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Dissolution of slightly Soluble Drugs. I. Influence of Particle Size on Dissolution Behavior[1]

Nobuyoshi Kaneniwa and Nobutoshi Watari

School of Pharmaceutical Sciences, Showa University[2]

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To clarify the influence of particle size on dissolution behavior, relationship between the particle size and dissolution rate was investigated using three powdered sulfonamides, and following results were obtained.

1) At particle size below 300 μ, the lines obtained by plotting dissolution rate *versus* time have positive intercepts and the values of intercepts increase qualitatively with decrease in particle size. At above 300 μ, the lines pass closely through the origin. The fact indicates that the critical particle size is at about 300 μ in the initial dissolution process.

2) Plot of the dissolution rate constants against rotating speed showed a straight line having an inflexion at 500 rpm (Nf) in spite of various particle sizes. Above Nf, the slopes of these lines do not vary with change in particle size but below Nf, these increase with decrease in particle size.

It is well known that the particle size of slightly soluble drugs affects its blood level or its clinical effect.[3] If drugs are given in the solid form it should dissolve in order to be absorbed. There are a large number of drugs which are only slightly soluble in gastrointestinal fluid and in such cases the dissolution rate of a solid dosage form is one of the most important factors determining the rate of absorption. From this point of view the particle size is an important parameter of dissolution process of water-insoluble powdered drugs.

Previously, many workers reported methods for measurement of dissolution rate, and many use the condition of constant surface area. Some use the condition of powders in which their surface areas are allowed to change with time in the dissolution process.[4] However, there is no report to explain a clear rank order of the particle size of powders for dissolution. Therefore, in order to clarify the influence of particle size on dissolution behavior, we investigated relationship between particle size and its dissolution rate using various particle sizes of powdered sulfonamides.

Theoretical

The dissolution rate of a solid in its own solution is described by the Noyes–Nernst equation:

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[1] Presented at the 93rd Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1973.

[2] Location: *Hatanodai, Shinagawa-ku, 142, Japan.*

[3] J.G. Reinhold, F.J. Phillips, and H.F. Flippin, *Am. J. Med. Sci.*, **210**, 141 (1945); E.M. Boyd and R.S. Dingwall, *ibid.*, **213**, 549 (1947); R.M. Atkinson, C. Bedford, K.J. Child, and E.G. Tomich, *Antibiot. Chemother.*, **12**, 232 (1962); *idem, Nature*, **193**, 588 (1962); K. Kakemi, T. Arita, and T. Koizumi, *Yakugaku Zasshi*, **82**, 261 (1962); K. Kakemi, T. Arita, and S. Ohashi, *ibid.*, **82**, 1468 (1962); J.H. Fincher, J.G. Adams, and H.M. Beal, *J. Pharm. Sci.*, **54**, 704 (1965); L. Renoz, *J. Pharm. Belg.*, **22**, 41 (1967); H.E. Paul, E.J. Hayes, M.F. Paul, and A.R. Borgmann, *J. Pharm. Sci.*, **56**, 882 (1967); J.H. Fincher, *J. Pharm. Sci.*, **57**, 1825 (1968); T. Takubo, S. Tsuchiya, and M. Hiura, *Yakuzaigaku*, **31**, 298 (1971).

[4] A.W. Hixon and J.H. Crowell, *Ind. Eng. Chem.*, **23**, 1002, 1160 (1931); P.J. Niebergall and J.E. Goyan, *J. Pharm. Sci.*, **52**, 29 (1963); P.J. Niebergall, G. Milosovich, and J.E. Goyan, *ibid.*, **52**, 236 (1963); I. Ullah and D.E. Cadwallader, *J. Pharm. Sci.*, **59**, 979 (1970); *ibid.*, **60**, 230, 1496 (1971).

$$\frac{dC}{dt}=\frac{DS}{\delta V}(C_s-C) \tag{1}$$

where dC/dt is the dissolution rate, S, the surface area of the solid, D, the dissolution coefficient, C_s, the saturated concentration, C, the solute concentration in the bulk medium, δ is the diffusion layer thickness, and V is the volume of the medium.

In the present study it was assumed that powder particles are all spherical. The total surface of the particles is expressed by the next equation:

$$S_0=\pi d_0^2 n \qquad S=\pi d^2 n \tag{2}$$

Likewise the total weight of this mass of particles is:

$$W_0=\frac{1}{6}\pi d_0^3 n\rho \qquad W=\frac{1}{6}\pi d^3 n\rho \tag{3}$$

where d_0 and d are the diameter of the particle at the initial and at time t, S_0 and S are the total surface area of the particles at the initial and at time t, W_0 and W are the total weight of the particles at the initial and at time t, n is number of particles in the constant weighted mass in each particle size grade, and ρ is the density of the particle. From Eq. (2) and (3), the next equation is induced:

$$S_0=\frac{6}{\rho d_0}W_0 \qquad S=\frac{6}{\rho d_0}W_0^{1/3}W^{2/3} \tag{4}$$

where $6/\rho d_0$ is the specific surface area of the powders.

Initially, $C\ll C_s$ and the surface area S and the volume V can be kept constant. Under these conditions and the conditions of constant agitation, Eq. (1) is reduced to:

$$\frac{dC}{dt}=\frac{DS}{\delta V}C_s \tag{5}$$

The surface ares, S, in Eq. (5) is replaced with S_0 in Eq. (4) and integrated under the condition that W' is equal to zero at time zero, and gives:

$$W'=K_1 t \tag{6}$$

where W' is the amount of the solid dissolved at time t, and $K_1=6DW_0C_s/\delta\rho d_0$ is the apparant dissolution rate constant.

Hixon–Crowell also derived an equation[5] for the dissolution of a single particle in which the surface area was allowed to change with time, using the following form of the Noyes–Whitney equation:

$$v\frac{dw}{dt}=-ks(w_s-w_0+w) \tag{7}$$

in which k is the rate constant, s is the surface area of the particle, w is the weight of particle at time t, w_s is the weight of solid required to saturate the volume, v, of a solvent, and w_0 is is the initial weight of the particle.

Using the property of geometrically similar solids, Hixon and Crowell replaced the surface area, s, by Eq. (4) and if the shape factor remains constant as the particle dissolves, their basic equation will be extended for use in multiparticulate systems by assuming a system of n equal-sized particles.

When the amount of solute needed to saturate a given volume of solvent is much greater than the concentration of material in solution, $C_s\gg C$, and Eq. (7) becomes:

$$V\frac{dW}{dt}=-6KW_0^{1/3}Ws/\rho d_0\ W^{2/3} \tag{8}$$

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[5] A.W. Hixon and J.H. Crowell, *Ind. Eng. Chem.*, 23, 923 (1931).

which, upon integration under the condition that W is equal to W_0 at time zero, gives:

$$W_0^{1/3}-W^{1/3}=K_2t \tag{9}$$

where $K_2=2KW_0^{1/3}W_s/\rho d_0V$ is the apparant dissolution rate constant.

Likewise when the amount of sample used is equal to the amount required to saturate the solutiom, W_s is equal to W_0, and Eq. (7) becomes:

$$V\frac{dW}{dt} = -6KW_0^{1/3}/\rho d_0\ W^{5/3} \tag{10}$$

which upon integration under the condition that W is equal to W_0 at time zero, gives:

$$W^{-2/3}-W_0^{-2/3} = K_3t \tag{11}$$

where $K_3=4KW_0^{1/3}/\rho d_0V$ is the apparant dissolution rate constant.

Experimental

Sample——Commercial sulfadiazine, sufisomezole and sulfamethizole used were of the JP grade. The different particle size grades were obtained by sieving twice through Ro-Tap testing sieve shaker, using Japan Industrial Standard (JIS) sieves. Of these sulfonamides, sulfisomezole occurs in polymorphic form and the sample used was found to be form I by the agreement of its X-ray diffraction and infrared (IR) spectral data with those reported by Yang and Guillory.[6] Particle size and other data are listed in Table I. The symbols in Table I are used in all the graphs in this report.

TABLE I. Sample Size

Compound	Sieving method											
	Tyler mesh	200/250	170/200	115/150	80/100	65/80	60/65	48/60	42/48	32/35	28/32	24/28
	Diameter (μ)	68	81	115	163	194	230	274	324	460	545	650
	Symbols	●	◑	⦶	◐	⊕	◓	⊖	◒	○	◎	⊙
Sulfamethizole	microscopic method (green diameter) d_{VS} (μ)	90	*a*)	191	272		380		525	740		996
Sulfisomezole						248	297	377	457	620		753
Sulfadiazine			132	186	332		529		570	686	*a*)	

a) not measured

About 500 particles of each fraction were taken to measure the Green diameter by the microscope method and their mean volume-surface diameter calculated from these values, are given in this table. As sulfadiazine was needle crystals, the mean volume-surface diameter became considerably larger than the arithmetic mean diameter of the sieve sample. In the present paper, this arithmetic mean diameter of sieve sample is taken as the mean diameter of the sulfonamides particles. All sample fractions sieved showed a normal distribution as indicated in Fig. 1.

Apparatus and Procedure for Measurement of Dissolution Rate——For the measurement of dissolution rate, the apparatus shown in Fig. 2 was used. Three-necked, round bottomed jacketed flask containing 500 ml of distilled water, was maintained at a constant temperature of 37°±0.05° by circulating water from a thermostatically controlled water bath through the jacket. The liquid in the flask was agitated by a stirrer, 8 mm steel shaft in diameter and with a three-blade propeller which was positioned 2.5 cm from the bottom of the flask at the center. Three-one moter (Shinto Scientific Corp.) was used to obtain the desired rotating speed. After bringing the dissolution medium to the desired temperature 37°, the stirrer was rotated. When it became stationary state at the desired rotating speed, constant weight of the sample in a boat was rapidly thrown into the dissolution medium at once. Then at certain intervals, 1 ml of the suspension was sampled out from the flask and was filtered immediately through a 0.025 μ membrane filter (Millipore VSWP 01300), and 0.5 ml of the filtered solution was diluted with distilled water at appropriate concentration to determine in each sulfonamide. The concentration of sulfonamides dissolved was determined spectrophotometrically using Hitachi Perkin-Elmer 139 UV-VIS spectrophotometer at the wave length of 264 nm for sulfadiazine, at 266 nm for sulfisomezole, and at 277 nm for sulfamethizole. All runs were made at least twice and the results were averaged.

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[6] S.S. Yang and J.K. Guillory, *J. Pharm. Sci.*, **61**, 26 (1972).

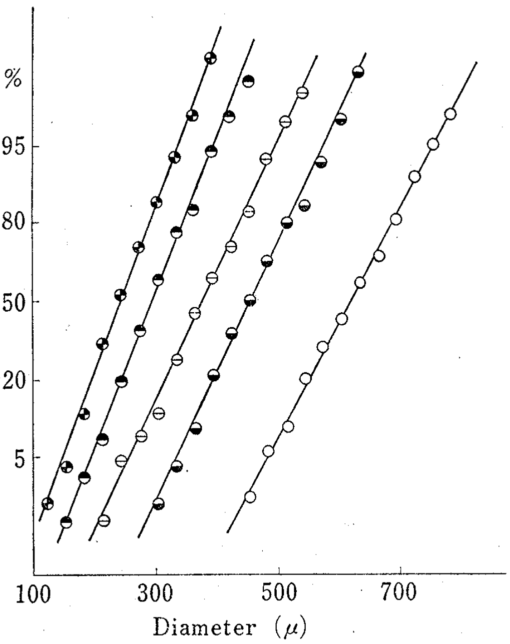

Fig. 1. Particle Size Distribution of Sulfisomezole shown on a Probability Diagram

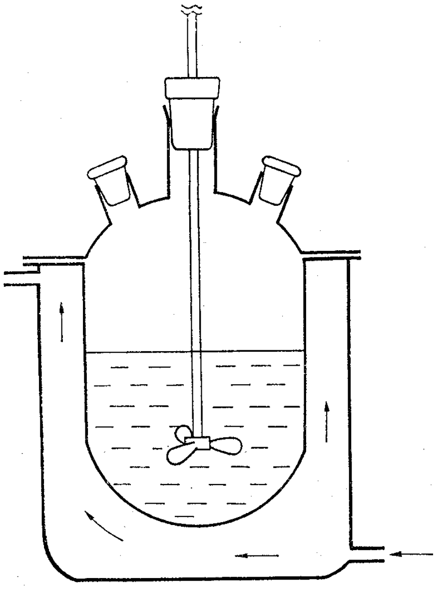

Fig. 2. Schematic Diagram of the Dissolution Apparatus

Solubility Determination——An excess of sulfadiazine or sulfisomezole, required to saturate medium, was placed in a flask containing 25 ml of distilled water. The flask was shaken (2 strokes/sec) at the amplitude of 3 cm, in a thermostatically controlled water bath at 37°±0.05°. One milliliter sample was removed every 6 hr using a warmed Millipore filter syringe with a filter pore size of 0.45 μ (Millipore HAWP 01300) and the filtrate was diluted with distilled water appropriately and assayed by spectrophotometry.

Result and Discussion

Influence of Particle Size on Dissolution Rate in Agitated Water

Four different particle sizes of sulfamethizole were used to test the dissolution rate under various agitation conditions in distilled water of 37°, and results are shown in Fig. 3.

The dissolution rate constant K_2 was plotted against rotating velocity N on a log-log graph and the values of b were obtained from the slopes of these lines. Each line showed an inflexion about 500 rpm (N*f*) and the following relationship was found:

$$K_2 = a(\mathrm{N})^b$$

where a and b are constants which depend on particle size. Some investigators[7] also found the same relationship between the dissolution rate and rotating velocity using other powdered drugs.

When agitator speed was greater than N*f*, suction of air was found to occur and the slopes of these curves became gentle in each line. It was seemed that at above N*f* the values of b did not vary with change in particle size but at below N*f* those increased with decrease in particle size.

It may be concluded that at above N*f*, the effective interface between a solid and a liquid is not influenced by agitation, and the degree of dispersion of powders is constant with agitation, but below N*f* the effective interface and the degree of dispersion of powders are influenced by agitation, and the logarithmic values of b *vs.* $1/d$ become linear, as shown in Fig. 4.

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7) A.W. Hixon and S.J. Baum, *Ind. Eng. Chem.*, 33, 478 (1941); *ibid.*, 34, 120 (1942); S. Nagata, M. Adachi, and I. Yamaguchi, *Mem. Fac. Eng. Kyoto Univ.*, 20, 72 (1958); P. Finholt, H. Kristiansen, O.C. Schidt, and K. Wold, *Med. Norsk Farm. Selskap.*, 28, 17 (1966).

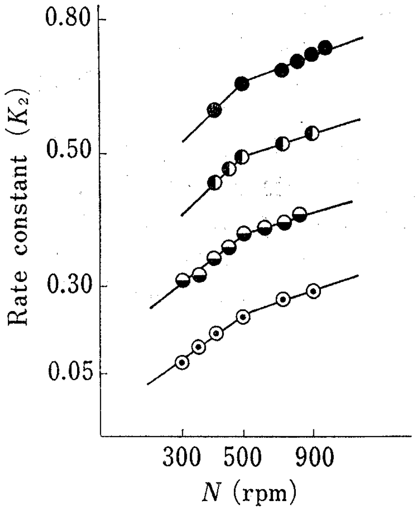

Fig. 3. Dependence of log Dissolution Rate Constant on log Rotating Velocity

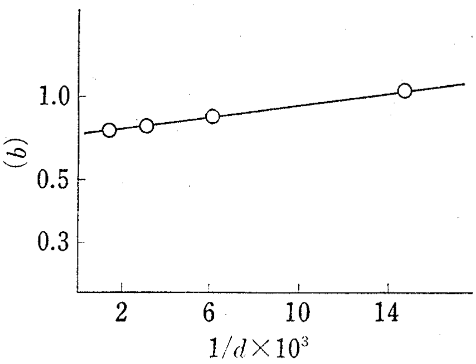

Fig. 4. Dependence of b on Particle Size

Influence of Particle Size on Dissolution of Three Sulfonamides

Three kinds of sulfonamides were sieved in particle size ranging from 60 to 700 μ and each fraction was used to investigate the dissolution behavior under the conditions of rotating velocity of 700 rpm, which was chosen as being rapid enough to insure complete suspension of the particles and instantaneous mixing in distilled water at 37°. The amount of sulfonamides used was just sufficient to saturate 500 ml of distilled water but the amount of sulfamethizole was 377 mg, which was less than its equilibrium solubility. These dissolution profiles are depicted in Fig. 5—7. The cumulative quantity (in mg) dissolved was plotted as a function of time. As expected, the plots were linear, Eq. (6) was applicable but in the case of sulfamethizole, which was more soluble than the others, its dissolution profile was not linear. Therefore, by applying Eq. (9), $(W_0^{1/3}-W^{1/3})$ was plotted against time and resulted in straight lines, which are shown in Fig. 8. The logarithmic plots of dissolution rate constants *vs.* particle size are shown in Fig. 9. The plots of apparant rate constants *vs.* particle size showed a straight line for each sulfonamide, having a slope of −1 for sulfisomezole and sulfamethizole, and −0.6 for sulfadiazine. These values of slopes agreed with those of slopes considered from Eq. (6) and (9) except for sulfadiazine. This disagreement of sulfadiazine

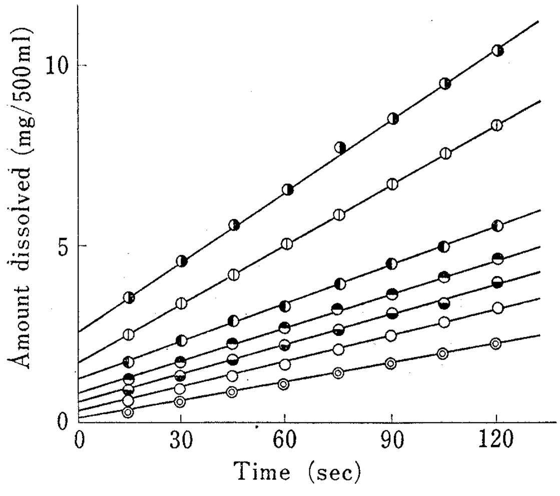

Fig. 5. Influence of Particle Size on Dissolution of Sulfadiazine

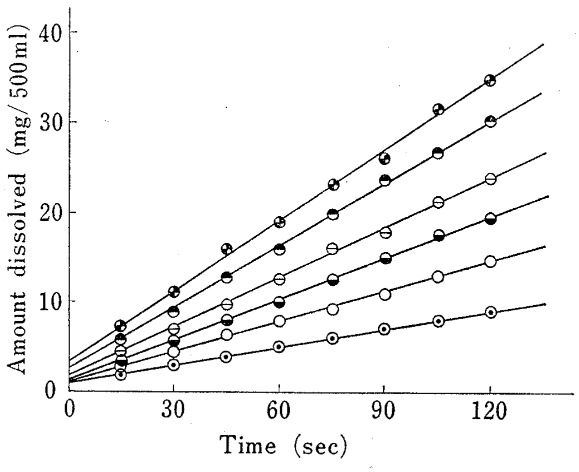

Fig. 6. Influence of Particle Size on Dissolution of Sulfisomezole

may be due to its crystal form which is a needle. From Eq. (6) and (9), the plots of these dissolution rate should be straight lines passing through the origin, but these lines did not pass through the origin and had positive intercepts, and the values increased qualitatively with decrease in particle size.

The large positive intercept of sulfisomezole in Fig. 6, in spite of larger particle size, may be due to its metastable form used. These positive intercepts were plotted as a function of the logarithm of particle size, shown in Fig. 10, in which the plots were linear lines having an inflexion at about 300 μ and in the region of the particle size smaller than 300 μ, the positive intercepts increased abruptly. This result indicates that when the particle size is below 300 μ.

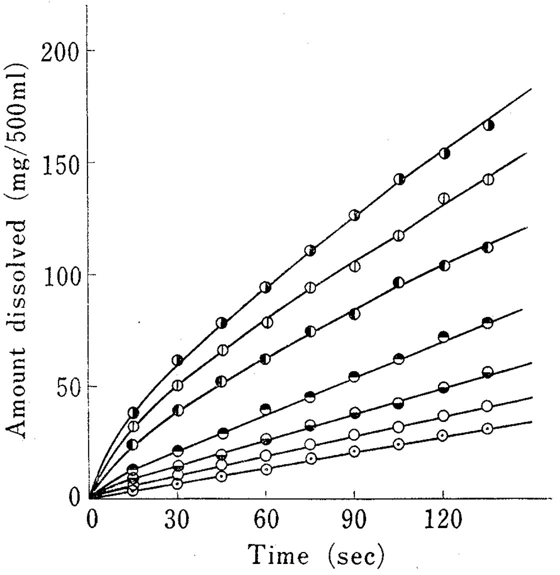

Fig. 7. Influence of Particle Size on Dissolution Profile of Sulfamethizole

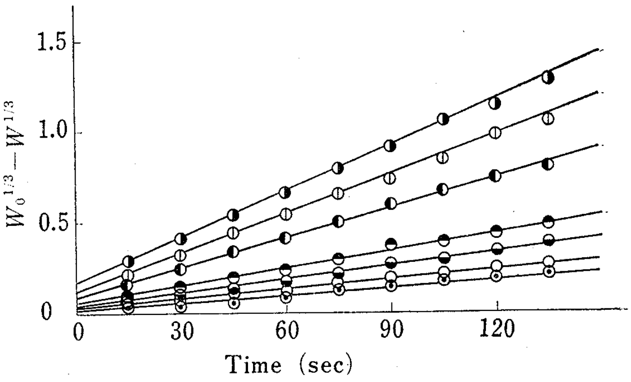

Fig. 8. Influence of Particle Size on Dissolution Rate of Sulfamethizole

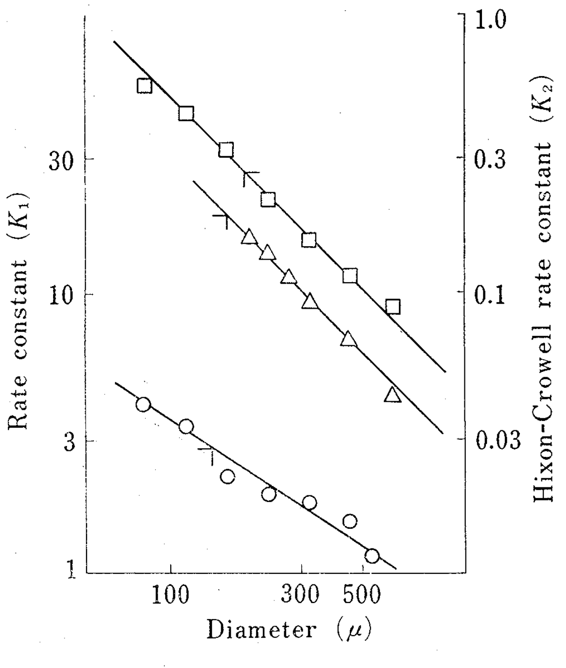

Fig. 9. Dependence of log Dissolution Rate Constants on log Particle Size

□: sulfamethizole, ○: sulfadiazine, △: sulfisomezole

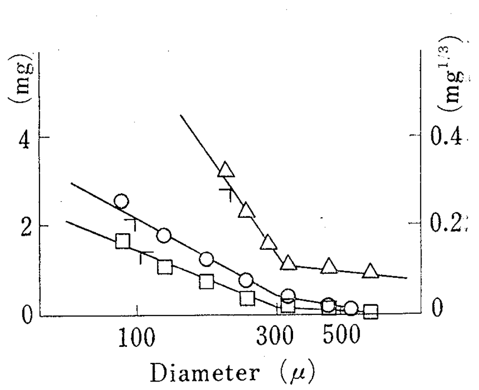

Fig. 10. Plot of the Positive Intercept *vs.* log Particle Size

□: sulfamethizole, ○: sulfadiazine, △: sulfisomezole the instantly dissolving parts increased with decrease in particle size and at first these parts dissolve instantly in the dissolution, and then the constant rate of dissolution followed. This fact suggests that surface free energy may play an important part in the initial dissolution process. The increase in the rate of dissolution with decrease in particle size is greater than that expected from the increase in surface area alone.

It is speculated that the active centers on the crystal are the edges and corners as well as points of crystal defects,[8] the increase of the surface free energy per gram of powder is considered to be due to the increase in the number of edges, corners, and crystal defects per gram with decrease in particle size.

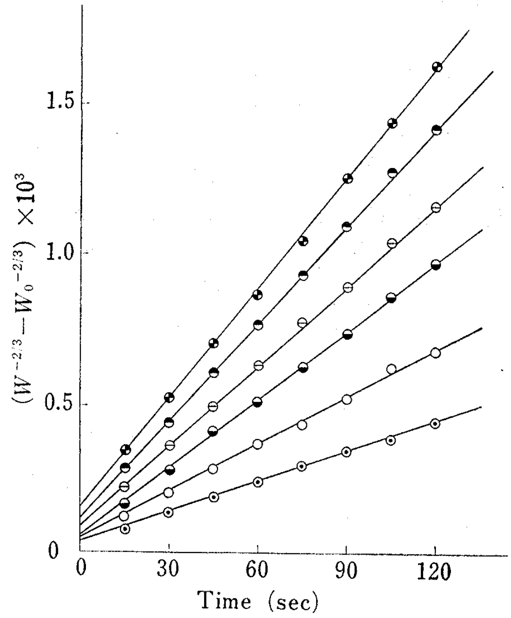

Fig. 11. Influence of Particle Size on Dissolution Rate of Sulfisomezole

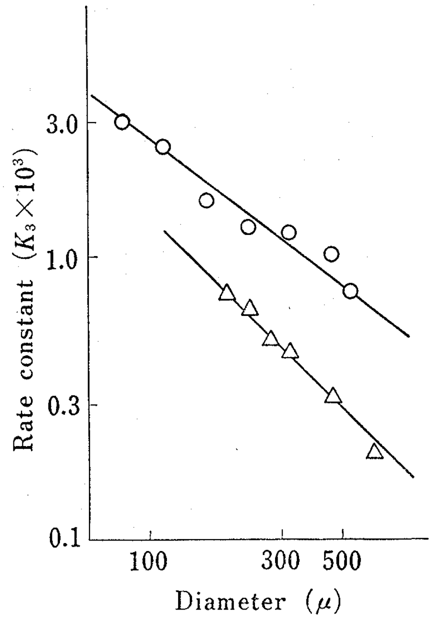

Fig. 12. Dependence of log Hixon-Crowell Rate Constant on log Particle Size

○: sulfadiazine, △: sulfisomezole

As the amount of sulfisomezole and sulfadiazine used was just sufficient to saturate the medium, $(W^{-2/3}-W_0^{-2/3})$ was plotted against time by applying Eq. (11), and shown in Fig. 11. The similar graph was also obtained in the case of sulfadiazine. Likewise logarithmic dissolution rate constants and the positive intercepts *vs.* logarithmic particle size are shown in Fig. 12 and 13 which give the same results as described above. The fact that positive intercepts abruptly increase with decrease in particle size to below 300 μ indicates that the critical particle size is at about 300 μ, and it is considered that with decrease in particle size the surface free energy may play an important part in the initial dissolution.

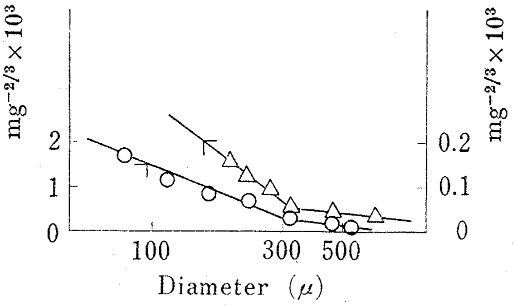

Fig. 13. Plot of the Positive Intercept *vs.* log Particle Size

○: sulfadiazine, △: sulfisomezole

We made further studies using the same sulfonamides adding a surfactant and the result will be reported in a future paper.

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[8] P.S. Roller, *J. Phys. Chem.*, 35, 1133 (1931); *ibid.*, 36, 1202 (1932).