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Dissolution of slightly Soluble Drugs. III. Surface Condition of Powder Particles and Their Initial Dissolution Behavior[1]

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Experiments were made to clarify the relationship between surface view of powder particles of sulfonamide and their initial dissolution behavior, and the following results were obtained.

1) A particle surface appearance, in each particle size grade sieved from commercial sulfisomezole and sulfamethizole, and recrystallized sulfanilamide, was observed by scanning electron microscope and very fine particles adhering on the particle were found irrespective of particle size. Very fine adhering particles were scarcely found on the recrystallized particles. To remove the very fine adhering particles, these samples were treated with distilled water, 0.2% sodium lauryl sulfate solution, saturated solution of sulfonamide, or 0.2% sodium lauryl sulfate solution saturated with sulfonamide. Surface appearance of these treated samples revealed no adhering particle on the particles except for those treated with saturated solution of sulfonamide. Agglomerated ball-milled samples were composed of very fine particles of diameter ranging from 0.1 to 1 μm.

2) Examination of initial dissolution rates revealed that an increase of instantly dissolving parts with decrease in particle size was due to the very fine particles adhering on the particle, but, in spite of no adhering particles on the particle, the instantly dissolving parts also increased with decrease in particle size. This result supports the observation that surface free energy of powder particles may play an important part in the initial dissolution with decrease in particle size. The instantly dissolving parts of ball-milled sample increased greatly for each sulfonamide and it was around 25% of saturation.

Keywords——surface condition; sulfonamide particles; washed particle; initial dissolution rate; ball-milled powder; surface free energy; edges-corners effect; reduced particle size effect; scanning electron photomicrograph

It is considered that the surface condition of particles may play an important part in the initial dissolution process. In our previous studies,[3] we determined the initial dissolution rate in each particle size grade of sulfonamide which was obtained by sieving through Ro-Tap testing sieve shaker, under the conditions where the specific surface area of different particle size of a powder affect the dissolution, and found that the instantly dissolving parts increased with decrease in particle size, that is, the increase in the rate of initial dissolution with decrease in particle size is greater than that expected from the increase in surface area alone. This fact suggested that there was a large amount of instantly dissolving part in a powder particle surface after decrease of particle size. Subsequently similar result was also obtained in a surfactant solution.[4]

The phenomenon which occurs in the initial dissolution should be considered to be due to the nature of surface condition of powder particles. To explain this phenomenon, we observed the surface conditions of the same powder particles used in our previous studies[3,4] using scanning electron microscope and further, observed the change of surface conditions of powder particles obtained by washing in several solvents and surface conditions of crystal particles recrystallized. Dissolution was tested with these samples and relationship between surface view of powder particles and their initial dissolution behavior was investigated.

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[2] Location: *Hatanodai, Shinagawa-ku, Tokyo, 142, Japan.*
[3] N. Kaneniwa and N. Watari, *Chem. Pharm. Bull.* (Tokyo), **22**, 1699 (1974).
[4] N. Watari and N. Kaneniwa, *Chem. Pharm. Bull.* (Tokyo), **24**, 2577 (1976).

Experimental

Materials——Different particle size grades of sulfamethizole were used in our previous work[3,4] and in the present work, sulfisomezole samples were obtained newly from a commercial bulk by sieving through the Ro-Tap testing sieve shaker using Japan Industrial Standard (JIS) sieves. Sulfanilamide was made newly by recrystallization from methanol and sieved informally. Sulfamethizole was recrystallized from water, sulfathiazole from ethanol, and sulfadimethoxine from ethyl acetate. The arithmetic mean diameter of sieved sample was taken as the mean diameter of the sulfonamide particles.

The ball-milled samples are listed in Table I. A sample of 50 g was placed in a ceramic pot, 8 cm in diameter and 450 ml in capacity. The mill containing 20 ceramic balls with true density of 2.4 g/cm^3, of which 5 were 2.5 cm in diameter and 15 were 1.9 cm in diameter, was revolved at the rate of 147 rpm for 50 hr. Characteristic X-ray powder diffraction patterns of ball-milled samples were obtained and showed no difference from those of unmilled ones. Surface area was measured by the air permeability method[5] and true density by use of a helium densitometer (Tsutsui Rikagaku Kikai Co., Ltd.).

Table I. Physicochemical Properties of Ball-Milled Sulfonamide

Sample	ρ	V(cm^3)	D(μm)
Sulfisomezole	1.61	31.1	2.12
Sulfamethizole	1.53	32.7	1.90(1.25)

V: true volume of a sample inserted in a mill
D: surface mean diameter determined by air permeability method
( ): determined in nitrogen gas by Brunauer Emmett Teller (BET) method

Procedure of Washing——Two grams of each particle size grade of sulfisomezole and sulfamethizole was placed in a flask containing 100 ml of distilled water (the saturation solubility was less than 0.05% at 25° for each sulfonamide) and the flask was stoppered and rapidly shaken for 30 sec. The solvent was immediately filtered in vacuum and the residue was further washed twice with 100 ml of a fresh water, and placed in a vacuum desiccator to dry. The same procedure was carried out with 0.2% sodium lauryl sulfate solution, saturated solutions of the two sulfonamides, and 0.2% sodium lauryl sulfate solutions saturated with both sulfonamides.

Observation of Particle Surface and Determination of Dissolution Rate——Scanning electron microscope JEOL JSM-35 was used for the observations of particle surface. The same apparatus and procedure were used for the determination of the amount of sulfonamide dissolved, and the dissolution rates were determined as described in our previous paper,[3] in which the equation obtained by integrating the Noyes-Nernst equation, was used under the conditions where the surface area would be postulated to be constant owing to the slight amount of the solid dissolved in the initial dissolution; the amount of the solid dissolved depended linearly on the dissolution time. In the derivation of the Hixson-Crowell cube root law[3,6] from the Noyes-Whitney equation, the following assumptions were made: (a) All the particles dissolve isotropically, (b) the particles are isometric, (c) thickness of the diffusion layer around each particle is constant, (d) there are no particle-size solubility effects, and (e) sink conditions exist. Furthermore, when the amount studied equals exactly to the amount needed to saturate the solution, the negative two-thirds law in the Hixson-Crowell equation[3,6] is derived under nonsink conditions and it is said that the data from other literature sources[7] adhere to the negative two-thirds equation to better than 80% of saturation.

Results and Discussion

A Surface View of Powder Particles

Different particle size grades of sulfisomezole and sulfamethizole were used to observe the powder particle surface by scanning electron microscope at low magnification (×100) first and then at higher magnification (×10000). These photomicrographs of sulfisomezole are shown in Fig. 1, which show that there were very fine particles adhering on the particle surface in each sample size. As shown in Fig. 1 under higher magnification, these very fine

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5) E. Suito, M. Arakawa, and M. Takahashi, *Kogyo Kagaku Zasshi*, **59**, 307 (1956).

6) A.W. Hixson and J.H. Crowell, *Ind. Eng. Chem.*, **23**, 923 (1931); *ibid.*, **23**, 1002 (1931); *ibid.*, **23**, 1160 (1931); A.W. Hixson and G.A. Wilkens, *ibid.*, **25**, 1196 (1933); A.W. Hixson and S.J. Baum, ibid., **33**, 478 (1941).

7) M. Patel and J.T. Carstensen, *J. Pharm. Sci.*, **64**, 1651 (1975).

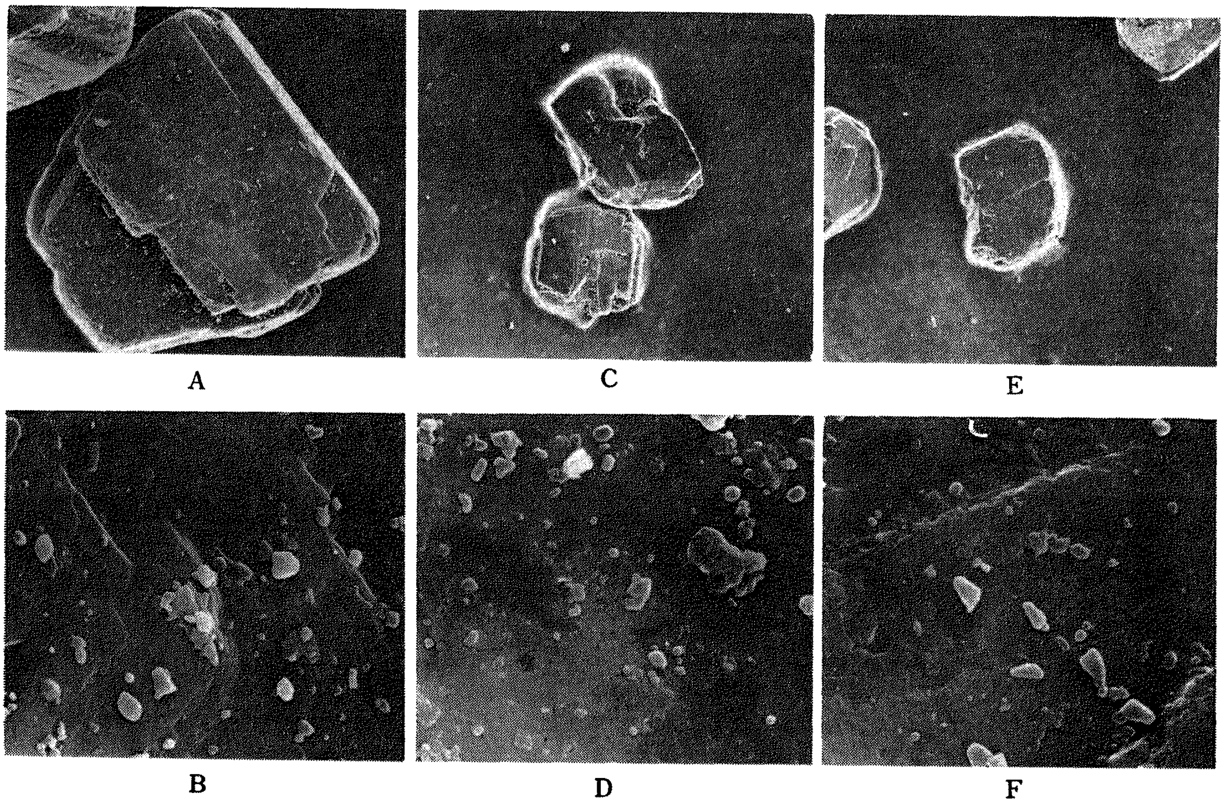

Fig. 1. Scanning Electron Photomicrographs of Sulfisomezole
A: 650 μm (×100) B: 650 μm (×10000) C: 230 μm (×100) D: 230 μm (×10000) E: 194 μm (×100) F: 194 μm (×10000)

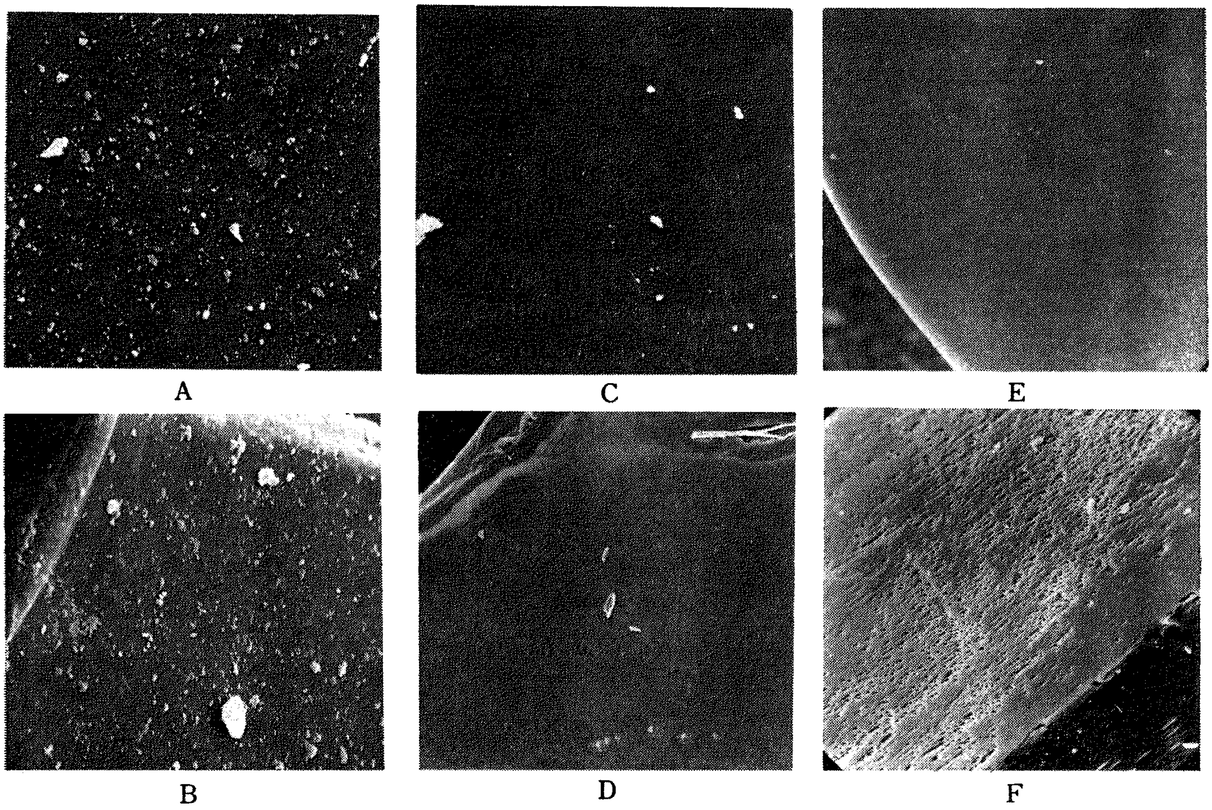

Fig. 2. Scanning Electron Photomicrographs of Sulfonamides, ×1000
A: sulfanilamide (32/48) B: sulfanilamide (48/80) C: sulfanilamide (methanol)
D: sulfamethizole (water) E: sulfathiazole (ethanol) F: sulfadimethoxine (ethyl acetate)
In parentheses shown Tyler mash and recrystallization solvent

particles had a diameter ranging from 0.1 to 1 μm and none were below 0.1 μm. It seemed that the distribution of very fine particles adhering on the particle surface was all the same irrespective of particle size. Similar observations were made with sulfamethizole.

Some photomicrographs of other sulfonamides recrystallized newly from appropriate solvents are shown in Fig. 2, in which there were scarcely very fine particles adhering on the recrystallized particle surface in each sulfonamide (C, D, E, and F in Fig. 2), but much of very fine adhering particles was found on the sieved particle surface of sulfanilamide (A and B in Fig. 2) and it seemed similar to the observations of the sieved particle surface of commercial sulfisomezole and sulfamethizole. Adhesion of very fine particles on the surface of sieved and recrystallized sulfanilamide particles is considered to be due to the procedure of sieving.

To investigate whether the presence of very fine particles adhering on the particle surface is responsible for the earlier observation[3,4] that the instantly dissolving part increases

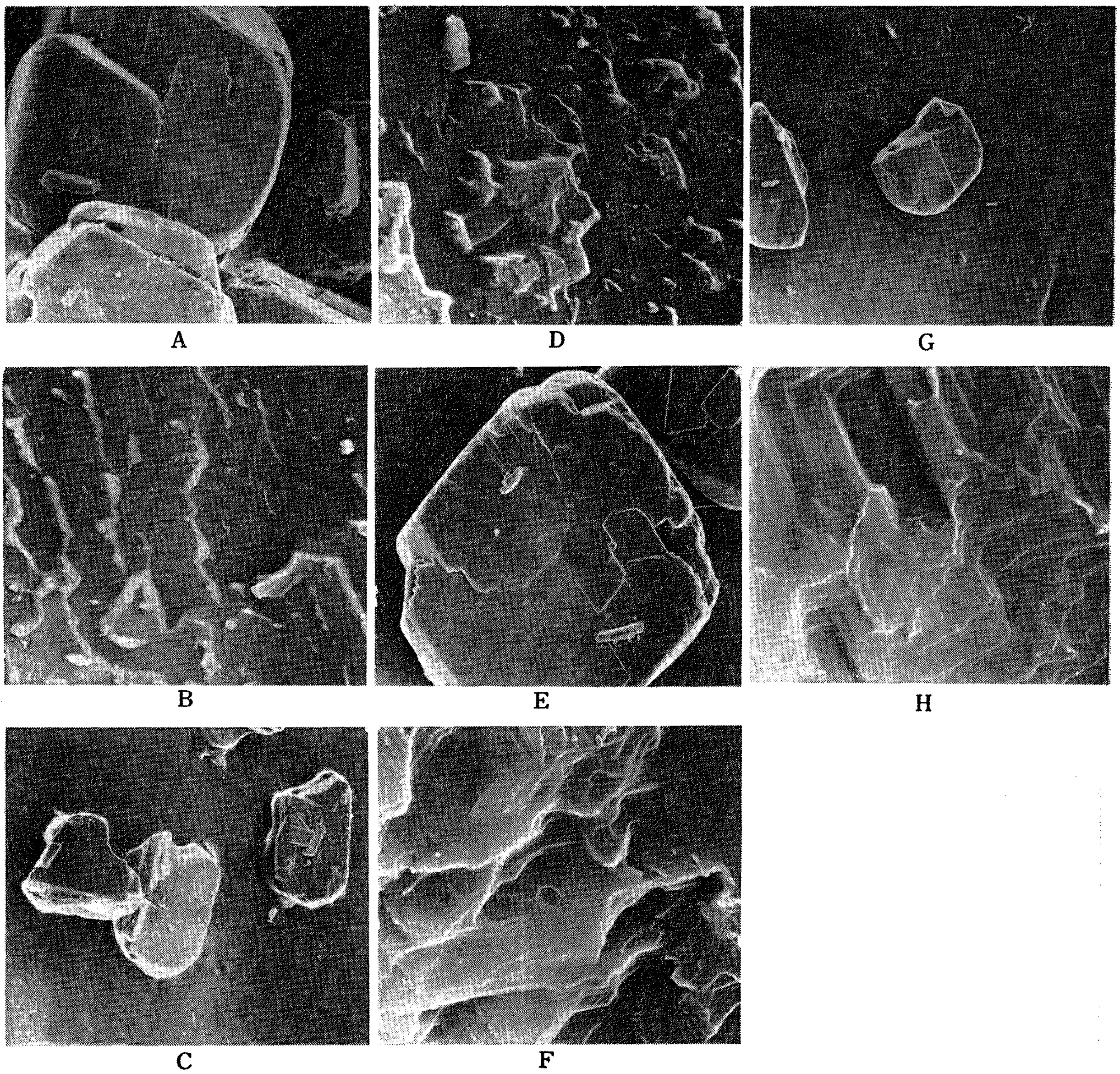

Fig. 3. Scanning Electron Photomicrographs of Sulfisomezole

A, B, C, D: washed with distilled water
E, F, G, H: washed with 0.2% sodium lauryl sulfate solution
A, E: 650 μm (×100) B, F: 650 μm (×10000)
C, G: 194 μm (×100) D, H: 194 μm (×10000)

with decrease in particle size in the initial dissolution, each representative particle size grade of sulfonamides was selected and treated with several solvents to wash out the very fine particles adhering on the particle surface, and scanning electron photomicrographs were taken of washed powder particle surface. These photomicrographs of sulfisomezole are shown in Fig. 3 and 4, in which there were no very fine particles adhering on the particle surface after each particle size grade was washed with distilled water, 0.2% sodium lauryl sulfate solution, or 0.2% sodium lauryl sulfate solution saturated with sulfisomezole. A small amount of very fine adhering particles remained on the particle surface after washing in saturated solution of sulfisomezole. Similar results were also obtained with sulfamethizole. Furthermore, the sample surface after washing with sodium lauryl sulfate solution seemed to be more smooth than that of a sample washed with distilled water.

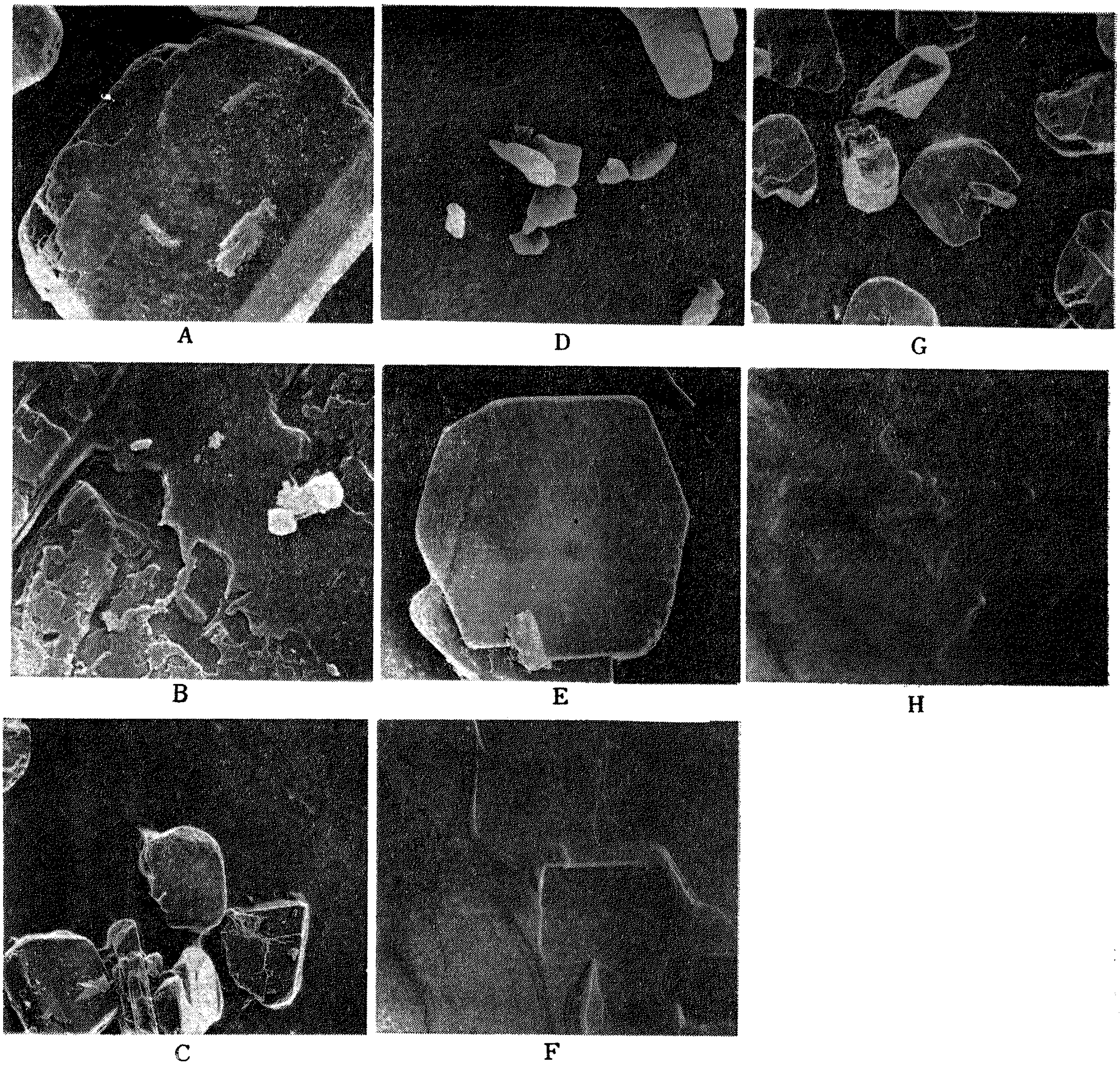

Fig. 4. Scanning Electron Photomicrographs of Sulfisomezole

A, B, C, D: washed with saturated solution of sulfisomezole
E, F, G, H: washed with 0.2% sodium lauryl sulfate solution saturated with sulfisomezole
A, E: 650 μm ($\times$100) B, F: 650 μm ($\times$10000)
C, G: 194 μm ($\times$100) D, H: 194 μm ($\times$10000)

Photomicrographs of samples ground by ball-milling are shown in Fig. 5, in which agglomerate of very fine particles was found and its particles were almost all in a diameter ranging from 0.1 to 1 μm for both sulfonamides.


A B

Fig. 5. Scanning Electron Photomicrographs of Ball-Milled Sulfonamide, × 10000

A: sulfisomezole; B: sulfamethizole

Effect of Particle Size of Sulfonamide on Initial Dissolution Behavior

The agitation speed was chosen at 700 rpm to insure complete suspension of particles and instantaneous mixing to make the specific surface area of a powder effective for initial dissolution when the samples were placed into 500 ml of distilled water at 37° and 313 mg of sulfisomezole, which was just sufficient to saturate the dissolution medium, and 377 mg of sulfamethizole, which was less than its solubility, were used to examine their initial dissolution behavior. These amounts were the same amount of sulfonamides as used earlier.[3,4]

As a large particle size, 650 μm in diameter, and as smaller ones, 230 and 194 μm diameter, of sulfisomezole were used to examine the effect of particle size on the initial dissolution rates, and sizes of 460, 230, and 163 μm were used for sulfamethizole.

The data for dissolution rate are illustrated in Fig. 6 and 7, in which each line is drawn through the points which represent an average of at least two dissolution runs and in all cases, the reproducibility was within the experimental error. The results obtained were similar to those of untreated samples for each sulfonamide as described in our previous paper.[3] The lines obtained by plotting the amount dissolved *vs.* time became linear for sulfisomezole, but they were somewhat convex for sulfamethizole and by applying the Hixson-Crowell cube root law, ($W_0^{1/3}-W^{1/3}$) *vs.* time became straight lines.

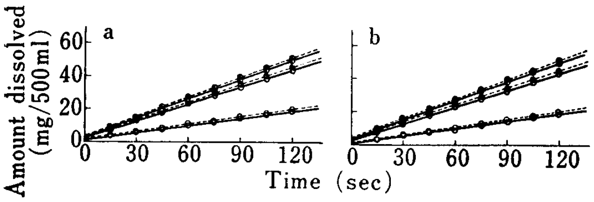

Fig. 6. Effect of Particle Size on Dissolution Rate of Sulfisomezole

○: 650 μm; ◓: 230 μm; ●: 194 μm
a : ——: washed with distilled water
------: washed with 0.2% sodium lauryl sulfate solution
b : ——: washed with saturated solution of sulfisomezole
------: washed with 0.2% sodium lauryl sulfate solution saturated with sulfisomezole

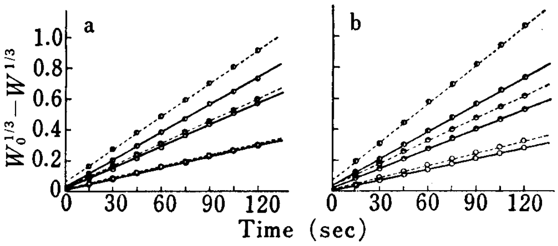

Fig. 7. Effect of Particle Size on Dissolution Rate of Sulfamethizole

○: 460 μm; ◓: 230 μm; ◐: 163 μm
a : ——: washed with distilled water
------: washed with 0.2% sodium lauryl sulfate solution
b : ——: washed with saturated solution of sulfamethizole
------: washed with 0.2% sodium lauryl sulfate solution saturated with sulfamethizole

As the amount of sulfisomezole used was just sufficient to saturate the medium, $(W^{-2/3}-W_0^{-2/3})$ was plotted against time and this resulted in straight lines. This graph was also similar to that of untreated samples of sulfisomezole, as reported earlier.3)

In our previous studies,3,4) the linear lines in these dissolution rate graphs had a positive intercept at a particle size below 300 μm and they passed closely through the origin at above 300 μm. As shown in Fig. 6 and 7, these linear lines also had a positive intercept with decrease in particle size.

Then, the positive intercepts and the slopes of lines which represent the apparent dissolution rate constant, were calculated by the least-squares method to compare with those of untreated samples of sulfisomezole and sulfamethizole as described in our previous paper3) and shown in Table II, in which the positive intercepts of samples treated with distilled water and saturated solution of sulfonamide decreased compared with those of untreated samples, and the decrease of positive intercept was evident with decrease in particle size but the values of intercept for two smaller particle sizes did not decrease to a greater extent than that of larger one in each sulfonamide. These results support the observation that an increase of intercept of untreated samples with decrease in particle size is considered to be due to the very fine particles adhering on the particle surface as observed above, because of the quantity of very fine adhesion particles increasing owing to an increase in the specific surface area of a powder with decrease in particle size, but, in spite of no adhesion of very fine particles on the particle surface in samples treated with distilled water, its positive inter-

TABLE II. Intercepts and Slopes of Sulfonamide in Dissolution Rate Graph

a) Values of Positive Intercepts

Sulfonamide	Particle size (μm)	Untreated	Solvent			
			Distd. water	0.2% SLS soln.	Sat. soln. of SA	0.2% SLS soln. sat. with SA
		(mg)	(mg)	(mg)	(mg)	(mg)
Sulfisomezole	650	1.3(0.52)	1.1(0.41)	1.4(0.52)	1.0(0.40)	2.1(0.86)
	230	3.1(0.89)	2.4(0.49)	4.4(1.5)	2.4(0.56)	3.2(0.91)
	194	4.0(1.2)	2.6(0.51)	4.1(1.3)	2.8(0.61)	3.5(0.89)
		($\mathrm{mg}^{1/3}$)	($\mathrm{mg}^{1/3}$)	($\mathrm{mg}^{1/3}$)	($\mathrm{mg}^{1/3}$)	($\mathrm{mg}^{1/3}$)
Sulfamethizole	460	0.015	0.012	0.014	0.0050	0.011
	230	0.040	0.020	0.029	0.023	0.043
	163	0.085	0.027	0.061	0.026	0.073

( ); $\mathrm{mg}^{-2/3}\times 10^4$

b) Values of Slopes

Sulfonamide	Particle size (μm)	Untreated	Solvent			
			Distd. water	0.2% SLS soln.	Sat. soln. of SA	0.2% SLS soln. sat. with SA
Sulfisomezole	650	8.70(.427)	8.73(.428)	9.02(.443)	8.94(.437)	8.81(.435)
	230	20.0(1.06)	20.5(1.10)	20.3(1.09)	20.9(1.11)	20.6(1.10)
	194	22.2(1.20)	23.9(1.30)	23.4(1.21)	23.3(1.26)	23.4(1.28)
Sulfamethizole	460	0.113	0.143	0.142	0.136	0.156
	230	0.213	0.277	0.282	0.253	0.286
	163	0.322	0.353	0.425	0.357	0.506

( ); $\times 10^{-3}$
In parentheses shown the results obtained from the negative two-thirds law of the Hixson-Crowell equation.
SLS=sodium lauryl sulfate, SA=sulfonamide

cepts increased with decrease in particle size in each sulfonamide. This fact may be considered due to that surface free energy of powder particles play an important part in the initial dissolution with decrease in particle size. As it is said that the active center on the crystal is considered to be the edges and corners as well as points of crystal defects[8] and the number of edges per gram is inversely proportional to the square of particle size and the number of corners inversely to the cube of particle size, the larger intercept of smaller particle size may be due to the increase in the number of edges and corners per gram of powder particles with decrease in particle size.

The positive intercepts of samples treated with sodium lauryl sulfate solution were also similar to those of samples treated with distilled water.

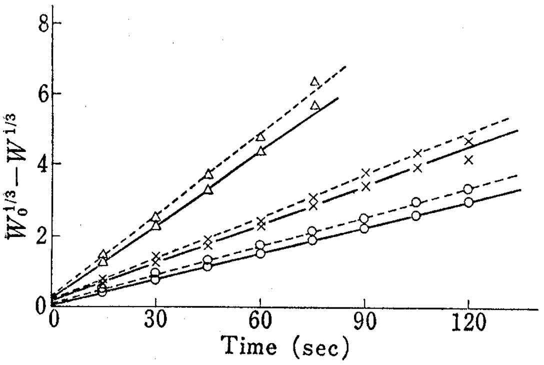

Fig. 8. Effect of Particle Size on Dissolution Rate of Sulfanilamide at 600 rpm

○: 16/32 mesh, ×: 32/48 mesh, △: 48/80 mesh, ——: 200 mg, ------: 300 mg

The slope of lines of samples treated with solvents was larger than those of untreated samples in each sample size for both sulfonamides and it is considered that the powder particle surface was dissolved somewhat in the procedure of washing.

The sieved and recrystallized sulfanilamide particles were also examined for the effect of particle size on the initial dissolution rate and, as shown in Fig. 8, the positive intercepts appeared and the values of intercept were larger with decrease in particle size and also, larger with increase in the amount of sulfanilamide used for dissolution. This phenomenon is quite similar to those of untreated samples of sulfisomezole and sulfamethizole.

The amount of ball-milled sulfamethizole used was equal to the amount required to saturate the dissolution medium and the dissolution profile of ball-milled samples is shown

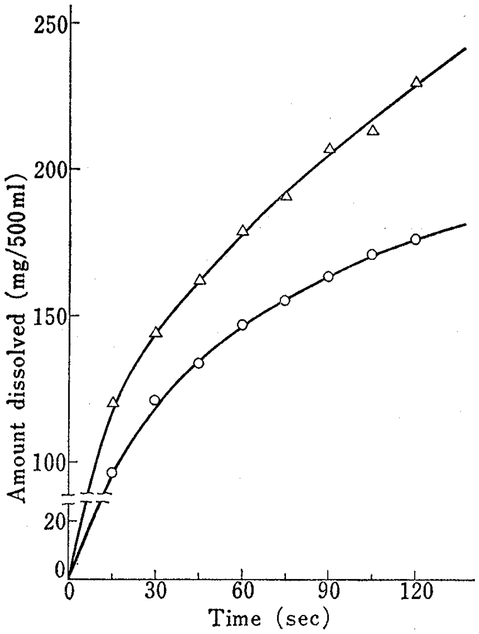

Fig. 9. Dissolution Profile of Ball-Milled Sulfonamide

○: sulfisomezole, △: sulfamethizole

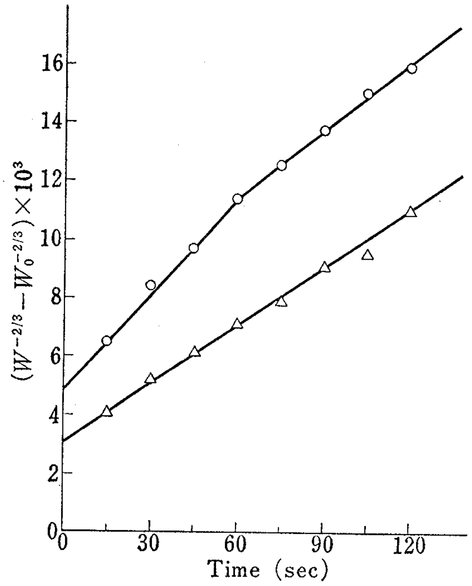

Fig. 10. Dissolution Rate of Ball-Milled Sulfonamide

○: sulfisomezole, △: sulfamethizole

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[8] P.S. Roller, *J. Phys. Chem.*, 36, 1202 (1932).

in Fig. 9, in which the amount of the sulfonamide dissolved is remarkably, because the reduction of particle size results in an increase of available surface area for dissolution. The amount dissolved during 120 sec was 56.1% of saturation for sulfisomezole and 52.1% for sulfamethizole. As in this case of each ball-milled sample, the amount used was just sufficient to saturate the dissolution medium, $(W^{-2/3} - W_0^{-2/3})$ was plotted against time, postulating that the phenomenon of increasing solubility with decreasing particle size[9] was negligible in the derivation of the negative two-thirds law of the Hixson-Crowell equation, and shown in Fig. 10, in which the line of sulfamethizole was linear, but the line of sulfisomezole was biphasic and this result seems to be a similar phenomenon as that reported by Carstensen and Patel.[10] As can be seen from this graph of dissolution rates, the lines of ball-milled sulfonamides had a positive intercept and the values of positive intercept increased greatly compared with those of unmilled ones. The amount dissolved instantly was 26.8% of saturation for sulfisomezole and 24.0% for sulfamethizole, which were calculated from the positive intercepts. This result was considered to be due to the nature of the remarkably reduced particle size by ball-milling and the reduction of particle size might cause a considerable increase in surface free energy of powder, resulting in an increase in the instantly dissolving part of a powder and thereby increasing the initial dissolution.

These facts support the observation that surface free energy of a powder may play an important part in the initial dissolution of a powder owing to the decrease in particle size and especially in ball-milled samples.

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9) D.R. May and I.M. Kolthoff, *J. Phys. Colloid Chem.*, **52**, 836 (1948); G.B. Alexander, *J. Phys. Chem.*, **61**, 1563 (1957); T. Higuchi, *J. Am. Pharm. Assoc., Sci. Ed.*, **47**, 659 (1958); B.V. Enustun and J. Turkevich, *J. Am. Chem. Soc.*, **82**, 4502 (1960); V.F. Smolen and D.O. Kildsig, *Am. J. Pharm. Educt.*, **31**, 512 (1967).

10) J.T. Carstensen and M. Patel, *J. Pharm. Sci.*, **64**, 1770 (1975).