CHEMICAL & PHARMACEUTICAL BULLETIN

Vol. 24, No. 11 November 1976

Regular Articles

Chem. Pharm. Bull. 24(11) 2577—2584 (1976)

UDC 615.31'7.011.4 : 615.014.24

Dissolution of Slightly Soluble Drugs. II. Effect of Particle Size on Dissolution Behavior in Sodium Lauryl Sulfate Solutions[1]

NOBUTOSHI WATARI and NOBUYOSHI KANENIWA

School of Pharmaceutical Sciences, Showa University[2]

(Received September 13, 1975)

Experiments were made to compare the effect of particle size of sulfonamide on the initial dissolution behaviour in sodium lauryl sulfate solution and in distilled water and the following results were obtained.

1) At agitation speed of 700 rpm, there was no difference of particle size on the initial dissolution in 0.1% and in distilled water but in 1% solution somewhat, and the difference appeared at agitation speed of 300 rpm with decrease in particle size. Results obtained in sodium lauryl sulfate solution showed a similar tendency while the instantly dissolving part increased with decrease in particle size, and this part dissolved instantly at first and the constant rate of dissolution followed in distilled water.

2) Plots of log dissolution rate constants *vs.* log agitation speed became linear with the same slope irrespective of particle size, when 0.1% and 1% solutions were used. Rank order for the dissolution rates of different particle size of powders was possible even at a relatively low agitation speed of 200 rpm.

In our previous study on sulfonamide particles[3] to examine the effect of particle size on dissolution behavior in distilled water, the critical particle size was at about 300 μm in the initial dissolution and it was possible to establish a clear rank order for the dissolution rates of different particle sizes under the employed agitation speed of 700 rpm.

A number of investigations were reported in which addition of a surfactant to the dissolution media increased the dissolution rate.[4] While a solubilization mechanism may be partly responsible for the increased dissolution rates observed when the concentration of the surfactant employed is above the critical micelle concentration (CMC),[4a–f] the solubilization mechanism is not responsible when concentration below the CMC is used.[4g–i] The increased dissolution rate observed with submicellar concentration of the surfactant is the result of a decrease in the interfacial energy between a solid and a liquid. One consequence of the reduction in interfacial energy is an improved wetting of the solid by the liquid, resulting in an increase

---

[1] Presented at the 94th Annual Meeting of the Pharmaceutical Society of Japan, Sendai, April 1974.

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

[3] N. Kaneniwa and N. Watari, *Chem. Pharm. Bull.* (Tokyo), **22**, 1699 (1974).

[4] *a*) D.E. Wurster and J.A. Seitz, *J. Am. Pharm. Assoc., Sci. Ed.*, **49**, 335 (1960); *b*) G. Levy and R. Gumtow, *J. Pharm. Sci.*, **52**, 1139 (1963); *c*) T.R. Bates, M. Gibaldi, and J.L. Kanig, *Nature*, **210**, 1331 (1966); *d*) T.R. Bates, S.L. Lin, and M. Gibaldi, *J. Pharm. Sci.*, **56**, 1492 (1967); *e*) P.H. Elworthy and F.J. Lipscomb, *J. Pharm. Pharmacol.*, **20**, 923 (1968); *f*) R.J. Braun and E.L. Parrott, *J. Pharm. Sci.*, **61**, 175 (1972); *g*) P.W. Taylor and D.E. Wurster, *ibid.*, **54**, 1654 (1965); *h*) P. Finholt and S. Solvang. *ibid.*, **57**, 1322 (1968); *i*) H. Weintraub and M. Gibaldi, *ibid.*, **58**, 1368 (1969).

in the effective surface area and thereby increasing the dissolution rate.[4a,h] Therefore, it seemed to be of interest to investigate the effect of the particle size of sulfonamide on dissolution in a surfactant solution, because dissolution may be influenced in a different manner than that expected in distilled water.

In the present work, the following studies were made with the same sulfonamide powders used previously[3] in the sodium lauryl sulfate solutions. First, because sulfonamide powder is slightly soluble and hydrophobic, we examined whether the powder would wet rapidly or not when the powder particles were thrown into the dissolution media. The difference between wetting in distilled water and in surfactant solution would influence the initial dissolution considerably. Secondly, whether it would be possible or not to establish a rank order differing from that obtained in distilled water for the dissolution rates of different particle size in a surfactant solution after the improved wetting of the sulfonamide powder by the surfactant solution.

Above the concentration of CMC, the effect of micelle-drug solubilization on the dissolution rate has been already reported,[5] in which the diffusion layer model[6] is said to show a reasonable agreement with the data of the initial dissolution rate under stirring, but nonstirring conditions, the Danckwerts model[7] shows excellent agreement with their experimental data. As, in this study, all experiments were made under stirring conditions, the experimental data were applied to the diffusion layer model.

Experimental

Materials——The same particle size grades of sulfonamides as in our previous study[3] were used and the arithmetic mean diameter of the sieved sample was taken as the mean diameter of the sulfonamide particles. Sodium lauryl sulfate was of a reagent grade (Wako Pure Chemical Industries, Ltd. Lot No. PAI 0233) and used without further purification.

Determination of the Dissolution Rate of Sulfonamide Particles in Sodium Lauryl Sulfate Solution——An identical apparatus and procedure were used for the determination of the amount of sulfonamides dissolved in sodium lauryl sulfate solution in concentration ranging from 0.01 to 6% at 37°±0.05°, and the dissolution rates were determined, as described in our previous paper.[3] The pH of sodium lauryl sulfate solutions was close to that of distilled water (5.7—5.8). At each concentration of the surfactant, dissolution runs were made at least twice and in all cases, the reproducibility was within experimental error.

Solubility Determinations——Sulfonamide solubility was determined in a series of aqueous solutions containing various concentrations of sodium lauryl sulfate. In each case, sulfonamide in excess of the amount required for saturation solubility was added to 15 ml of the surfactant solution contained in a 50 ml flask and the flask was shaken (2 strokes/sec, at the amplitude of 3 cm) in a water bath of 37°, and equilibrated for 3—5 days. The equilibrium concentration was determined by repetitive sampling. Assay procedures for sulfonamide were made as reported in earlier.[3]

Viscosity Determinations——Viscosity of the solutions was measured at 37° uisng an Ubbelohde type viscometer. The densities of the solutions were measured using a pycnometer.

Results and Discussion

Effect of the Concentration of Sodium Lauryl Sulfate on Dissolution Rate of Sulfonamide

As reported in earlier studies in distilled water,[3] the effective interface between the solid and the liquid in each particle size grade varied with change in agitation speed when the agitation speed was smaller than 500 rpm, and a rank order for the dissolution rate of different particle size did not agree with that considered from the theoretical equations[3]

---

[5] *a*) W.I. Higuchi, *J. Pharm. Sci.*, **56**, 315 (1967); *b*) E.L. Parrott and V.K. Sharma, *ibid.*, **56**, 1341 (1967); *c*) M. Gibaldi, S. Feldman, R. Wynn, and N.S. Weiner, *ibid.*, **57**, 787 (1968); *d*) P. Singh, S.J. Desai, D.R. Flanagan, A.P. Simonell, and W.I. Higuchi, *ibid.*, **57**, 959 (1968); *e*) A.P. Simonell, D.R. Flanagan, and W.I. Higuchi, *ibid.*, **57**, 1629 (1968); *f*) R.J. Braun and E.L. Parrott, *ibid.*, **61**, 592 (1972).

[6] W.I. Higuchi, *J. Pharm. Sci.*, **53**, 532 (1964).

[7] P.V. Danckwerts, *Ind. Eng. Chem.*, **43**, 1460 (1951).

that the dissolution rate was inversely proportional to the particle size. Therefore, the agitation speed was selected at 700 rpm for sulfamethizole with a sample size of 460 μm, and 600 rpm for sulfadiazine with a sample size of 274 μm in order to compare the dissolution rate in various concentrations of sodium lauryl sulfate solution with that in distilled water.

The dissolution rates and the solubility of sulfamethizole and sulfadiazine in the aqueous solutions of various concentrations of sodium lauryl sulfate are shown in Table I.

Table I. Dissolution Rate and Solubility of Sulfonamides in Various Concentrations of Sodium Lauryl Sulfate Solution

Surfactant concn. (%, W/V)	Sulfamethizole			Sulfadiazine		
	Dissolution rate constant	*Cs* Total solubility (mg/ml)	*Cs*-*Co* Micellar solubility (mg/ml)	Dissolution rate constant	*Cs* Total solubility (mg/ml)	*Cs*-*Co* Micellar solubility (mg/ml)
0	0.170	0.884		1.15	0.127	
0.01	0.200	0.864		1.19	0.124	
0.05	0.189	0.877		1.20	0.132	
0.10	0.193	0.899	0.015	1.26	0.151	0.024
0.25	0.239	1.00	0.12	1.63	0.165	0.038
0.50	0.275	1.36	0.48	1.86	0.179	0.052
1.00	0.335	1.86	0.98	2.20	0.207	0.080
2.00	0.379	2.64	1.76	2.41	0.258	0.131
3.00	0.415	3.42	2.54	2.52	0.309	0.182
4.00	0.445	4.05	3.17	2.72	0.361	0.234
5.00	—	—	—	—	0.410	0.283
6.00	0.498	5.45	4.57	2.98	0.463	0.336

—: not measured

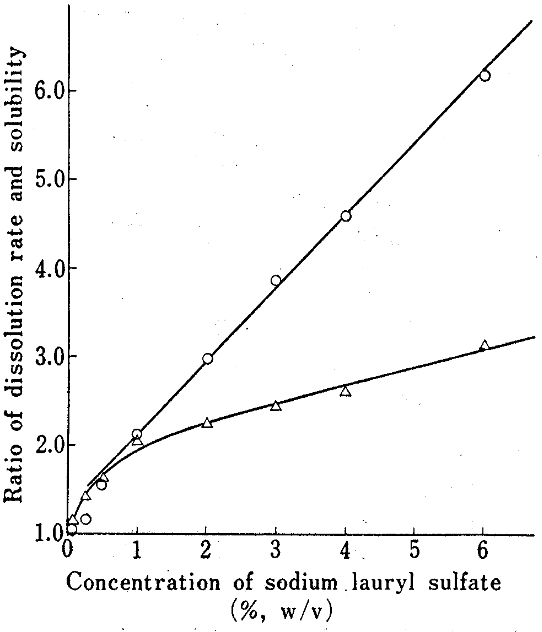

Fig. 1. Ratio of Dissolution Rates and Solubilities of Sulfamethizole in Surfactant Solution to Those in Distilled Water

△: ratio of dissolution rate constant
○: ratio of solubility

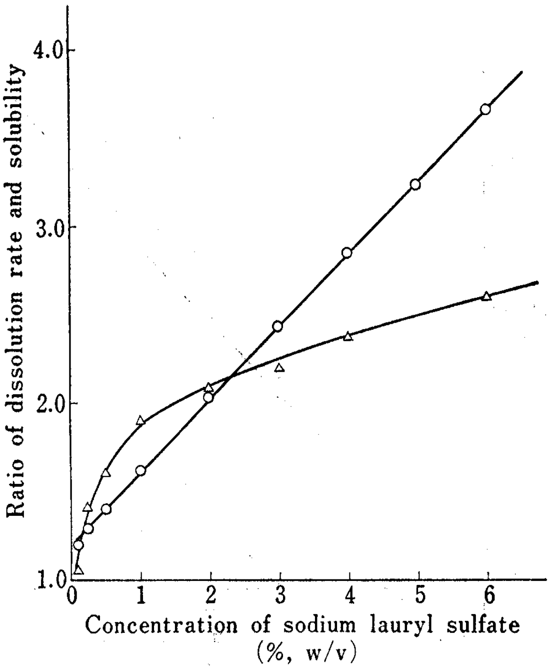

Fig. 2. Ratio of Dissolution Rates and Solubilities of Sulfadiazine in Surfactant Solution to Those in Distilled Water

△: ratio of dissolution rate constant
○: ratio of solubility

In this table the amount of sulfonamides solubilized by the micelle-drug interaction (Cs–Co) is represented by the difference between the total solubility (Cs) in the solution of the surfactant and the solubility (Co) in distilled water. No solubilization is evident at low sodium lauryl sulfate concentrations, however, a marked solubilization effect results at fractional concentrations of the CMC, which was about 0.25% in water at 37°.[8] This effect has been observed previously and explained.[4g] In Fig. 1 and 2, the ratio of the dissolution rate constant in the solution of sodium lauryl sulfate to that in distilled water, and the values of Cs/Co were plotted *vs.* the concentration of sodium lauryl sulfate for each sulfonamide.

When the concentration of sodium lauryl sulfate was below the CMC, the dissolution rate increased considerably. As will be seen below, with the use of 0.1% of sodium lauryl sulfate solution, the effective interface between the solid and the liquid in each particle size fraction was not influenced by even a low agitation speed of 200 rpm on the initial dissolution rate. These results support the fact that the increased dissolution rate observed is due to improved wetting of a solid by a liquid, resulting in the increase of effective interface and thereby increasing the dissolution rate.

When concentrations above the CMC were used, the value of (Cs–Co) was linearly dependent on the concentration of sodium lauryl sulfate but the ratio of dissolution rate was not linear, as shown in Fig. 1 and 2. Similar phenomena were reported in some papers,[4e,f,5b–d] in which the dissolution rate became progressively less with an increase of the concentration of the surfactant, and this effect was considered due to an increase of the viscosity, because the viscosity is reflected in the diffusion layer model in the diffusion coefficient which by Stokes-Einstein equation is inversely proportional to the viscosity. It was also considered that micellar solubilization had a significant role in the dissolution rate.[5f] The viscosity of sodium lauryl sulfate solution is shown in Fig. 3, in which the viscosity increase remarkably with an increase of the concentration of sodium lauryl sulfate.

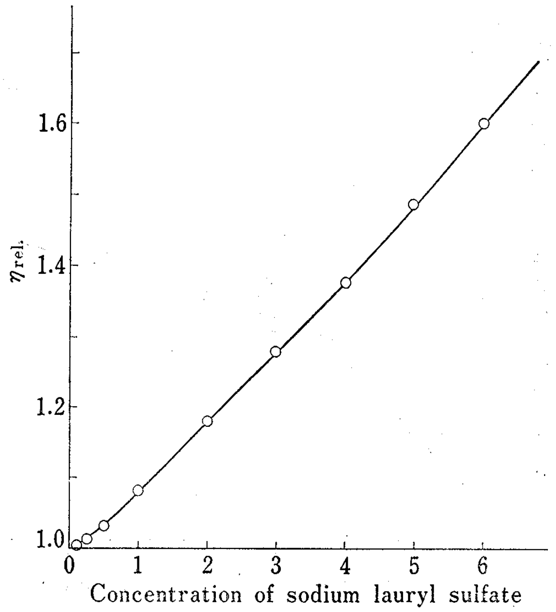

Fig. 3. Relatite Viscosities of Various Sodium Lauryl Sulfate Solutions

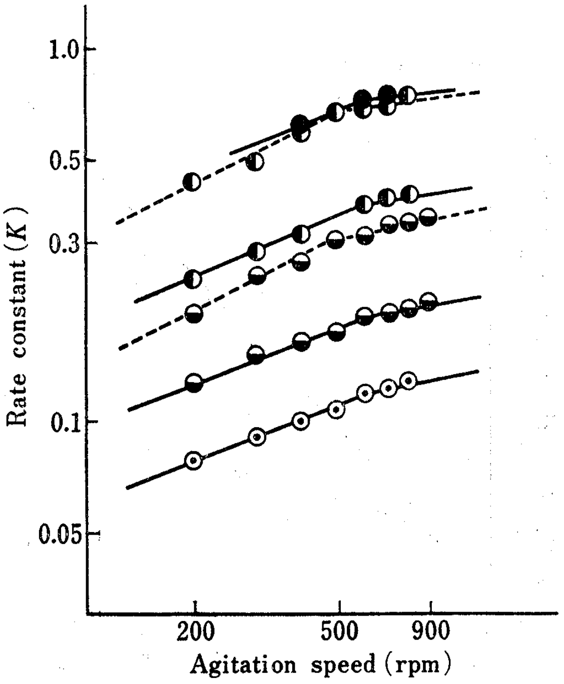

Fig. 4. Dependence of Dissolution Rate Constant on Agitation Speed in Various Particle Sizes

●: 68 μm, ◐: 163 μm, ◒: 324 μm, ⊙: 650 μm;
——: in 0.1% sodium lauryl sulfate solution;
------: in 1% sodium lauryl sulfate solution

Effect of Particle Size on Dissolution Rate in Agitated Surfactant Solutions

Sulfamethizole of four grades in size were used to investigate the relationship between the dissolution rate and the agitation speed in the aqueous solutions of 0.1% and 1% of sodium lauryl sulfate. Logarithmic plot of the dissolution rate constant *vs.* the agitation speed showed a straight line having an inflexion at about 600 rpm and 500 rpm for the solution of 0.1% and 1%, respectively, as shown in Fig. 4, and the following relationship was found:

$$K = a \cdot N^b$$

where K is the dissolution rate constant, N, the agitation speed, and a and b are parameters. This relationship is similar to the result obtained with distilled water previously.[3)]

When agitation speed was smaller than the point of inflexion, the relationship between the logarithmic values of b and the reciprocal of the particle size became linear in distilled water[3)] but when the concentration of sodium lauryl sulfate was 0.1%, the values of the slope (b) were constant irrespective of the particle size. Similar result was observed with 1% sodium lauryl sulfate solution. These facts support the observation that in these surfactant solutions, the wetting and the degree of dispersion of powders are improved by a decrease in the interfacial energy, and the effective interface between the particles of each size and the sufactant solutions is not influenced within the range of the agitation speed employed in this experiment. These same constants of b in each surfactant solutions indicate that the rate of change in diffusion layer thickness induced by the rate of change in agitation speed is equally independent of particle size. The values of b were 0.35 for 0.1% solution and 0.47 for 1% solution, which were consistent with that observed in the other reactions.[9)] The difference in values of b between 0.1% and 1% solutions seemed to be due to the change in its solubilization mechanism by micellar solubilization, when the concentration was 1%.

Above the point of this inflexion, the values of b for each particle size became smaller, and drawing of air into the media was found. Therefore, the effective interface for dissolution decreased by the drawing of air and the increase of dissolution rate with an increase of the agitation speed decreased.[3)]

With respect to the determination of the rank order for dissolution rates of different particle size of slightly soluble powders such as sulfonamide, there are problems due to flotation and flocculation of powders. Unless these floating floccules could be broken up and the powder distributed in such a way that the specific surface area of different particle size of powders would be available for dissolution, a rank order in the dissolution would not be possible. Finholt *et al.*[10)] encountered these problems in their attempt to study the effect of particle size on dissolution rates and while comparing the dissolution rates of powders with granules and tablets at a low agitation speed (50 rpm). Lin *et al.*[11)] also found similar problems in the rank order in the dissolution rates of different particle size of powders at the relatively high agitation speed (600 rpm). In this present study, when the concentration of sodium lauryl sulfate was 0.1% and 1%, a clear rank order for the dissolution rates of different particle size of powders was found even at a relatively low agitation speed such as 200 rpm. It was considered that addition of the surfactant to the dissolution media prevented the flotation and flocculation of powders owing to improved wetting of the solid by the liquid.

Effect of Particle Size on Dissolution Rate in Aqueous Solution of Sodium Lauryl Sulfate

From the results of the effect of the concentration of sodium lauryl sulfate on the dissolution rates and the solubilities of sulfadiazine and sulfamethizole, it is considered that the rate and the solubility of sulfisomezole are similar to those of the other sulfonamides.

---

8) B.D. Flockhart and A.R. Ubbelohde, *J. Colloid Sci.*, **8**, 428 (1953); E.D. Goddard and G.C. Benson, *Can. J. Chem.*, **35**, 986 (1957).

9) L.L. Bircumshaw and A.C. Riddiford, *Quart. Rey.* (London), **6**, 157 (1952).

10) P. Finholt, H. Kristiansen, O.C. Schmidt, and K. Wold, *Medd. Norsk Farm. Selskap*, **28**, 17 (1966); P. Finholt, R.H. Pedersen, S. Solvang, and K. Wold, *ibid.*, **28**, 238 (1966).

11) S.L. Lin, J. Menig, and L. Lachman, *J. Pharm. Sci.*, **57**, 3143 (1968).

Then, 313 mg of sulfisomezole which was equal to the amount required to saturate 500 ml of distilled water at 37°, and 377 mg of sulfamethizole which was less than its equilibrium solubility in distilled water at 37° were used to examine the effect of particle size on the initial dissolution rate in the sodium lauryl sulfate solutions. These amounts of sulfonamides used were the same amounts as used in distilled water[3] and less amounts to saturate the dissolution media used in this experiments.

As, in aqueous solution of sodium lauryl sulfate, a rank order in the dissolution rates of different particle size of powders was possible at a relatively low agitation speed of 200 rpm, the agitation speed was used at 300 rpm for sulfisomezole but at 700 rpm for sulfamethizole which was the same speed used in distilled water.[3]

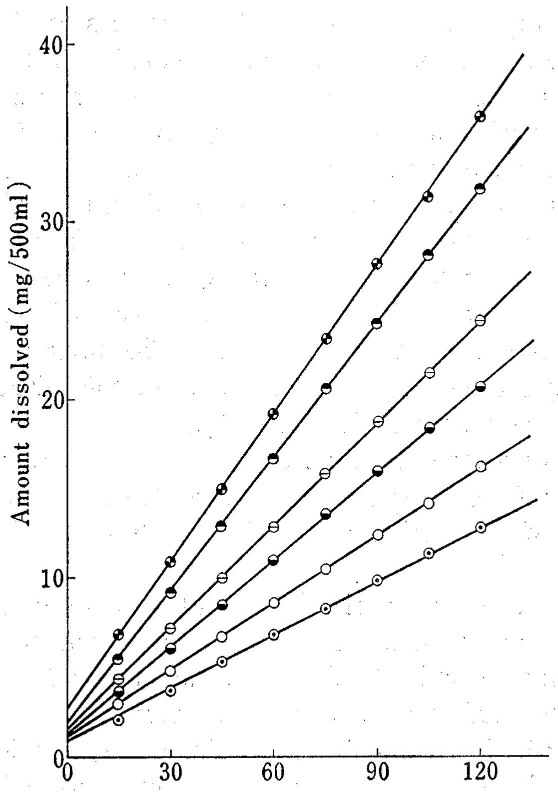

Fig. 5. Effect of Particle Size on Dissolution of Sulfisomezole in 0.1% Sodium Lauryl Sulfate Solution at 300 rpm

⊕: 194 μm, ●: 230 μm, ⊖: 274 μm, ◒: 324 μm, ○: 460 μm, ⊙: 650 μm

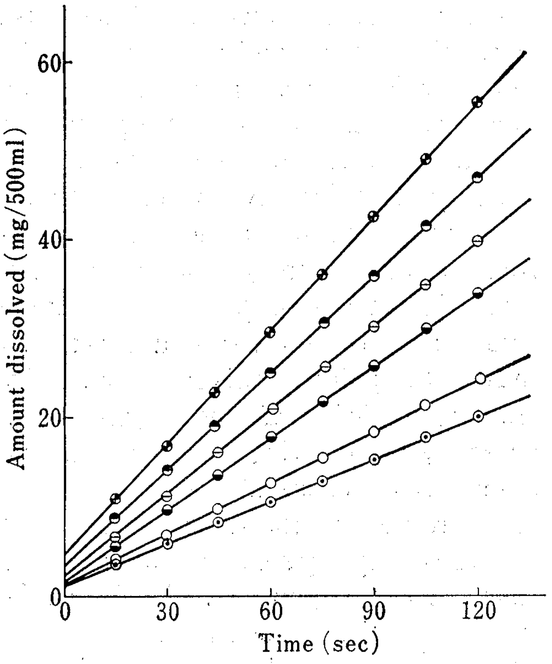

Fig. 6. Effect of Particle Size on Dissolution of Sulfisomezole in 1% Sodium Lauryl Sulfate Solution at 300 rpm

⊕: 194 μm, ●: 230 μm, ⊖: 274 μm, ◒: 324 μm, ○: 460 μm, ⊙: 650 μm

The dissolution profiles of sulfisomezole are illustrated in Fig. 5 and 6. The cumulative amount (in mg) dissolved was plotted *vs.* the dissolving time. The plots of sulfisomezole were linear; the amount dissolved increased linearly with the lapse of the time but those of sulfamethizole were not linear. Therefore, by applying the Hixon-Crowell cube root law,[3,12] $(W_0^{1/3}-W^{1/3})$ was plotted against the time for sulfamethizole, as described in our previous paper[3] and this resulted in a atraight line, as shown in Fig. 7 and 8.

Theoretically, the plots of these dissolution rates should be straight lines passing through the origin[3] but these lines in Fig. 5, 6, 7, and 8 did not pass through the origin and had positive intercepts with decrease in particle size. Then, the positive intercepts in these dissolution rate graphs were plotted as a function of the logarithmic particle size and shown in Fig. 9,

---

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

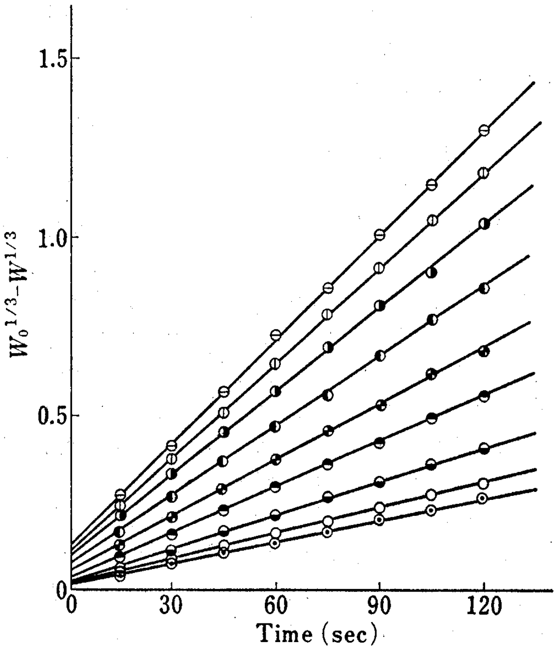

Fig. 7. Effect of Particle Size on Dissolution Rate of Sulfamethizole in 0.1% Sodium Lauryl Sulfate Solution at 700 rpm

⊖: 97 μm, ⦶: 115 μm, ◑: 137 μm, ◐: 163 μm, ◕: 194 μm, ◓: 230 μm, ◒: 324 μm, ○: 460 μm, ⊙: 650 μm

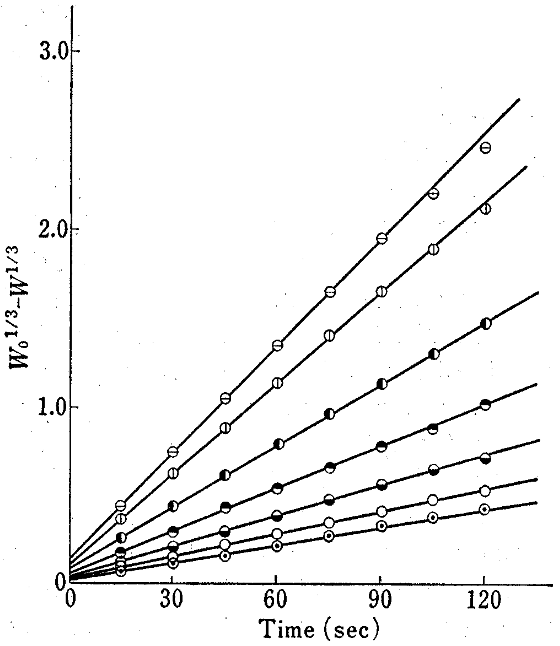

Fig. 8. Effect of Particle Size on Dissolution Rate of Sulfamethizole in 1% Sodium Lauryl Sulfate Solution at 700 rpm

⊖: 97 μm, ⦶: 115 μm, ◐, 163 μm, ◓: 230 μm
◒: 324 μm, ○: 460 μm, ⊙: 650 μm

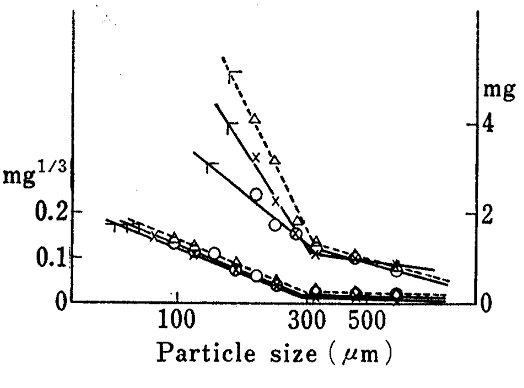

Fig. 9. Plot of Positive Intercept in Dissolution Rate Graph *vs.* log Particle Size.

The upward three lines show sulfisomezole and the downward lines sulfamethizole;
—×—: in distilled water
—○—: in 0.1% sodium lauryl sulfate solution
···△···: in 1% sodium lauryl sulfate solution

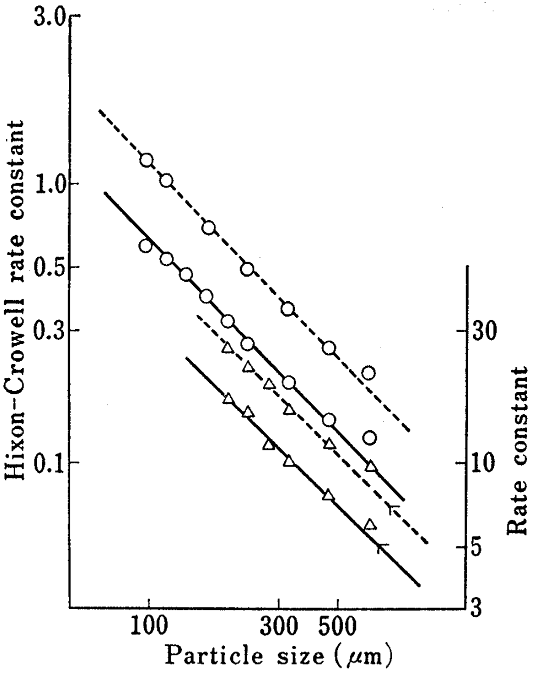

Fig. 10. Dependence of log Dissolution Rate Constants on log Particle Size in Sodium Lauryl Sulfate Solutions

○: sulfamethizole, △: sulfisomezole
——: in 0.1% solution, ------: in 1% solution

in which the plots were linear lines having an inflexion at about 300 μm. When the particle size was smaller than that of the inflexion, the positive intercept increased qualitatively with decrease in particle size. In this graph, the symbol x in each sulfonamide shows a resultant relationship obtained in distilled water at the agitation speed of 700 rpm, as reported in earlier.[3)]

Comparison of the intercepts observed in the surfactant solutions with that in distilled water indicates that when the agitation speed was 700 rpm for sulfamethizole, the difference of intercepts was scarcely found in 0.1% solution but in 1% solution, the value of intercept was somewhat larger than that in the others as shown by the downward three lines in Fig. 9, and it is considered due to the largest solubility. When the agitation speed was 300 rpm for sulfisomezole, the values of intercept in 1% solution was the highest in each particle size grade in spite of low agitation speed compared to that in distilled water, and this considered to be due to the largest saturation solubility by micelle solubilization. In 0.1% solution, an increase of the intercepts with decrease in particle size was slightly less than that in the others. As the saturation solubility in 0.1% solution is less than that in 1% solution and the agitation speed is also less than that in distilled water, it may be considered that the decrease in the wetting of powders between the solid and the liquid lowered the intercepts than in the others.

A large intercept was found for sulfisomezole in spite of a large particle size in each solution and this may be due to its metastable form used, as reported in earlier.[3)]

The logarithmic plots of dissolution rate constants *vs.* particle size are shown in Fig. 10, in which the line became a straight line having a slope of -1 for each line; this fact shows that the specific surface area of the powders is proportional to the initial dissolution rate constant.

All resultant relationships between the positive intercepts and the logarithmic particle size mentioned above show that these intercepts increased with decrease in particle size, and indicate that the increase in the rate of the initial dissolution with decrease in particle size is greater than that expected from the increase in surface area alone, and suggest that there is a large amount of instantly dissolving part in a powder surface after the decrease of the particle size.