then $\frac{Q}{W}\cdot\frac{dM}{dt}$ is related to S, since W, Q, and K are constants. Therefore, the change of surface area is estimated by temperature rise of the reaction system. Furthermore, the relation between particle size, r_0, and the disappearance time of particles, τ, was represented by Suito, *et al.*[5] as follows :

$$\tau=\frac{3}{k'}\left(\frac{4}{3}\pi\rho\right)^{1/3}\cdot r_0 \tag{4}$$

where $k'=k\cdot[H^+]$ and ρ is the density of a particle. The number of particles is written as follows :

$$\frac{d^2M}{dt^2}=\frac{2}{9}k'^3n(\tau-t) \tag{5}$$

where n is the number of particles. From Eqs. (4) and (5), linear relation is found between r_0 and t, and the slope is related to the number of particles.

When the curve of $\frac{d^2M}{dt^2}$ vs. t is obtained, then the particle size distribution of powder being tested is represented graphically as the procedure at sedimentation analysis as follows : The tangent is drawn at each point of reaction time, the cross-point with the axis of $\frac{d^2M}{dt^2}$ is obtained, and the difference of each cross-point is related to the amount of powder. In this case, reaction time (τ) corresponds to the radius of powder as shown by Eq. (4) and this relation is determined as will be described in the following paper[6] of this series.

As understood from the theoretical considerations described above, the proposed method is useful when the tablet ingredient dissolves or reacts with the testing solution. Therefore the disintegration of enteric coated tablet may be examined in a simulated intestinal juice. When the heat of solution is determined, the solution rate of water-soluble substance may be discussed using the relations of Noyes-Whitney[7] or Hixon-Crowell.[8]

4) E. Suito : Rev. Phys. Chem. Japan, **13**, 74(1937).
5) E. Suito, *et al.* : Nippon Kagaku Zasshi, **72**, 713(1951).
6) Part III : This Bulletin, **7**, 337(1959).
7) A. A. Noyes, W. R. Whitney : J. Am. Chem. Soc., **19**, 930(1897).
8) A. W. Hixson, J. H. Crowell : Ind. Eng. Chem., **23**, 923, 1002(1931).

A typical result on thermal analysis of tablet disintegration is given in Fig. 1.

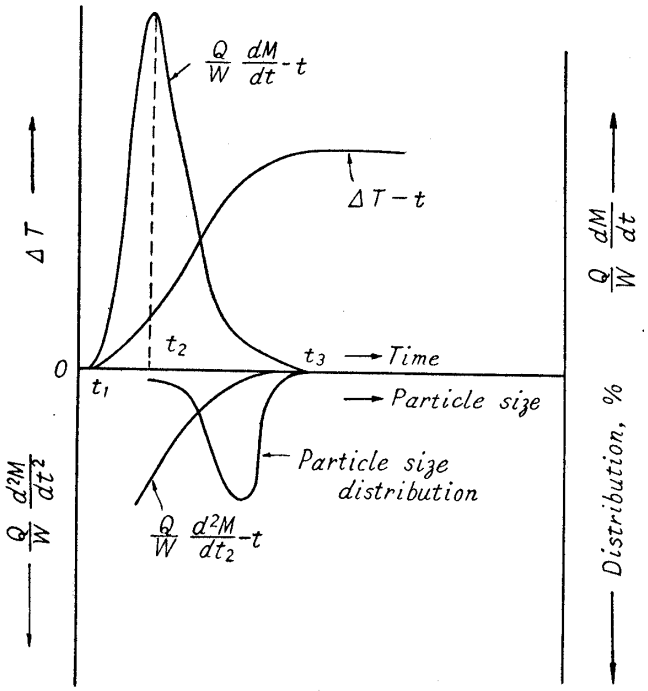


Fig. 1.
Typical Result of Tablet Disintegration by Thermal Analysis

Disintegration of a tablet is divided into the following four stages:

I. $0 \sim t_1$: A tablet to be tested is dropped into the reaction liquid at time 0. The rise of temperature is not seen in this period and original form of the tablet remains in the liquid.

II. $t_1 \sim t_2$: The increase of surface area and the rate of temperature rise are observed by disintegration. The smaller particles dissolve into the reaction liquid in this period and the difference between increase and decrease of surface area is measured, but the amount of particles dissolved may not be great when the tablet disintegrates within a short period.

III. $t_2 \sim t_3$: In this period, the increase of surface area by disintegration may not be recognized and rate of temperature change decreases in a good tablet. The disintegration almost reaches the final stage and dissolution is a rate-determinant for the decrease of surface area. If a large granule disintegrates in this period, an irregular decrease may be observed.

IV. $t_3 \sim$: All particles are dissolved and surface area becomes zero at t_3. The change of temperature follows the cooling constant of the reaction system.

As the particle-size distribution may be known from thermal analysis of a powder, "apparent particle-size distribution" of a tablet may be obtained when the curve $t_2 \sim t_3$ is handled as a powder. This apparent particle-size distribution of a tablet means that if smaller particles disappearing before t_2 is disregarded, the tested tablet has quite the same medicinal effect as the powder which is presumed to be taken at t_2 and to have the apparent particle-size distribution described above. By comparing the apparent particle-size distribution of a tablet with the one of original powder or granule, characteristics of disintegration may be estimated. Therefore, disintegration of a tablet can be evaluated by thermal analysis from both points, the time 0 to t_2 and from apparent particle-size distribution in Fig. 1.

Experimental

Apparatus—Dewar's flask method was employed in this study as shown in Fig. 2. Capacity of the flask is 250 cc. and a rubber stopper is provided with the Beckmann's thermometer A, stirrer B, sample tube C, and gas outlet tube G. The whole flask is kept in a thermostatically controlled water bath of 30.15°±0.08°.

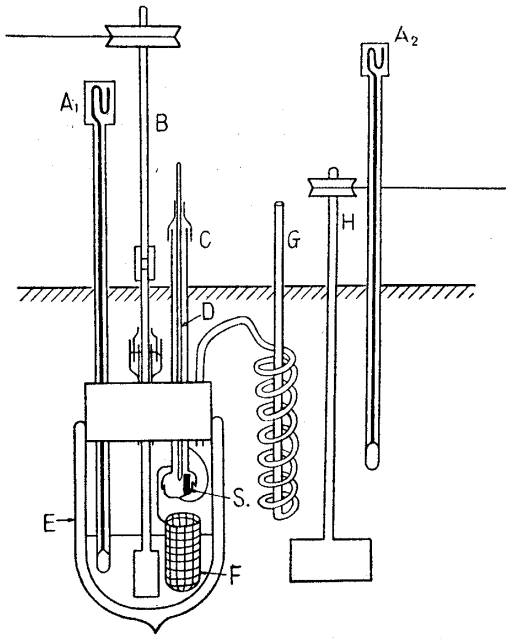


Fig. 2.
Apparatus for
Thermal Analysis

A_1, A_2 Beckmann's thermometer
B Stirrer
C Sample tube
D Glass rod
E Dewar's flask
F Paraffin-coated cage
G Gas outlet tube
H Stirrer
S Sample

i) Stirring : The stirrer is 1.2×2.4 cm. in size and kept 1 cm. above the bottom of Dewar's flask. Supply voltage for a series motor is controlled by a trasformer and stirred at 600±50 r.p.m.

ii) Sample tube : Structure of the sample tube is shown in Fig. 2. The test sample S is placed in the tube and ground-glass joint bottom is attached at the bottom of S. Glass rod D is inserted through the tube C and kept air-tight. The test sample falls into paraffin-coated 10-mesh cage, but the bottom of the sample tube does not fall into testing liquid and the stirring is not interfered, since the bottom is connected to tube C.

iii) Temperature rise of reaction system : A rise in temperature of 5×10^{-3} degree is observed by the Beckmann's thermometer A_1 using a magnifying glass.

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

Material Used—$CaCO_3$: Extra pure grade reagent was passed through 80-mesh sieve and kept in a desiccator over $CaCl_2$ after drying over P_2O_5 at 80° for 72 hr. in vacuum.

Potato starch : J. P. grade, dried for 72 hr. in a desiccator.

Dried potato starch paste : Potato starch paste used for granulation was concentrated on a water bath, dried in warm air stream at a controlled temperature of 50°, passed through a 100-mesh sieve, and kept in a desiccator.

Granulation—194 g. of $CaCO_3$ was mixed with the paste prepared from 6 g. of potato starch and about 50 cc. of water, passed through a 20-mesh sieve, dried in warm air stream at 50°, and kept in a desiccator.

Compression of Tablet—Flat-faced tablet, 13 mm. in diameter, was compressed with the force of 0.5, 1.0, 1.5, and 2.0 tons using an oil press.

Cooling Constant—The constant was determined by the following Newton's formula :

$$-\frac{dT}{dt}=K\Delta\theta$$

where K is the cooling constant and $\Delta\theta$ the temperature difference. This equation may be rewritten as follows :

$$K=\frac{\log(T_1-T_0)-\log(T-T_0)}{t}$$

where T_0 is the temperature of water bath, and T_1 and T_2, the temperature of the reaction system at $t=0$ and $t=t$. The result is given in Table I.

9) S. Horiba, K. Sato : Rev. Phys. Chem. Japan, **6**, 16(1932).

Table I. Cooling Constant

Temp. difference $T_1 \sim T_0$ (°C)		Cooling constant (°C/min.) $K \times 10^3$
0.24		3.4
0.46		3.5
1.67		3.6
1.75		3.5
	mean	3.5

T_1 : Temp. of reaction system
T_0 : Temp. of external system

Procedure—The test sample is kept in the tube C. The stirring is begun after the whole apparatus is immersed in the water bath. The sample is dropped into the reaction liquid when the temperature becomes constant and the temperature rise is recorded after a suitable interval until the temperature change follows the condition represented by Newton's formula.

Temperature Change of Calcium Carbonate—The result is given in Table II.

Table II. Temperature Rise of Calcium Carbonate in 1*M* Acetate Buffer (pH 4.2) (°C/g.)

0.45		0.45
0.44		0.43
0.42	mean	0.44
0.43		

Result and Discussion

The temperature rise of potato starch powder used as disintegrator and dried starch paste is given in Fig. 3, in which the curve (1) reaches the maximum very rapidly but the curve (2) reaches the same level after about 8 mins., and only 0.10° of temperature rise is observed after 30 minutes. The temperature rise caused by the starch paste contained in a 500-mg. tablet is 1.5×10^{-3} degree and may be neglected, since the tablet contains 3% of the starch paste.

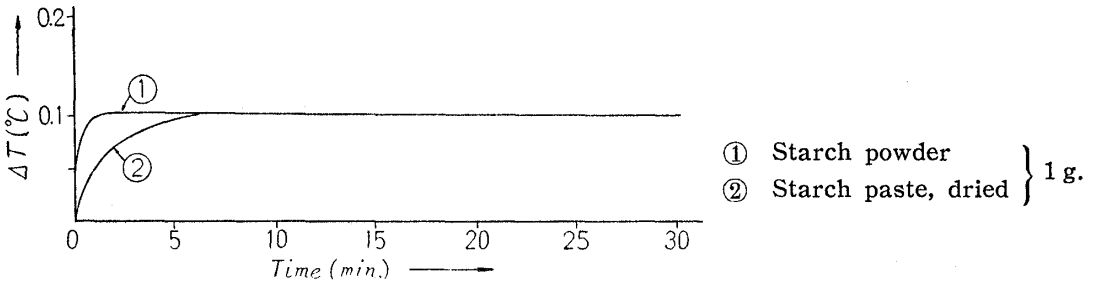
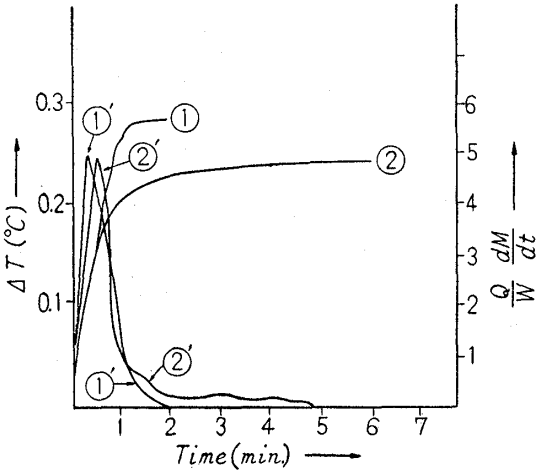


Fig. 3. Reaction Rate of Potato Starch Powder and Dried Starch Paste

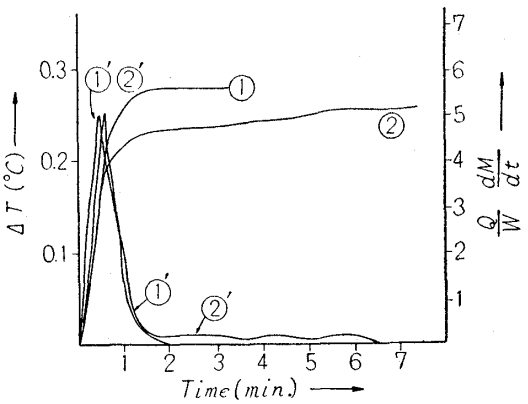
Original powder of $CaCO_3$ and the granule prepared with this powder were examined as shown in Fig. 4, in which curves (1) and (2) are the temperature rise observed and the curves (1′) and (2′) show the change of surface area. The curve (2′) is nearly the same as (1′), but it was seen that the tail of (2′) prolonged and it might mean that larger particles remained at the final stage of disintegration.

The result shown in Fig. 5 was obtained with a tablet compressed from the original powder or granule with the force of 1.0 ton, where the curves (1) and (2) are the temperature rise of these tablets, and (1′) and (2′) are the increase and the decrease of surface area. As seen in this figure, the curve (1′) is quite similar to the curve (1′) in Fig. 4 and it might mean that the tablet disintegrated very rapidly. The curve (2′) in Fig. 5 is somewhat similar to the curve (2′) in Fig. 4, but the tail prolonged further to 7 minutes. These phenomena may have been caused by (a) attractive force of $CaCO_3$ may not be strong in the tablet, (b) the contact angle of the powder may be small, or (c) by evolution of CO_2.



① Powder
② Granule

Fig. 4. Reaction Rate of Calcium Carbonate, Original Powder, and Granule



① Tablet made of pure powder
② Tablet made of granule

Fig. 5. Disintegration of Calcium Carbonate Tablet (Compressed with the force of 1 ton)

The disintegration time of $CaCO_3$ tablet was about 75 seconds by U. S. P. method and comparing this result with the tablet of basic $MgCO_3$ described in the following paper,[6] in which the tablet disintegrated slowly, it may be estimated that (a) or (b) is the principal reason.

The reproducibility of this method is indicated in Fig. 6, where five tablets are determined and thd curves are located within the solid and dotted curves.

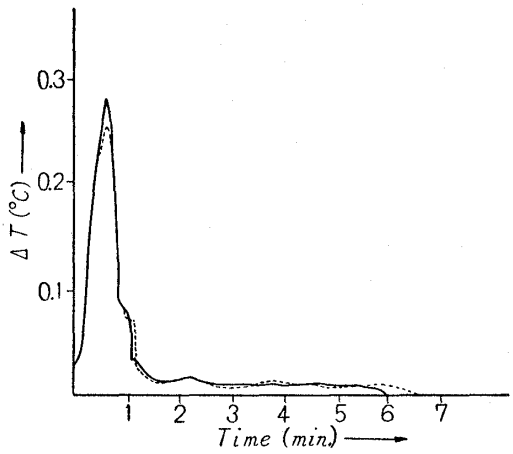


Fig. 6. Reproducibility of Thermal Analysis

Judging from these results, $CaCO_3$ tablet disintegrated too rapidly and is not suitable for examining the effect of disintegrator and binder.

Summary

A new mothod for examining the disintegration of a tablet and a granule continuously and in detail was proposed. The beginning of disintegration, the time necessary for the maximum surface area of tablet ingredient, and the time required for a powder to dissolve completely were determined precisely.

This method was applied to the tablet of calcium carbonate in the acetate buffer of pH 4.2 and the following conclusions were drawn.

a) The tablet prepared from $CaCO_3$ powder by direct compression disintegrated and dissolved very rapidly, and difference between the original powder and the tablet

was not recognized.

b) The disintegration and solution rate of $CaCO_3$ granule that contained starch paste was not rapid and larger particles remained undissolved in the final stage.

c) It was evidenced that the tablet prepared from $CaCO_3$ granule disintegreted more slowly than the tablet prepared by direct compression.

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65. Hisashi Nogami, Jun Hasegawa, and Yoshinobu Nakai*1 : Studies on Powdered Preparations. III.*2 Studies on Disintegration of Basic Magnesium Carbonate Tablet.

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In the preceding paper,*2 a new method for testing disintegration of a tablet and granule was proposed, and the result on calcium carbonate was reported. Because calcium carbonate was not suitable for studying the effects of binder, disintegrator, and compressional force, these effects were examined with basic magnesium carbonate, and apparent particle-size distribution of a tablet was compared and described in this report.

Experimental

Materials—Basic Magnesium Carbonate : Reagent grade, 1st class, was dried over P_2O_5 at 80° for 72 hr. and kept in a $CaCl_2$ desiccator. About 0.3 g. of the powder passed through 100-mesh sieve was weighed and used for thermal analysis.

Granule : Two kinds of granule were prepared.

Granule A : 190 g. of basic magnesium carbonate was mixed with 4 g. of potato starch, prepared from 6 g. of starch and 50 cc. of water, granulated with 20-mesh sieve, dried in warm air stream of 50°, and kept in a desiccator. This granule contained 95.2% of the carbonate.

Granule B : Starch paste described above was added to a mixture of 186 g. of basic magnesium carbonate and 8 g. of starch, granulated, dried, and kept in the same manner. This granule contained 93.1% of the carbonate.

Temperature rise of the starch and the dried starch paste was determined as described in the preceding paper.*2 The tablet prepared from 300 mg. of the granule B contains 12 mg. of starch and 9 mg. of dried starch paste, and the temperature rise caused by them, 2.1×10^{-3}°, is negligible as described before.

Apparatus, Procedure, etc.—Same as described in the previous paper. Temperature rise of basic magnesium carbonate is given in Table I.

Table I. Temperature Rise of Basic Magnesium Carbonate in 1*M* Acetate Buffer (pH 4.2) (°C/g.)

1.91.	1.86,	1.85,	1.85,	1.86,	1.78
	mean		1.85		

Result and Discussion

The disintegration and solution were studied as shown in Fig. 1, in which the curves (1), (2), and (3) show the temperature change of basic magnesium carbonate powder, the granule A, and the graule B, and the curves (1′), (2′), and (3′) show the change of surface area of these materials. Marked difference in the results obtained with the

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*2 Part II. This Bulletin, **7**, 331(1959).

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