UDC 615.412.5-011

110. Yoshinobu Nakai: Studies on Powdered Preparations. V. Studies on Particle Size Determination and Tablet Disintegration of Acetylsalicylic Acid by Thermal Analysis.

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In previous papers, detailed studies were described for disintegration in calcium carbonate,[1] basic magnesium carbonate,[2] and magnesium oxide[3] by thermal analysis of reaction heat.

Thermal analysis has only been used for measurement of heat of reaction to date. However, many water-soluble substances are used as tablet ingredient and it is desirable to apply thermal analysis to water-soluble medicinals. Heat of solution is measured in this case and theoretical consideration must be examined since equation of solution rate is different from the one of reaction rate as shown by the following discussion. The rate of solution is given by Noyes and Whitney[4] as follows:

$$dC/dt = kS(C_S - C) \qquad (1)$$

where C_S is the saturated concentration, C, the concentration at time t, S, the surface area, and k is the rate constant. In equation (1), rate of solution consists of two variables, surface area, S, and concentration difference from saturated solution, $(C_S - C)$. Therefore, the rate of solution as such cannot be applied to thermal analysis. However, the equation (2) may be derived from equation (1),

$$dC/dt = kSC_S(1 - C/C_S) \qquad (2)$$

and if C/C_S is negligible, equation of solution rate will be given as follows:

$$dC/dt = kSC_S \qquad (3)$$

In equation (3), rate of solution is dependant only on surface area same as in equation (4) of the reaction rate.

$$dM/dt = kS[H^+] \qquad (4)$$

where k is the rate constant, S, the surface area, and $[H^+]$ is the hydrogen ion concentration. Hixson and Crowell[5] studied the rate of solution in following systems and proved the availability of equation (3) within a certain range of concentrations.

naphthalene—benzene	$C/C_S = 1/26.5$
cupper sulfate—water	$C/C_S = 1/8.1$
sodium chloride—water	$C/C_S = 1/18$

If equation (3) is available for the study of tablet disintegration, relationship between rate of solution and rate of solution heat in thermal analysis will be given by the following equation, same as in reaction heat.

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1) H. Nogami, J. Hasegawa, Y. Nakai: This Bulletin, **7**, 331(1959).
2) *Idem*: *Ibid.*, **7**, 337(1959).
3) Part IV: *Ibid.*, **8**, 634(1960).
4) A. A. Noyes, W. R. Whitney: J. Am. Chem. Soc., **19**, 930(1897).
5) A. W. Hixon, J. H. Crowell: Ind. Eng. Chem., **23**, 927, 1002(1931).

$$dT/dt+K\Delta\theta=Q/W\cdot dC/dt=Q/W\cdot kSC_S \qquad (5)$$

where T is the temperature, K, the cooling constant, $\Delta\theta$, the temperature difference between reaction system and thermostatic bath, Q, the solution heat with 1 g. of sample, and W is the water equivalent of the reaction system. Using equation (3), thermal analysis can be applied for water-soluble powders or tablets.

In the present series of work, the system of acetylsalicylic acid and 0.5M sodium citrate solution were used and concentration limit, C/C_S, might be neglected in the equation (2) was determined. Particle size distribution and disintegration of tablets were studied, and particle size distribution was compared with the one obtained by microscopic method.

Experimental

Material—Acetylsalicylic acid J. P. VI was used.
Sodium citrate : Reagent class.
Tablet : Market product of acetylsalicylic acid tablets which contain 0.5 g. acetylsalicylic acid in each tablet was used for measurement of disintegration.

Apparatus for Thermal Analysis—Same as described in a previous paper.[3]

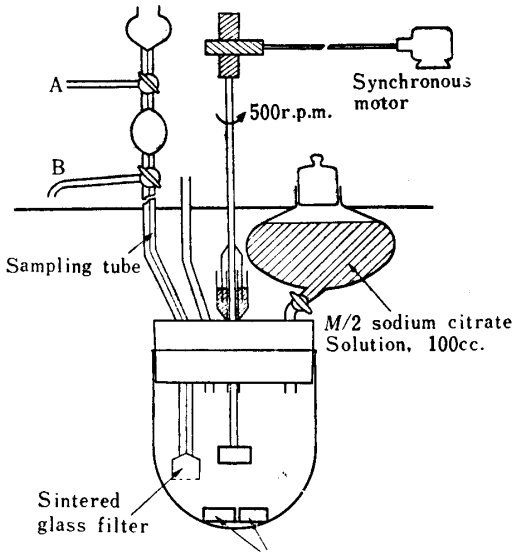

Fig. 1. Apparatus for Measurement of the Rate of Solution

Apparatus for Measurement of the Rate of Solution—Apparatus is shown in Fig. 1. In the bottom of the flask, two acetylsalicylic acid disks are fixed by paraffin wax. These disks are made of acetylsalicylic acid powder, compressed by pressure of 4 tons, to a diameter of 13 mm. The side and bottom of these disks are covered by paraffin wax and only upper surface is in contact with the liquid. Therefore, the surface area S of two disks in equation (3) will be given by

$$S=\pi D^2/2=2.653\ \mathrm{cm}^2$$

Whole apparatus is dipped into thermostatic bath adjusted to $30^\circ\pm2^\circ\times10^{-3}$ and the liquid is stirred by synchronous motor at 500 r.p.m.

Measurement of the Rate of Solution—Into the flask, 100 cc. of 0.5M sodium citrate solution is introduced. Every 2 min., 2 cc. is taken out through a sampling tube fitted with a sintered-glass filter. After one sample is taken, the solution remaining in the sampling tube is driven back by air pressure through the hole A, in Fig. 1. The pipet is washed with the vehicle solution in the reaction system before next sampling, then 2 cc. of new sample is taken out, and 2 cc. of the vehicle solution is added immediately after each sampling. The sampling is repeated 4 times, requring a total of 8 min. The vehicles contained 0, 0.5, 0.6, 0.75, or 1.0 g. of acetylsalicylic acid in 0.5M sodium citrate solution.

Concentration of acetylsalicylic acid in the solution was determined as will be described later and the results are given in Fig. 2. From gradients of the straight line, solution rate constant, k, at each initial concentration of acetylsalicylic acid was calculated as g./min./cm² of surface area of acetylsalicylic acid/100 cc. of vehicle (0.5M sodium citrate solution).

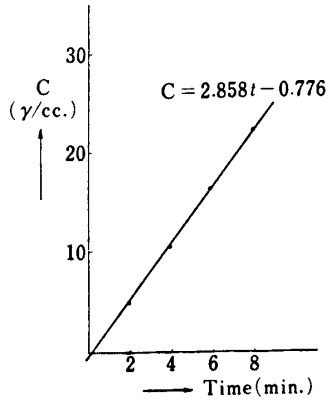

Fig. 2. Relationship between Concentration and Time

$C_0=0$
$S=\pi D^2/2$
$=2.653\ cm^2$
$C=\gamma/cc.$
concentration
100 × dilution

Determination of Acetylsalicylic Acid—One cc. of the sampling solution was diluted with 0.01N NaOH and acetylsalicylic acid was hydrolyzed to salicylic acid completely in 24 hr. at 40°. Its concentration was measured by spectrophotometer at 296 mμ. The concentration of acetylsalicylic acid was calculated from the following equations:

$$y=40.077\varepsilon-0.034, \qquad x=180/138y$$

where ε is the extinction, y, the concentration of salicylic acid, and x, the concentration of acetylsalicylic acid.

Results and Discussion

Solution rate, k, at each initial concentration is shown in Table I.

Table I. Solution Rate at Each Initial Concentration
(C_S=7.1 g./100 cc. 0.5M sodium citrate)

C_0 (g./100 cc.)	$k\times10^3$/min./cm²/100 cc.	Mean
0	1.516	1.528
	1.518	
	1.549	
0.5	1.518	1.521
	1.538	
	1.507	
0.6	1.507	1.510
	1.549	
	1.475	
0.75	1.358	1.422
	1.443	
	1.464	
1.00	1.305	1.299
	1.294	

From these values, it may be considered that the solution rate is nearly constant within the range of 0~0.6 g./100 cc. Therefore, equation (3) is available within this concentration and thermal analysis was carried out with 0.6 g. of the sample.

C_S was measured at every hour. As hydrolysis of acetylsalicylic acid occurs, the solution process over a long period of time may become complex, but the hydrolysis does not affect thermal analysis since the measurement continues for only 8 minutes and the linear

TABLE II. Saturated Concentration of Acetylsalicylic Acid
(g./100 cc. 0.5*M* sodium citrate solution)

hrs.	C_S	
1	7.3	7.1
2	7.1	7.0
3	7.1	7.1
4	7.2	7.1
Mean	7.2	7.1
Total mean	7.1	

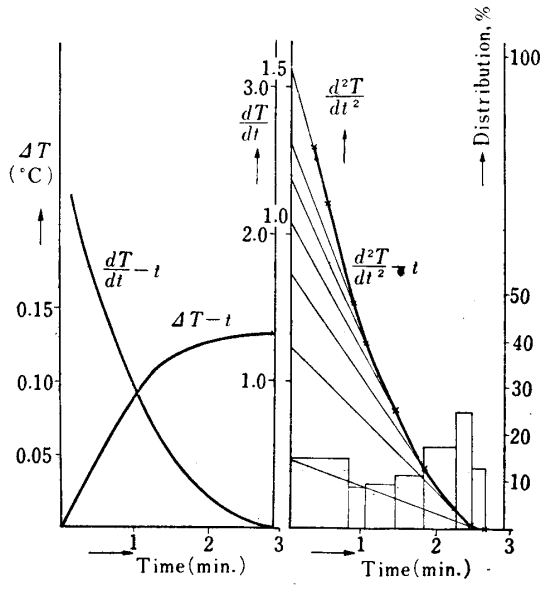

Fig. 3. Thermo-analytical Result on Acetylsalicylic Acid Powder (32-Mesh stop)

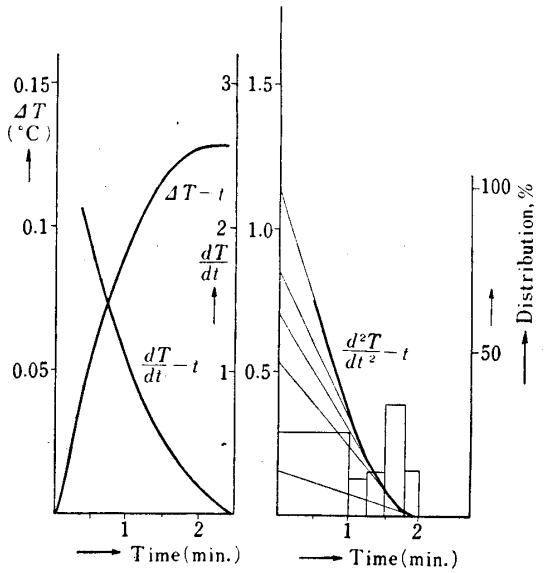

Fig. 4. Thermo-analytical Result on Acetylsalicylic Acid Powder (32/60 Mesh)

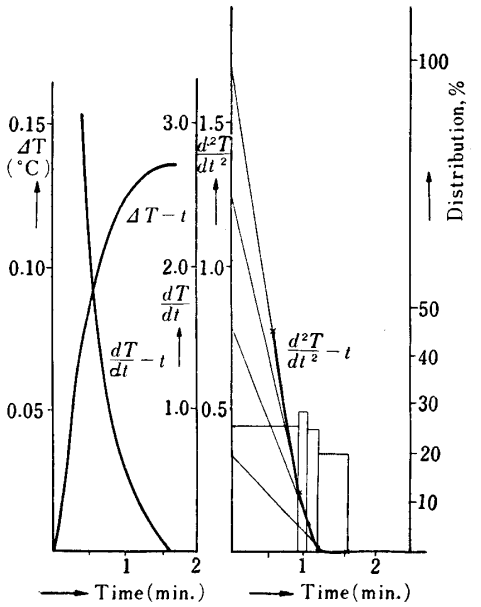

Fig. 5. Thermo-analytical Result on Acetylsalicylic Acid Powder (60-Mesh pass)

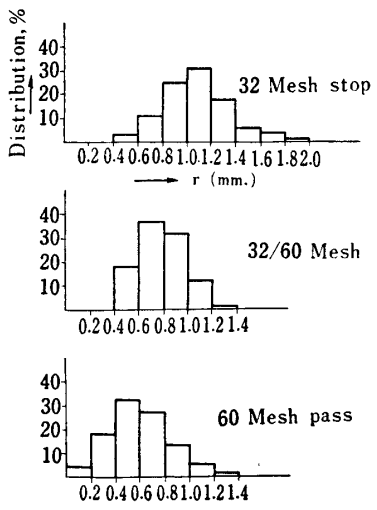

Fig. 6. Particle-size Distribution on Acetylsalicylic Acid by Microscopic Method

relationship between concentration and time was obtained and availability of equation (3) was proved. It may also be considered that the equilibrium of saturated concentration is attained within 1 hour as shown in Table II.

By applying these theory and fundamental experiments to acetylsalicylic acid powder, its particle size distribution was measured. Acetylsalicylic acid powder was separated by Tailor sieves into three particle-size groups of 32 mesh and over, 32/60 mesh, and 60 mesh and under, and their particle sizes were measured by thermal analysis and microscopic method. Total temperature rise was −0.275 degree/g. Results are shown in Figs. 3, 4, 5, and 6.

Linear relationship between thermo-analytical and microscopic methods was observed as shown in Fig. 7. Some deviation is observed in this result, but it may be due to experimental error.

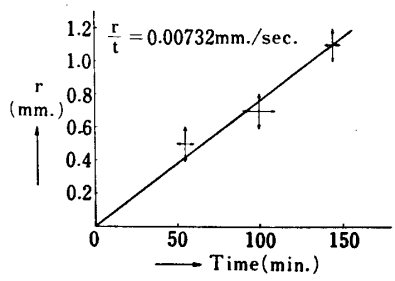

Fig. 7. Relationship between Diameter and Time in Thermal Analysis

Applying the method proposed above, change of the surface area in tablet disintegration and apparent particle-size distribution of tablets were measured. Results obtained with marketed tablets are shown in Fig. 8. Disintegration of these tablets was very rapid and many fine particles smaller than 70 μ were observed in apparent particle-size distribution curve.

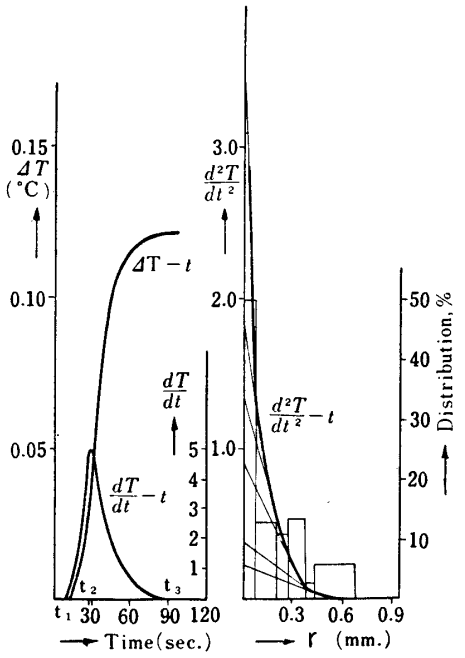

Fig. 8. Thermo-analytical Result and Apparent Particle-size Distribution of Acetylsalicylic Acid Tablet

When these tablets disintegrated in water, presence of many fine particles of acetylsalicylic acid, about 50~70 μ, was observed under the microscope. These observations agree well with the thermo-analytical results.

From these experiments, it may be considered that the fine disintegration process of acetylsalicylic acid tablets can be studied by thermo-analytical method as was anticipated, but a question remains in the fact that 0.5*M* sodium citrate solution is used, because the solution rate of acetylsalicylic acid varies with the kind of a solvent used. To measure disintegration *in vitro* is to study the process of tablet disintegration *in vivo* and this process can be evaluated by apparent particle-size distribution which is independent of the rate of solution. In other words, each solvent has its linear gradient in the relationship between particle diameter and corresponding time of thermal analysis, as shown in Fig. 7. However, particle-size distribution calculated from the gradient of each solvent must be identical with the same sample. Therefore, it seems that the solution rate of tablets can be found by measuring apparent particle-size distribution of tablets and solution rate of crystals in various solvents.

The author expresses his thanks to Prof. E. Suito of the Institute for Chemical Research, Kyoto University, for his kind advices, and to Prof. H. Nogami and Dr. J. Hasegawa, University of Tokyo, for their constant guidance.

Summary

Theoretical considerations were made and fundamental experiments were carried out for thermal analysis by heat of solution. Acetylsalicylic acid—0.5*M* sodium citrate solution system was used and it was determined that thermal analysis was possible within a limit concentration of 0.6 g./100 cc.

The particle-size distribution of acetylsalicylic acid powder was measured thermally and compared with microscopic method. Linear relationship was observed between particle diameter by microscopic method and solution time by thermal analysis.

Disintegration processes of marketed tablets was elucidated by thermal analysis of heat of solution, same as the heat of reaction.

(Received May 6, 1960)