Use of Microcalorimetry in the Field of Pharmaceutical Sciences. I. Measurement of Drug Dissolution from Solid Dosage Forms[1)]

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A microcalorimetric method for measurement of the dissolution rate of sodium chloride was presented. The method applied the deconvolution theory to heat conduction microcalorimetry. When a calorimetric curve for the heat of dilution was regarded as the response for a unit impulse input (heat conduction profile), a calorimetric curve for the heat of solution was considered to be the convolution of dissolution profile and heat conduction profile. Thus, the dissolution profile was calculated from the calorimetric curves for the heat of dilution and for the heat of solution by a numerical deconvolution. Dissolution rate determined by the calorimetric method coincided well with that obtained by a titration method.

Keywords microcalorimetry; dissolution rate; deconvolution; dilution heat; solution heat

It is well known that the drug dissolution from solid dosage forms influences their bioavailability. There are many reports on dissolution tests of solid dosage forms, and the factors affecting drug dissolution have also been investigated. In the dissolution tests reported to date,[2)] the concentration of drug in bulk solution was measured with the time lag.

A microcalorimeter is commonly used to measure accurately and precisely the total quantity of the heat generated with the chemical and physical changes of substances, and it is also possible to detect even a small amount of heat generated with very slow reaction. Since most of the chemical and physical reactions are accompanied by heat generation, the kinetics of the reaction has been investigated by calorimetry.[3,4)] Furthermore, tablet disintegration, drug dissolution and particle size reduction with drug dissolution were estimated by thermal analysis.[4)]

In the present paper, a new method is described for the determination of dissolution rate of a drug using a heat conduction microcalorimeter. This technique has the advantage of determining the quantity of dissolved drug instantaneously in the vicinity of the solid surface.

Experimental

Materials Sodium chloride (Koso Chemical Co., Ltd.) was of reagent grade. Powder classified between 150—180 μm was used. The powder was stored in a desiccator containing P_2O_5 for more than a week before experiments.

Tabletting Tablets were prepared using a UPF-6 tabletting machine (Nichiei Seiko Co., Ltd.) equipped with a load cell at an upper punch. The sample powders (0.30 g) were compressed under a pressure of 1000—3000 kg/cm^2 with flat-faced punches in a die 7.0 mm in internal diameter.

Microcalorimetry Calorimetric measurements were made using a twin type heat conduction microcalorimeter CM-204D1 (Applied Electric Laboratory, Ltd.). The microcalorimeter system is illustrated in Fig. 1. The microcalorimeter had attached break-ampoule type attachments and a reaction vessel coated with Teflon. Fifty ml of distilled water was used as solvent. Measurements were carried out at 298.15 K in a room maintained at 298 ± 1 K. The solvent in the reaction vessels was stirred at 60 rpm. using a stirring device. After the thermal stationary state had been attained, both an ampoule containing the sample and an empty ampoule as reference were broken simultaneously. Integral enthalpies were determined by comparing the observed area under the calorimetric curve with that for the heat evolved by a calibration heater. For the measurement of the heat of dilution, 1 ml of sodium chloride solution (5.07, 2.53 or 1.52 mol/l) was placed in an ampoule and the tip of it was sealed with Parafilm. A powdered sample of sodium chloride was placed in an ampoule, and the ampoule was sealed in the same manner. A tablet was placed in an ampoule cut out at the bottom and sealed at the top, then the bottom was sealed with Parafilm. The heat of immersion of sodium chloride powder or tablet in distilled water saturated by the sodium chloride was negligible, because little heat was generated.

Dissolution Test Dissolution rate was determined by a conventional analytical method as follows: the reaction vessel of the microcalorimeter was employed, and 50 ml of distilled water was used as the solvent. Measurements were carried out at 298.15 K. Aliquots were taken from the vessel, and the concentration of sodium chloride was determined by titration with 0.1 N $AgNO_3$ using K_2CrO_4 as an indicator.

Theory

A general convolution theorem was applied to the heat conduction calorimetry. If a response is linear with respect to an input in a certain experimental system, the response for an arbitrary input is expressed by the convolution equation (Eq. 1).

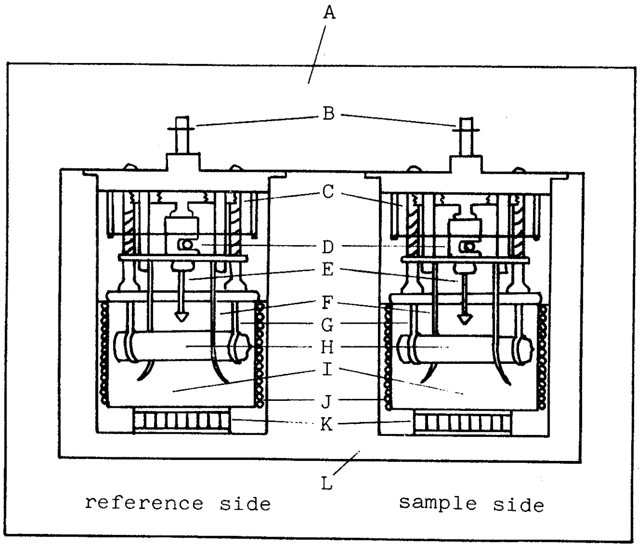

Fig. 1. Diagram of a Twin Type Heat Conduction Microcalorimeter

A, thermostat; B, shaft; C, spring; D, stopper; E, break-ampoule device; F, stirring device; G, ampoule holder; H, ampoule; I, reaction vessel; J, heater; K, thermomodule; L, thermal heat sink.

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$$g(t)=\int_0^t h(t-u)f(t)\,du \qquad (1)$$

where $g(t)$ is the response given by the experimental system corresponding to an arbitrary input signal $f(t)$, and $h(t)$ is the response for a unit impulse input. The operation which derives $f(t)$ from $h(t)$ and $g(t)$ is known as deconvolution. It was assumed that when an ampoule containing sodium chloride solution was broken in the reaction vessel, the heat absorbed by dilution was generated instantaneously. The thermogram would correspond to an impulse response, $h(t)$, expressing the heat conduction behavior from the reaction vessel to the constant temperature wall in the calorimeter. Furthermore, as the thermogram for the dissolution of sodium chloride powder or tablet was considered to be a response to an arbitrary input, $f(t)$ would correspond to the rate of heat evolution with dissolution of solid. So, if heat conductivity in the calorimeter was considered as a linear process, $f(t)$ would be calculated from the thermograms for dilution and dissolution of sodium chloride by a deconvolution operation. If the linear relationship between the heat of solution and weight of sample was observed, $f(t)$ should represent the dissolution rate of sodium chloride.

Results and Discussion

Procedure of Deconvolution Method The least-squares deconvolution method developed by Pedersen[5] was used in the present study. The procedure was as follows: $h(t)$ could be simulated well by a 4 exponential function (Eq. 2).

$$h(t)=A(\exp(-\alpha t)-\exp(-\beta t))+B(\exp(-\gamma t)-\exp(-\delta t)) \qquad (2)$$

where A, B, α, β, γ and δ are the least squares parameters. $f(t)$ may be adequately approximated by polynomial (Eq. 3),

$$f(t)=\sum_{i=0}^{N} X_i t^i \qquad (3)$$

Polynomial coefficients, X_i, were determined by a multiple linear regression analysis so as to make the convolution products of $h(t)$ and $f(t)$ coincide with $g(t)$.

Heat of Dilution and Solution of Sodium Chloride Figure 2 shows thermograms for the dilution of sodium chloride solutions, and Fig. 3 shows their semilogarithmic plot. Heat absorbed with dilution and least-squares parameters calculated from the thermograms for the first 20 min are summarized in Tables I and II, respectively. These results indicate that the thermograms exhibit similar figures independent of the heat evolved. These results also indicated that the heat conduction behavior from the reaction vessel to the constant temperature wall in the calorimeter was considered as a linear system. Therefore, the thermograms for the dilution corresponded to the

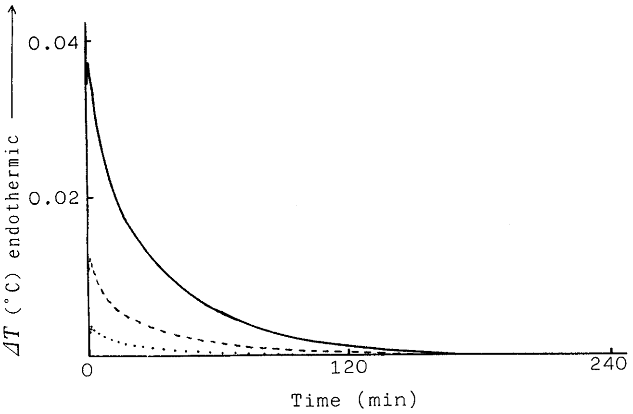

Fig. 2. Thermograms for Dilution of Sodium Chloride Solutions

——, 5.07 mol/l; ––––, 2.53 mol/l; ······, 1.52 mol/l.

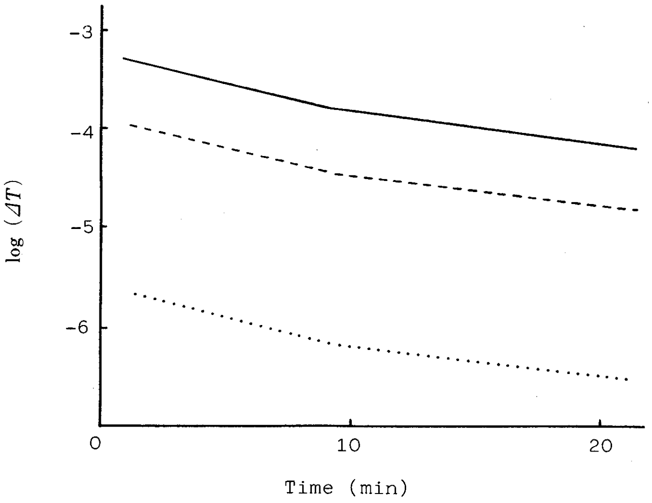

Fig. 3. Semilogarithmic Plot of Thermograms for Dilution of Sodium Chloride Solutions

——, 5.07 mol/l; ––––, 2.53 mol/l; ······, 1.52 mol/l.

Table I. Heat of Dilution of Sodium Chloride

Concentration of sodium chloride (mol/l)	Heat ± S.D. (J)
5.07	11.44 ± 0.05
2.53	3.25 ± 0.12
1.52	0.88 ± 0.15

Each value represents the mean ± S.D. of 4 experiments.

Table II. Least-Squares Parameters Obtained by Fitting Thermograms for the Dilution of Sodium Chloride Solutions to Eq. 2

Concentration of sodium chloride (mol/l)	A (°C × 10^2)	α (min^{-1} × 10^5)	β (min^{-1} × 10^7)	B (°C × 10^2)	γ (min^{-1} × 10^6)	δ (min^{-1} × 10^5)
5.07	−4.31	4.14	4.03	−1.39	3.58	4.14
2.53	−1.40	4.14	4.03	−0.51	3.58	4.14
1.52	−0.43	4.14	4.03	−0.15	3.58	4.14

Each value represents the mean of 4 measurements. $h(t)=A(\exp(-\alpha t)-\exp(-\beta t))+B(\exp(-\gamma t)-\exp(-\delta t))$.

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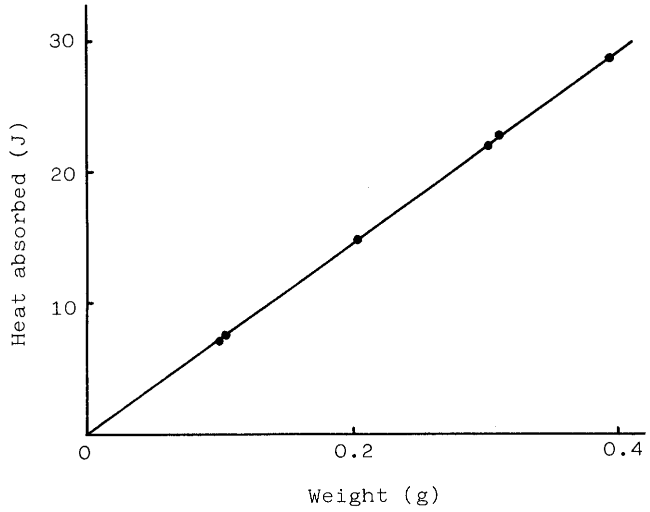

Fig. 4. Relationship between Weight of Sodium Chloride Powder and Heat Absorbed by Dissolution

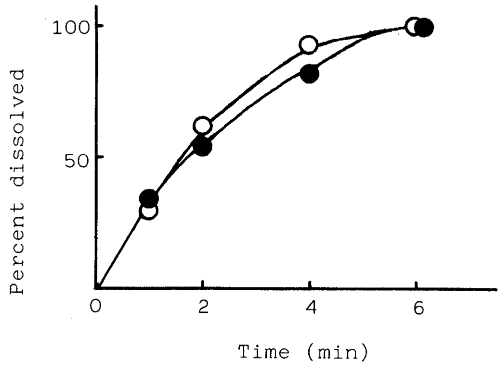

Fig. 5. Dissolution Rates of Sodium Chloride Tablet Compressed under 1000 kg/cm^2

●, calorimetric method; ○, titration method.

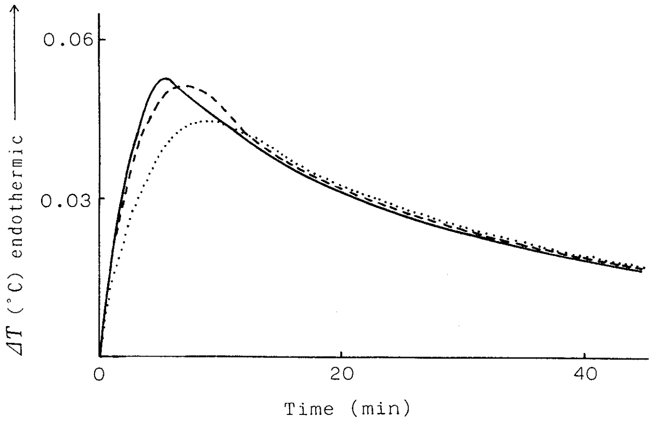

Fig. 6. Thermograms for Dissolution of Sodium Chloride Tablets

Compression pressure: ——, 1000 kg/cm^2; ----, 2000 kg/cm^2; ······, 3000 kg/cm^2.

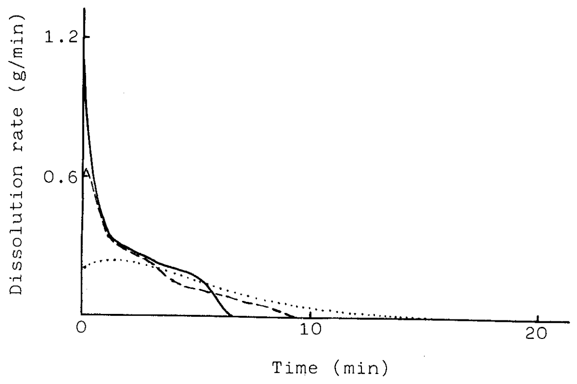

Fig. 7. Dissolution Rates of Sodium Chloride Tablets Calculated by the Calorimetric Method

Compression pressure: ——, 1000 kg/cm^2; ----, 2000 kg/cm^2; ······, 3000 kg/cm^2.

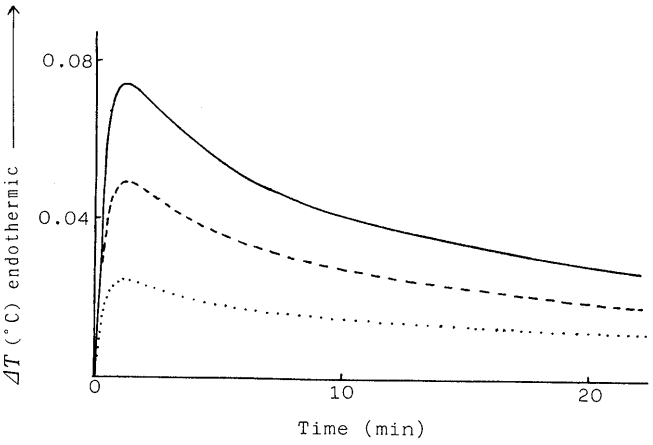

Fig. 8. Thermograms for Dissolution of Sodium Chloride Powder

——, 0.3 g; ----, 0.2 g; ······, 0.1 g.

impulse response, h(t). Figure 4 shows the relationship between the weight and heat absorbed with dissolution of sodium chloride powders. A linear relationship between the heat of solution and weight of sample was observed in the weight range between 0 and 0.4 g. The heat absorbed with dissolution of the powder was almost the same as that of tablet. These results indicated that the rate of heat evolution, f(t), obtained by the deconvolution method was proportional to the dissolution rate of the tablets and powder. Consequently, the dissolution rate can be measured accurately by this method.

Dissolution Rate of Sodium Chloride Tablets Figure 5 shows the dissolution behavior of sodium chloride tablets compressed under 1000 kg/cm^2, determined by the titration and calorimetric method. Dissolution behavior obtained by the calorimetric method agreed well with that obtained by the titration method. Figure 6 shows the thermograms for the dissolution of sodium chloride tablets compressed under various pressures between 1000 and 3000 kg/cm^2. Figure 7 shows the dissolution rate of sodium chloride tablets determined by the calorimetric method, the rate decreased markedly with increasing compression pressure.

Dissolution Rate of Sodium Chloride Powder Figure 8 shows thermograms for the dissolution of sodium chloride powders. The dissolution rates determined by the calorimetric method are shown in Fig. 9. These results indicated that sodium chloride powders dissolved independently of weight within the same period of time. There are several reports concerning the application of the cube root law$^{6)}$ to the dissolution process.$^{7,8)}$ Pedersen suggested that

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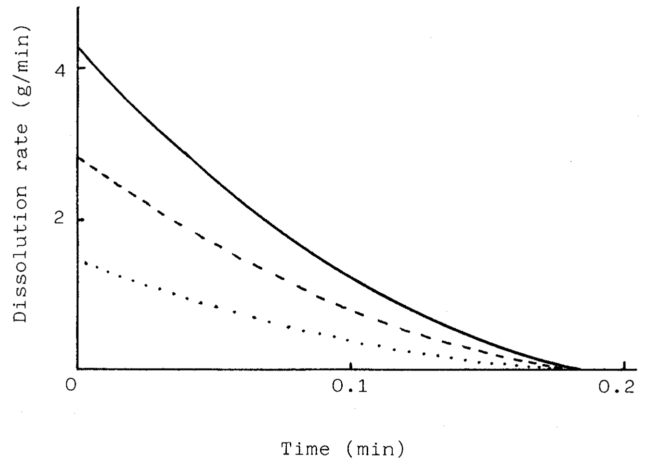

Fig. 9. Dissolution Rates of Sodium Chloride Powder Calculated by the Calorimetric Method

——, 0.3 g; ----, 0.2 g; ······, 0.1 g.

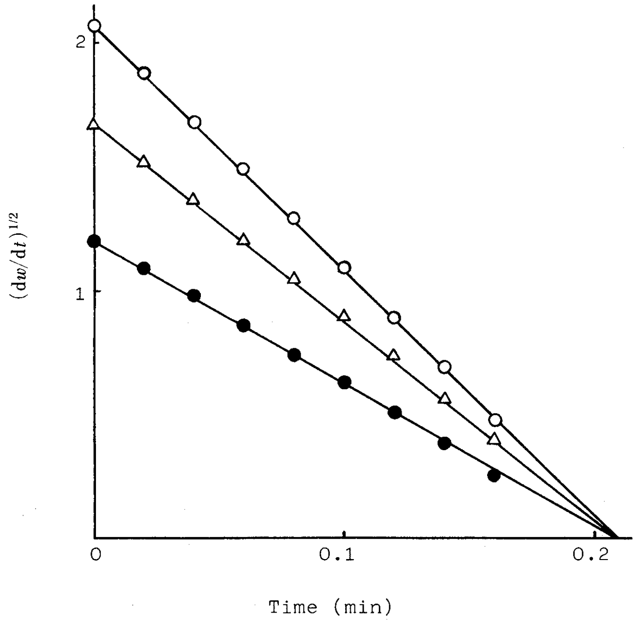

Fig. 10. Relationship between $(\mathrm{d}w/\mathrm{d}t)^{1/2}$ and t

○, 0.3 g; △, 0.2 g; ●, 0.1 g.

when a single particle dissolved according to the cube root law, a linear relationship should be obtained between the square root of the dissolution rate ($\mathrm{d}w/\mathrm{d}t$) and time (t).[8] Figure 10 shows the square root of dissolution rates of sodium chloride powders plotted against time. From Fig. 10 it is clear that a plot of $(\mathrm{d}w/\mathrm{d}t)^{1/2}$ *vs.* t is shown to be a straight line, regardless of the sample weight. This further confirms that the results obtained by the calorimetric method were valid.

In conclusion, the dissolution rate of sodium chloride can be determined by the calorimetric method, and this method may also be applicable to many other pharmaceuticals.

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