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Dissolution Behavior of Solid Drugs. I. Improvement and Simplification of Dissolution Rate Measurement, and Its Application to Solubility Determinations[1]

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A stationary disk method for dissolution rate measurement in aqueous solution was improved and simplified. Also its application to solubility determination has been attempted for substances such as salicylic acid and benzoic acid, and satisfactory results were obtained in rather short time. Polyvinylchloride (PVC) powder was used as an inert solid "binder," and was mixed with sample powder to form into disks, if a substance cannot be prepared into the compressed disk in pure powder form. No effect of PVC on solubility determination was observed. Also, results obtained by application of the method to sulfathiazole polymorphic forms were discussed, and their solubilities were determined to be 479.2 mg/liter and 819.2 mg/liter for the stable form and the metastable form, respectively.

A drug administered orally in solid dosage form must generally dissolve before it can be absorbed. There are a large number of organic medicinals which are only slightly soluble in gastrointestinal fluids, and in such cases the dissolution rate of a solid dosage form is one of the most important factors determining the rate of absorption. Therefore, a knowledge of the dissolution rate of each medicinal is useful for pharmaceutical formulation, and improvements or simplifications of the method of dissolution rate measurement are of significance to pharmaceutical technology.

A number of studies on dissolution rate measurement have been presented recently in the literature. In particular, dissolution rate measurements utilizing a constant sample surface area have received much attention. Disks provide a convenient means of insuring a constant and reproducible sample surface area, and various disk methods have been developed,[3] such as the rotating or stationary disk procedures. However, a basic requirement for disk methods is that powder of sample material can be formed into a disk by heavy compression. Thus, substances which cannot be formed in this manner are not able to be studied by disk methods.

In the present study, a modified disk method to obtain the dissolution rate more easily and rapidly was proposed and applied for determining the solubility of the dissolving solid. Also, the use of a solid "binder" which is completely insoluble in the dissolution medium and is inert to the sample material was attempted to make the method applicable even to substances which cannot be formed into disks in pure state. Dissolution rates for disks of both pure sample and sample-binder mixtures were determined by a stationary disk method. The results obtained were compared and the applicability of the disk containing an inert "binder" to the dissolution rate measurement was discussed.

Theoretical

The analysis of experimental dissolution rate data is generally based on the assumption that the Noyes-Whitney and Noyes-Nernst equations are valid if the dissolution process

1) Presented at the 90th Annual Meeting of Pharmaceutical Society of Japan, Sapporo, July 1970.
2) Location: *9-1, Shirokane 5 chome, Minato-ku, Tokyo.*
3) G. Levy and B.A. Sahli, *J. Pharm. Sci.*, **51**, 58 (1962); G. Levy and W. Tanski, *ibid.*, **53**, 679 (1964); E. Nelson, *Chem. Pharm. Bull.* (Tokyo), **10**, 1099 (1962); H. Nogami, T. Nagai, and A. Suzuki, *ibid.*, **14**, 329 (1966); G. Levy, *J. Pharm. Sci.*, **52**, 1039 (1963); E. Nelson, *J. Am. Pharm. Assoc., Sci. Ed.*, **47**, 297, 300 (1958); E. Nelson, *ibid.*, **46**, 607 (1957).

at the solid-liquid interface is rate-limited by diffusion from the very thin-layer of saturated solution at the solid surface into the bulk liquid, as expressed by,

$$\frac{dC}{dt} = K(C_s - C) \tag{1}$$

and

$$\frac{dC}{dt} = \frac{SD}{V\delta}(C_s - C) \tag{2}$$

where dC/dt is the dissolution rate of a drug, C_s is its saturated concentration, C is the concentration at time t during dissolution, S is the surface area of the solid, D is the diffusion coefficient, δ is the thickness of the diffusion layer, and V is the volume of dissolution medium. In the present study, since the sample surface area was kept constant from sample to sample by preparing a disk, a constant volume of aqueous solution was employed as the dissolution medium, an agitation rate which is constant and large enough that its variation had no effect on the dissolution rate was used, and a sample holder was used to fix the location and orientation, $SD/V\delta$ in Eq. (2) should be constant for a given sample material and is expressed as Eq. (1). Under these experimental conditions, Eq. (1) predicts a linear relationship between dC/dt and C. When the dissolution rate of the sample is relatively small, the following relation in Eq. (3) will be held, providing that the sample disk is hard enough to maintain a constant surface area for dissolution during the test interval and that small values of Δt are chosen.

$$\frac{dC}{dt} \fallingdotseq \frac{\Delta C}{\Delta t} = K(C_s - C) \tag{3}$$

Therefore, if the initial dissolution rates $\Delta C/\Delta t$ of such sample substance in its solutions having various fixed concentrations are plotted against these concentrations, a linear curve will be obtained. The extrapolation of the line to its intersection with the concentration axis will give the solubility of the sample (C_s) at the experimental temperature. It is said that the solubility of a metastable polymorphic substance is difficult or impossible to determine by usual equilibrium method because rapid conversion to the stable form occurs usually when it comes into contact with its solution. Such a metastable solubility will be, however, easily estimated by application of the above dissolution method, if the time of exposure is short enough to sustain the polymorphic transition.

Result and Discussion

In order to test whether the method outlined above is applicable or not, salicylic acid (SA) and benzoic acid (BA) which are slightly soluble in water were chosen as model drug substances. As an inert "binder" for disk preparation, polyvinylchloride (PVC) powder was used, since it is completely insoluble in water.

It is widely known that the solubility of the metastable form of sulfathiazole at lower temperatures (β-form of ST) is difficult to determine in aqueous solution because of rapid conversion to the stable form (α-form of ST).[4,5] Although only Kuhnert-Brandstätter, *et al.*[6] have reported that they could obtain the individual solubility of each form of ST in water and in isopropanol by solubility equilibrium method, they gave only simplified results and the numerical data were omitted. Therefore, sulfathiazole was adopted in the present study as a representative for determining metastable solubility.

Relationship between Dissolution Rate and Particle Size

Disks made from different particle sizes of BA were used to determine the effect of particle size on dissolution rate. However, no size effect was observed as shown on Table I,

4) W.I. Higuchi, P.D. Bernardo, and S.C. Mehta, *J. Pharm. Sci.*, **56**, 200 (1967).
5) G. Milosovich, *J. Pharm. Sci.*, **53**, 484 (1964).
6) M. Kuhnert-Brandstätter and A. Martinek, *Mikrochim. Acta*, **5–6**, 909 (1965).

in agreement with the findings of Milosovich.[5] The sample particle size in the range of 63—149 μ was used throughout the study.

TABLE I. Effect of Particle Size of Benzoic Acid on Dissolution Rate in Water at 25°

Particle size of BA used for disk preparation	Dissolution rate (mg/ml·min) × 10^3	
	Pure BA disk	BA:PVC(2:1)disk
63—149μ	9.9	4.8
149—250μ	9.9	4.9
Larger than 590μ	9.9	4.8

Relationship between Dissolution Rate and Compression Force

It was found experimentally that compression force over five tons exerts no influence on dissolution rate as shown in Fig. 1. For the data presented below, all disks were prepared under evacuation with a compression force of 10 tons, applied for 5 minutes.

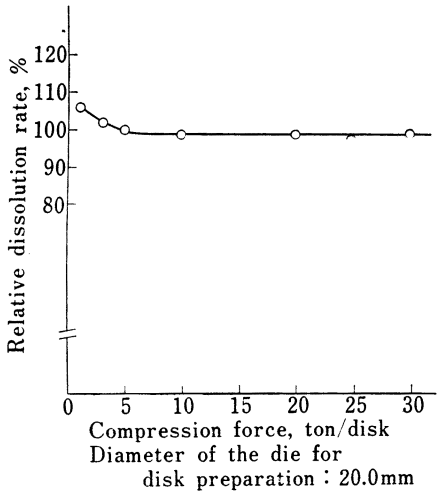

Fig. 1. Effect of Compression Force on Dissolution Rate of Benzoic Acid in Water at 25°

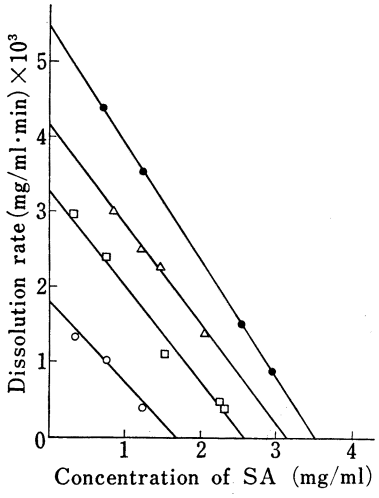

Fig. 2. Dissolution Rate versus Concentration of SalicylicAcid, at 20° (○), 30° (□), 35° (△), and 40° (●)

Solubilities determined by the Dissolution Rate Measurement

i) **Salicylic Acid**——The relationship between dissolution rate $\Delta C/\Delta t$ and the starting concentration of the bulk solution of SA at experimental temperatures are shown in Fig. 2.

TABLE II. Solubility of Salicylic Acid determined by Dissolution Rate Measurement and by Conventional Equilibrium Method in Water at Various Temperatures

Temperature (°C)	Solubility, obtained by	
	Dissolution rate	Conventional method
20	1.66 mg/ml	1.79 mg/ml
30	2.57	2.58
35	3.12	3.14
40	3.51	3.69

The straight lines in the figure were drawn by the least squares method. The values of solubility at 20°, 30°, 35°, and 40° were found to be 1.66 mg/ml, 2.57 mg/ml, 3.12 mg/ml, and 3.51 mg/ml, respectively, by the extrapolation of each line. They are in very good agreement with the values obtained by conventional solubility equilibrium method as shown on Table II.

ii) Benzoic Acid——The powder mixtures of BA and PVC at various mixing ratios could be formed into compressed disks which were rigid enough for the present dissolution measurement. At a temperature of 25°, the relationship between $\Delta C/\Delta t$ and the starting concentration of BA for pure BA disk and for disks made from mixtures of BA and PVC (precisely 2: 1 and 1: 1 in the weight ratio) are shown in Fig. 3. In regard to solubility, the values obtained from the disks made from BA–PVC powder mixtures, (2: 1) and (1: 1), were 3.22 mg/ml and 3.25 mg/ml, respectively, although the dissolution rate does not vary in direct proportion to the weight fraction of BA used in preparation of the disk. These are in good agreement with the values 3.21 mg/ml obtained from pure BA disks and 3.33 mg/ml obtained by the conventional solubility equilibrium method. Thus, it is said that Eq. (3) is applicable to the analysis of dissolution rate data for SA and BA, under the conditions of these experiments, including the utilization of a 15 minute exposure time (Δt), and that the use of PVC as a solid binder yields successful results for estimation of solubility. In addition, to confirm the dissolution rate remained essentially constant during the 15 minute exposure time, bulk phase concentrations were measured automatically by an ultraviolet (UV) spectrophotometer attached with a flow cell type of apparatus.[7] No detectable difference between ($\Delta C/\Delta t$) at $\Delta t \to$o and at Δt=15 minutes was observed.

iii) Sulfathiazole——The characterization of the sulfathiazole crystal forms were done by differential scanning calorimetry (DSC), infrared spectrophotometry (IR), and X-ray diffractometry. Recording charts are shown in Fig. 6—8. Higuchi, *et al.*[4] and Milosovich[5] reported that the conversion of β-form to α-form should be rapid in water and in aqueous alcohol. We also noticed the conversion with the crystals of β-form which were obtained by heat conversion of α-form or by crystallization from *n*-propanol in early stage of the investigation. However, it was observed that even such an "unstable" crystals remained

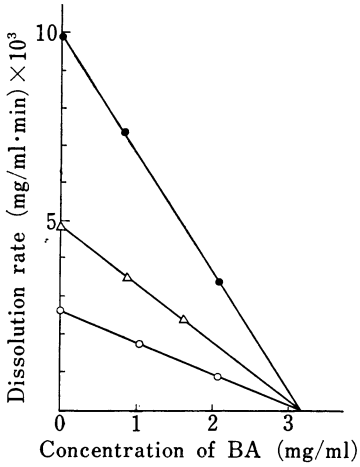

Fig. 3. Effect of PVC on Dissolution Rate of Benzoic Acid in Water at 25°

●: disks made from pure BA
△: BA:PVC (2: 1)
○: BA: PVC (1: 1)

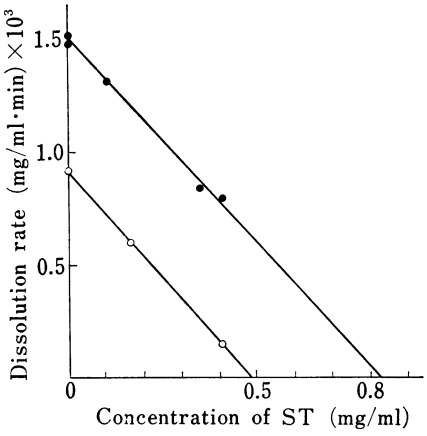

Fig. 4. Dissolution Rate versus Concentration of Sulfathiazole Polymorphs in Water at 25°

○: disks made from α-ST: PVC (2: 1)
●: β-ST: PVC (2: 1)

7) The wavelength of 259.5 mμ was used for the determination of concentrations, and the apparatus and procedure adopted were the same as those being described in succeeding publication.

unchanged, if an exposure time was limited within several minutes. In addition, after many trials of crystallizations from *n*-propanol, we had succeeded in obtaining the crystals of β-form which were practically very stable, even though they were metastable from a thermodynamic standpoint. No conversion of the β-form to the α-form was, in this case, detected in water medium during dissolution measurements and conventional solubility determination in the present study. Characteristic patterns of X-ray diffraction, DSC, and IR of the practically "stable" crystals of β-form were identical with those of "unstable" crystals of β-form which were also obtained from *n*-propanol and converted into α-form in water medium very rapidly. We presume that the stability of the "stable" crystals is thought to be due to few lattice defect. The dissolution rates of both forms of ST were determined by use of disks made from ST-PVC powder mixtures, because compression of ST powder was rather difficult. The dissolution data of both forms obtained are shown in Fig. 4, and solubilities for α- and β-ST were estimated to be 0.479 mg/ml and 0.819 mg/ml, respectively. The solubility values for both forms of ST determined by conventional equilibrium method are being presented in succeeding publication.

The diffusion coefficient D in equation (2) would be expected to be the same for both forms of ST. Thus, the dissolution rate constant K in equation (1) should be the same for both forms. If this is the case, then even if the metastable form is unstable under the experimental conditions, the dissolution rate can still be measured at only one concentration, using a short term measurement to avoid conversion. The solubility of β-form can then be calculated from this dissolution rate and the K obtained from dissolution rate data of stable α-form. It is apparent from Fig. 4, that the plots obtained by dissolution rate measurements of α-form and β-form are very nearly parallel. This indicates that the experimental K values for both forms are essentially equal, and the calculation of β-form solubility described above is valid.

Experimental

Materials——Salicylic acid and benzoic acid of the JP grade were purified twice by recrystallization from distilled water. The α-form, or form I, of sulfathiazole which is stable at lower temperature range was obtained by crystallization from distilled water and melted on rapid heating at 173—175°, while β-form, or form II, of sulfathiazole which is stable at high temperature was obtained by recrystallization of JP VII grade product from *n*-propyl alcohol and melted at 200—202°. Polyvinylchloride, OPALON 440, Mitsubishi Monsanto Co. Ltd., mean particle size less than 1 μ was used as a solid binder, because it is completely inert and insoluble in water medium and was easily compressed into disks at various mixing ratios with sample powders under investigation in this study. 0.01N NaOH solution and Bromothymol Blue (BTB) indicator were used for titration of SA and BA.

Preparation of Sample Disks——Preparation of disks were done by compressing approximately 800 mg of powder in an evacuable die between 20 mm diameter punches, using hydraulic press. The sample disks

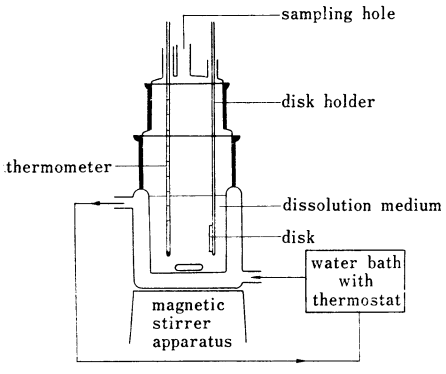

Fig. 5. Apparatus for Dissolution Rate Measurement

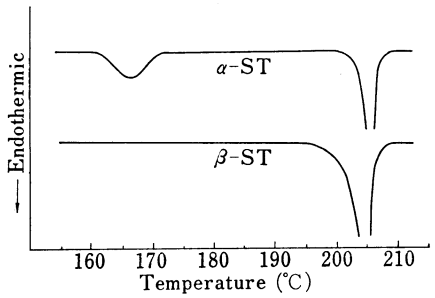

Fig. 6. DSC Curves of Sulfathiazole Polymorphs using Solid Sample Pan (Semi-closed Condition)

heating rate: 8°/min
sample weight: 10.0 mg

were prepared from pure SA, pure BA, mixture of BA and PVC (precisely 2: 1 and 1: 1 in the weight ratio), mixtures of α-ST and PVC (2: 1), and of β-ST and PVC (2: 1). The die walls and punches were not lubricated.

Apparatus and Procedure——The apparatus adopted for dissolution rate experiments is shown in Fig. 5. A disk prepared as described above was mounted on a glass disk holder with molten paraffin (mp 65°). Only the upper face of the disk was left free of paraffin so that a constant surface area was exposed. 100 ml of distilled water or solution of specific drug concentrations for BA and ST, and 50 ml for SA were placed in the water jacketed measurement cell. A constant cell temperature was maintained by circulating water from a thermostatically controlled water bath through the cell jacket. The teflon coated magnetic stirrer was used at a constant speed of 600 rpm using a synchronous motor. After bringing the dissolution medium to the desired temperature, the sample disk, mounted on the disk holder, was introduced into the cell and fixed at a position 1.5 cm from the bottom of the cell, with the exposed surface of the disk facing the center of the cell. 15 minute exposure times were adopted for SA and BA, and 3 minute exposures for both forms of ST to avoid possible conversion from metastable form to the stable one.

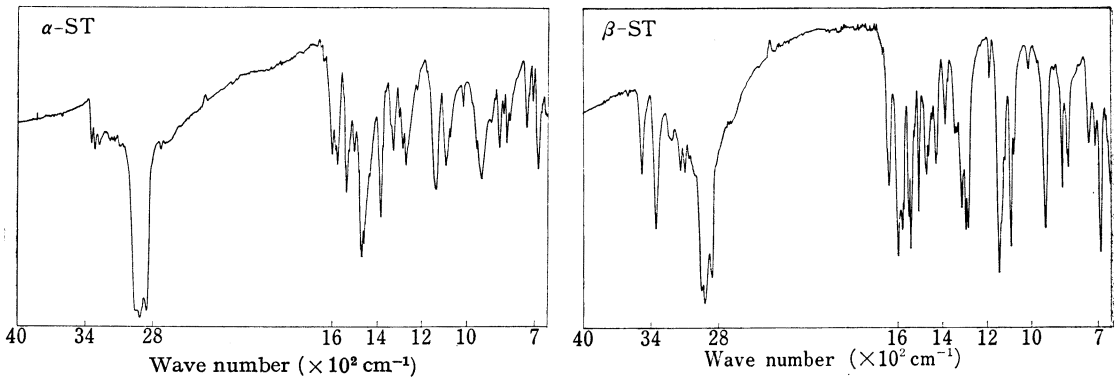

Fig. 7. Infrared Absorption Spectra of Sulfathiazole Polymorphs (nujol mull)

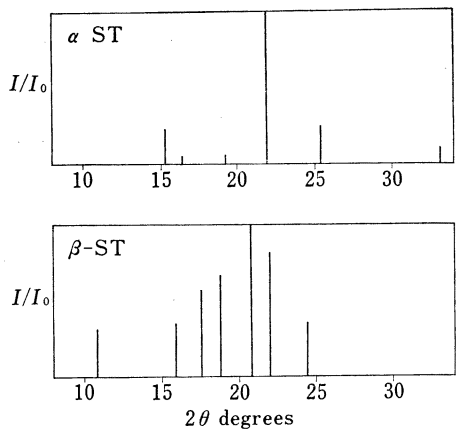

Fig. 8. X-Ray Diffraction Patterns of Sulfathiazole Polymorphs

Determination of Sample Concentrations——An aliquot of dissolution medium were withdrawn and filtered through a 0.45 μ membrane filter (Millipore HAWP 01300). The sample solution of SA and BA were suitably diluted and titrated with 0.01N NaOH solution, using BTB indicator. Concentrations of sample solutions of α- and β-ST were determined using an ultraviolet (UV) spectrophotometer (Hitachi Perkin-Elmer 139) at the wave length of 283 mμ, after suitable dilution of the sample solution.

Characterization of ST Polymorphic Forms——Three methods were used for determination of polymorphic forms of ST. These were: Differential scanning calorimetry (DSC), using a Perkin-Elmer DSC-1B Differential Scanning Calorimeter. Infrared spectrophotometry (IR), using a Jasco IRA-1 Grating Infrared Spectrophotometer. X-ray diffraction analysis, using a Rigaku Geigerflex 2030 X-ray Powder Diffraction Analyzer (Ni filter, Cu-Kα ray $\lambda = 1.542$ Å). The detailed experimental conditions are shown in Fig. 6—8.

Solubility Measurement by Equilibrium Method——Excess sample powder was placed in water contained in the jacketed cell which is the same type of apparatus used for dissolution rate measurement. Concentrations of BA and SA were measured half-hourly intervals until attaining the concentration equilibrium at 25° for BA and 20°, 30°, 35°, and 40° for SA. The detailed data on ST are going to be presented in succeeding publication.

Conclusion

The dissolution rate measurement method proposed in this study is rather simple, and the data obtained were analized easily based on the Noyes-Whitney equation. Applying

the method to solubility determination, the reliable values for SA and BA, as well as for polymorphic crystal forms of ST were obtained in rather short time. Although it is said that solubility of ST metastable form is difficult to obtain in aqueous solution practically, because conversion of metastable form to the stable one is occurred rapidly in solution medium, we could determine the metastable solubility by the present dissolution rate measurements adopting a very short exposure time. Furthermore, if a substance cannot be prepared into the compressed disk in pure state, mixing of PVC powder with the sample powder promotes successful disk formation and allows the application of the disk method to solubility determination of many kinds of pharmaceuticals. In addition, it was confirmed that the dissolution for SA and BA is considered to be the diffusion-controlled process under the experimental conditions, because (1) the thickness of diffusion layer at 25° were calculated to be 2.31×10^{-3} cm and 2.97×10^{-3} cm for SA and BA,[8] respectively, and (2) the activation energy for dissolution of SA was calculated to be 3.13 kcal/mole.

8) Those values were calculated by the following equations in which values of K were obtained from the experimental data.

$$D=\frac{kT}{6\pi\mu r}\text{(Stokes–Einstein Eq.)} \tag{4}$$

$$K=\frac{SD}{V\delta} \tag{5}$$

D: diffusion coefficient, k: Boltzmann constant, T: absolute temperature, μ: viscosity (values of water were adopted), r: radius of a solute molecule