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Dissolution of slightly Soluble Drugs. IV.[1] Effect of Particle Size of Sulfonamides on *in Vitro* Dissolution Rate and *in Vivo* Absorption Rate, and Their Relation to Solubility[2]

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Effect of particle size on absorption rate of rabbit and *in vitro* rate of dissolution was examined using sulfonamide powder drugs with the solubility ranging from 0.1 to 1 mg/ml at 37° in suspension, and the following results were obtained.

1) The dependence of particle size on absorption rate constants and dissolution rate constants obtained with *in vitro* test under sink conditions showed the strongest correlation in the case of the lowest solubility drug of sulfadiazine and this relation decreased with an increase in solubility.

2) Blood level showed that the peak time of the aqueous solution was the fastest of all other samples for each sulfonamide as to the relative order of peak time after the administration of different dosage forms. This fact indicated that the dissolution rate was the rate-limiting step on the absorption of these sulfonamides. Effect of particle size on absorption rate was marked but its effect on the extent of bioavailability was almost constant irrespective of particle size.

3) Plot of percentage unabsorbed *vs.* time for each sulfonamide was linear and the lines for larger particle size had an inflexion about 3 hr after administration of the drug. This fact indicated that absorption of these sulfonamides was apparently first order and an inflexion for larger particle size was considered due to that passage of the drug in the gastrointestinal tract resulted in the change of dissolution environment. It was further considered that the time of an inflexion appearing at 3 hr corresponded to the gastric emptying time.

Keywords——*in vitro–in vivo* correlation and solubility; particle size; solubility; powder sulfonamide absorption; powder sulfonamide dissolution; compartmental analysis; bioavailability

The particle size of a slightly soluble drug has attracted the attention of many researchers in relation to biopharmaceutics.[4] Since absorption occurs only after the solid drug is in solution, orally administered drugs in solid dosage form must first dissolve in the gastrointestinal fluid. In the relationship between dissolution process and absorption process of a drug in the gastrointestinal tract, if the dissolution rate is much less than the diffusion rate to the site of absorption and the absorption rate itself, the dissolution rate is the rate-limiting step, whereas, if the absorption rate is much less than the others, the absorption rate will be the rate-limiting step. Thus the former is obvious in the case of the absorption of slightly soluble drugs and effect of particle size on absorption will be marked.

Bioavailability is the extent to which and the rate at which an active drug reaches the systemic circulation in the body.[5] Therefore, the rate of dissolution is an important determinant for the evalution of bioavailability of slightly soluble drugs and particle size is one of

1) Part III: N. Kaneniwa and N. Watari, *Chem. Pharm. Bull.* (Tokyo), **25**, 867 (1977).
2) Presented at the 95th Annual Meeting of Pharmaceutical Society of Japan, Nishinomiya, April 1975.
3) Location: *Hatanodai, Shinagawa-ku, Tokyo, 142, Japan.*
4) J.G. Wagner, *J. Pharm. Sci.*, **50**, 359 (1961); G. Levy, *Am. J. Pharm.*, **135**, 78 (1963); K.A. Lees, *Pharm. J.*, 289 (1963); J.G. Dare, *Aust. J. Pharm.*, **45**, S-58 (1964); L. Renoz, *J. Pharm. Belg.*, **22**, 41 (1967).
5) "Guidelines for Biopharmaceutical Studies in Man," APhA Academy of Pharmaceutical Sciences, Washington, D.C., 1972; L.Z. Benet, "Drug Design," Vol. IV, ed. by E.J. Ariëns, Academic Press, New York, 1973, p. 1; T, Suzuki, "Yakubutsu-no Bioavailability," Yakugyojihosha, Tokyo, 1976.

the most important factors in relation to physicochemical properties of a drug which affects bioavailability.[6]

Many reports have been published on the effect of particle size on blood level and clinical effect, being discussed qualitatively.[7] Only in griseofulvin, which is a practically insoluble drug, it was demonstrated that logarithm of specific surface area of the powder drug was proportional to the relative absorbability for the extent of availability.[8]

The present paper deals with the effect of particle size on the *in vitro* dissolution rate and *in vivo* absorption rate, and their relation to solubility, using sulfonamide powder particles with the solubility ranging from 0.1 to 1 mg/ml.

Experimental

Material——Powder drugs of four sulfonamides-sulfadiazine (SD), sulfisoxazole (SIX), sulfathiazole (ST), and sulfamethizole (SMT) used were J.P. grade. The different particle size grades used were obtained by sieving through a Ro-Tap testing sieve shaker, using Japan Industrial Standard (JIS) sieves. The arithmetic mean diameter of sieved samples was taken as the mean diameter of the sulfonamide particles. The ground samples were obtained by ball-milling as described previously,[1] and the surface mean diameter was determined by the air permeability method[9] and shown in Table I. True density was measured by the use of a helium densitometer.

Table I. Abbreviation, Physical Constants, and Physicochemical Properties of Sulfonamides

Sulfonamide	Abbr.	pKa_1	pKa_2	M.W.	D_{sp} (μm)	Density (ρ)	Solubility[a] (mg/ml)
Sulfadiazine	SD	2.00	6.48	250.3	1.08	1.59	0.128
Sulfisoxazole	SIX	1.55	5.10	267.3	1.94	1.61	0.292
Sulfathiazole	ST	2.36	7.12	255.3	2.95	1.71	0.879
Sulfamethizole	SMT	2.00	5.45	270.3	1.90	1.53	0.884

D_{sp}: surface mean diameter of ball-milled sample.
a) Measured in distilled water at 37°.

Procedure——Male albino rabbits weighing 2.3—2.5 kg were used and fasted for 48 hr before the experiment to minimize the influence of admixture in the stomach but water was given freely. Experiments with a rabbit was repeated every 7 days for different particle size dosage forms of a drug. Under these conditions, rabbit weight was almost constant at the maximum limit within 10% and, if necessary, food was controlled.

Sulfonamide solution (200 mg/20 ml) was prepared by dissolving in distilled water with sulfonamide sodium salt, and was administered orally as the standard reference and controlling the volume appropriately for intravenous injection. Each particle size grade was prepared as the aqueous suspension (200 mg/20 ml) adding distilled water after the sample was well wetted with 1 ml of 0.2% sodium lauryl sulfate solution in order to exert total surface area of powder particles effective in the dissolution and administered orally through a catheter.

Food was withheld for 10 hr after the experiment and blood specimens (0.5 ml) were taken from the aural vein at certain intervals. Urine was collected for 48 hr after medication.

Assay——Sulfonamide in blood was determined as total sulfonamide, and as free and total sulfonamide in urine using the Bratton-Marshall method.[10]

6) "Biological Availability—A Statement by the Department of Pharmaceutical Sciences, Pharmaceutical Society of Great Britain," *Pharm. J.*, **4**, 438 (1972); L.F. Chasseaud and T. Taylor, *Annu. Rev. Pharmacol.*, **14**, 35 (1974); J. Koch-Weser, *New Eng. J. Med.*, **291**, 233 (1974): *idem*, *ibid.*, **291**, 503 (1974).
7) J.H. Fincher, *J. Pharm. Sci.*, **57**, 1825 (1968); L.F. Prescott, R.F. Steel, and W.R. Ferrier, *Clin. Pharmacol. Ther.*, **11**, 496 (1970).
8) R.M. Atkinson, C. Bedford, K.J. Child, and E.G. Tomich, *Antibiot. Chemother.*, **12**, 232 (1962); *idem*, *Nature* (London), **193** (1962).
9) E. Suito, M. Arakawa, and M. Takahashi, *Kogyo Kagaku Zasshi*, **59**, 307 (1956).
10) A.C. Bratton and E.K. Marshall, *J. Biol. Chem.*, **128**, 537 (1939).

***In Vitro* Dissolution Rate and Solubility**——An identical apparatus and procedure, as reported earlier,[11] were used for the determination of the amount of sulfonamides dissolved in distilled water, and the dissolution rates were determined. Solubility of sulfonamide was also determined in the same manner as described previously[11] and shown in Table I. Sulfonamides were assayed by spectrophotometry.

Results and Discussion

Effect of Particle Size of Sulfonamide on Blood Level in the Rabbit

Particle size of four grades, ball-milled one, and an aqueous solution as the standard were used to examine the effect of particle size of a sulfonamide on the blood level in a rabbit. Each sulfonamide was tested with three rabbits and shown in Fig. 1, which revealed that the peak time of the aqueous solution was the fastest of all other samples for each sulfonamide as to the relative order of peak time after the administration of different dosage forms. This fact indicated that the dissolution rates were the rate-limiting step on the absorption of these sulfonamide powders and relative order of peak time of blood level was considered to correspond to the rank order of the dissolution rates of different particle size of powder particles in the gastrointestinal fluids. Furthermore, in the case of sulfathiazole and sulfamethizole, it seemed that the effect of particle size on blood level was less than those of sulfadiazine and sulfisoxazole.

Effect of Particle Size on the Extent of Bioavailability

The extent availability may be measured either using drug concentration in the blood or amount of a drug in the urine. The area under blood concentration-time curve (AUC) for the drug from different dosage forms is a measure of the extent of availability. The amount of active drug collected in the urine after the administration of various dosage forms may also be used as a relative measure for the extent of availability.

The AUC and the amount excreted in the urine during 48 hr after oral administration of various dosage forms of sulfonamide are shown in Table II, in which free and total sulfonamide excreted were almost constant irrespective of dosage forms in each sulfonamide. It was also found that the AUC was similar to the results obtained by the measurment of drug collected in the urine.

It was found that sulfadiazine was largely metabolized after ingestion of the drug but no difference was found among the particle sizes. In the case of sulfathizole No. 2, individual difference among rabbits was found in relation to the ability of metabolism. This tendency was also found in the paper reported by Yamazaki, *et al.*,[12] and the ratio of the amount of metabolized product excreted to the total amount excreted was also similar to their experimental data.

Approach to the Best Estimation of the Absorption Rate Constant from the Observed Data

The rate of drug ingestion from blood level data is determined as follows: When the absorption rate process is assumed to be the first order, the blood concentration of a drug is described as a two-term exponential equation.[13] Determination of the absorption rate constant from this method is made from blood level data by the method of curve-fitting, that is, method of residuals (Feathering method)[14] or nonlinear regression analysis.[15]

11) N. Kaneniwa and N. Watari, *Chem. Pharm. Bull.* (Tokyo), **22**, 1699 (1974).
12) M. Yamazaki, M. Aoki, and A. Kamada, *Chem. Pharm. Bull.* (Tokyo), **16**, 707 (1968).
13) T. Teorell, *Arch. Intern. Pharmacodyn.*, **57**, 205 (1937).
14) *a*) J.G. Wagner, *Clin. Pharmacol. Therap.*, **8**, 211 (1967); *b*) J.G. Wagner and C.M. Metzler, *J. Pharm. Sci.*, **56**, 658 (1967); *c*) R.E. Notari, "Biopharmaceutics and Pharmacokinetics-An Introduction," Marcel Dekker, Inc., New York, 1971, p. 72.
15) R.G. Wiegand and P.G. Sanders, *J. Pharmacol. Exptl. Therap.*, **146**, 271 (1964); J.F. Borzelleca and W. Lowenthal, *J. Pharm. Sci.*, **55**, 151 (1966); W. Lowenthal and B.L. Vitsky, *ibid.*, **56**, 169 (1967); F.W. Mueller and S.V. Lieberman, *ibid.*, **59**, 514 (1970).

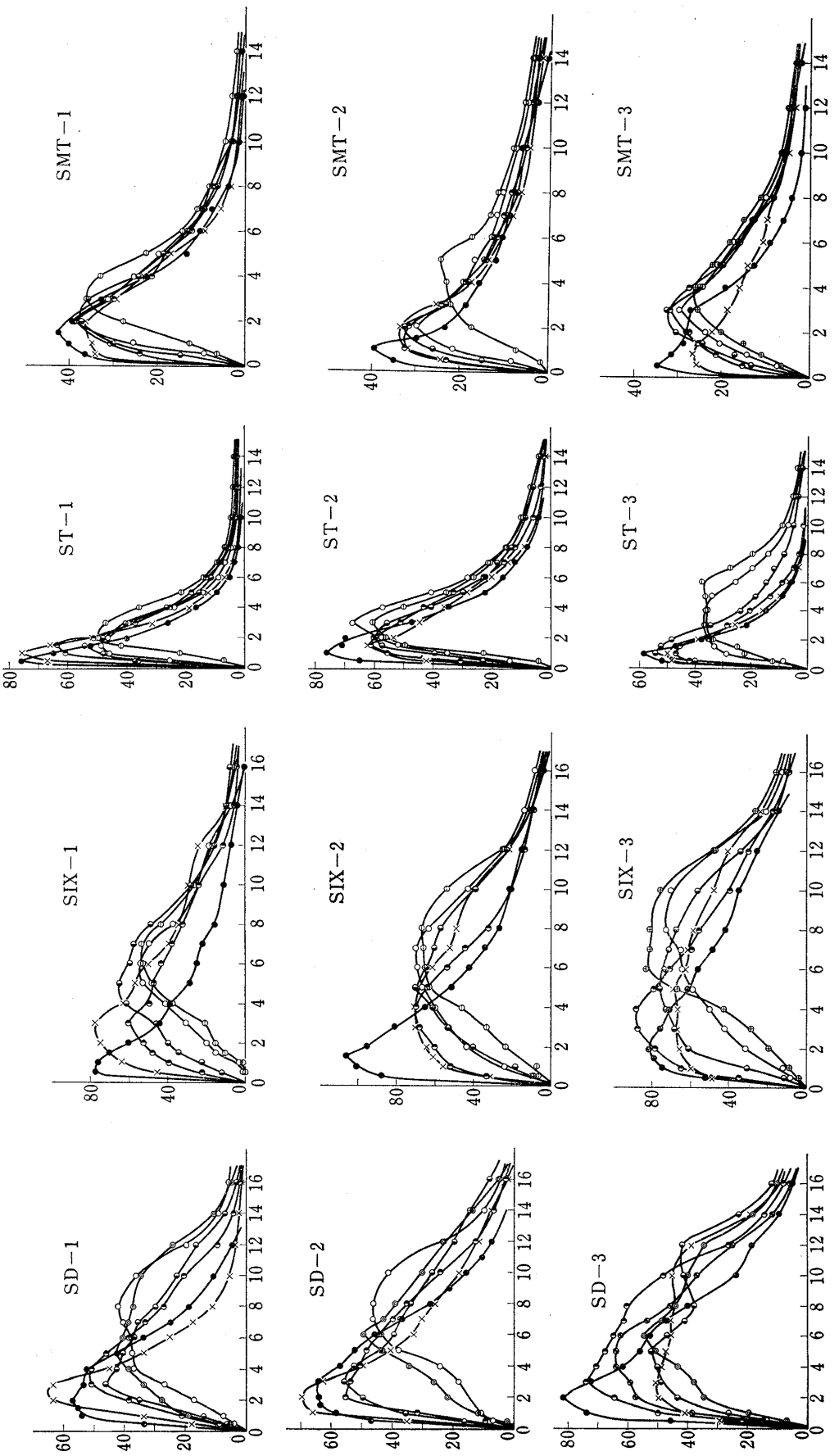

Fig. 1. Effect of Particle Size on Blood Levels of Sulfonamides

Ordinates show the blood concentration of sulfonamides in μg/ml and abscisas the time in hour after orally administered sulfonamides, particle size in diameter (μm).
●: solution, ×: ball-milled, ◑: 81, ◔: 115, ◐: 163, ◎: 230, ○: 324, ⊕: 545, ⊖: 650.

TABLE II. Effect of Particle Size on the Extent of Bioavailability after Oral Administration of Aqueous Suspension of Sulfonamide

Sulfonamide		Particle size (μm)	Amount excreted for 48 hr (%)		AUC (μg·hr/ml)	Metabolized ratio (%) (total-free/total)
			Free	Total		
SD	No. 1	Soln.	4.6	95.3	388	95.2
		Ball-milled	9.1	79.3	329	88.5
		81	14.0	92.7	389	84.9
		163	16.3	89.7	396	81.8
		230	13.0	84.8	445	84.7
		324	9.8	81.4	417	88.0
	No. 2	Soln.	1.0	88.2	485	98.9
		Ball-milled	18.3	91.8	464	80.1
		81	15.1	86.7	471	82.6
		163	18.2	99.6	513	81.8
		230	12.8	89.7	440	87.2
		324	7.6	86.7	428	91.2
	No. 3	Soln.	24.9	92.2	581	73.0
		Ball-milled	26.5	91.8	636	71.1
		81	21.1	96.5	747	78.1
		115	20.9	94.1	628	77.8
		163	24.8	92.1	628	73.1
		230	16.4	82.1	593	80.0
SIX	No. 1	Soln.	81.8	92.3	389	11.4
		Ball-milled	66.4	86.1	639	22.9
		81	68.6	90.4	486	24.1
		163	60.8	103.7	590	41.4
		324	71.2	84.4	410	15.6
		650	64.2	84.6	430	24.1
	No. 2	Soln.	63.9	88.6	658	27.9
		Ball-milled	95.7	100.4	696	4.7
		81	91.7	91.8	587	0.2
		163	85.0	89.3	622	4.8
		324	69.6	84.1	684	17.3
		650	97.0	98.6	620	1.6
	No. 3	Soln.	83.1	89.9	792	7.6
		Ball-milled	57.0	76.2	886	25.2
		81	80.0	93.2	863	14.2
		163	71.1	94.8	845	25.0
		324	87.5	96.1	788	8.9
		545	78.9	90.2	883	12.6
ST	No 1.	Soln.	35.4	80.4	201	56.0
		Ball-milled	31.7	83.4	232	62.0
		81	34.2	82.2	257	58.3
		163	53.0	84.3	243	37.1
		324	51.9	85.0	210	38.9
		650	31.6	80.9	228	61.0
	No. 2	Soln.	69.2	83.6	475	17.2
		Ball-milled	58.3	77.1	300	24.4
		81	62.5	82.5	329	24.2
		163	57.9	76.5	334	24.4
		324	63.5	81.2	371	21.8
		650	78.5	100.9	344	22.2
	No. 3	Soln.	21.6	92.1	175	77.1
		Ball-milled	18.8	84.6	174	77.7
		81	19.3	78.8	178	75.5
		163	13.4	52.9	252	74.6
		324	22.2	90.0	264	75.3
		650	23.2	88.6	297	73.8

Sulfonamide		Particle size (μm)	Amount excreted for 48 hr (%)		AUC (μg·hr/ml)	Metabolized ratio (%) (total-free/total)
			Free	Total		
SMT	No. 1	Soln.	—	96.2	188	—
		Ball-milled	—	83.4	174	—
		81	—	77.4	182	—
		163	—	83.1	185	—
		324	—	69.2	183	—
		650	—	82.0	185	—
	No. 2	Soln.	—	56.9	167	—
		Ball-milled	—	83.3	173	—
		81	—	74.7	187	—
		163	—	62.5	175	—
		324	—	61.4	195	—
		650	—	75.3	186	—
	No 3.	Soln.	87.9	93.8	161	6.35
		Ball-milled	74.7	83.4	170	10.4
		81	77.1	89.8	203	14.1
		163	77.1	86.5	198	10.9
		324	80.2	87.0	188	7.83
		545	70.0	79.9	190	12.4

—; Not measured.

However, when the dissolution rate is a rate-limiting step in the drug absorption, estimation of apparent absorption rate constant (k_a) by a nonlinear regression analysis may lead to error with a few exceptions such as the solution of a drug administered.[16] As shown below, in the case of low solubility drug such as sulfadiazine and sulfisoxazole, the lines of percentage unabsorbed *vs.* time plots for larger particle size had an inflexion about 3 hr after administration of the drugs and further, percentage unabsorbed-time plots of these solutions was not linear and showed concave descending-type curves. Therefore, in this case of sulfonamide, it was not possible to estimate the k_a by nonlinear regression analysis.

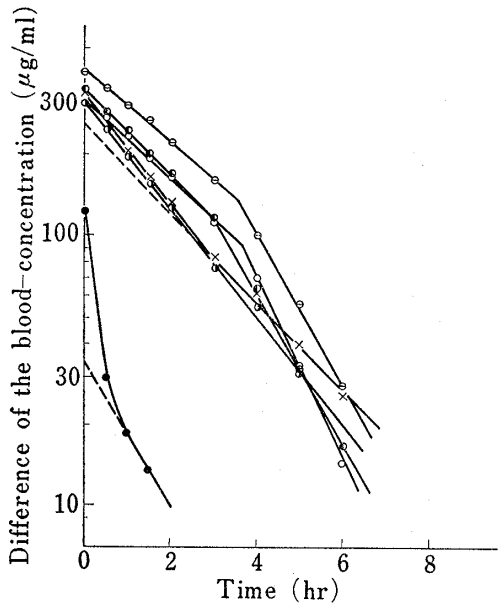

Fig. 2. Plot of the Logarithmic Difference *vs.* Time for Sulfisoxazole No. 1

Particle size in diameter (μm)
●: solution, ×: ball-milled, ◑: 81,
◐: 163, ○: 324, ⊖: 650.

Furthermore, in the case of the method of residuals, it is based on the assumption that a plot of ln C_p (the blood concentration) *vs.* time will become linear with slope of $-k_e$ (the elimination rate constant) after the drug concentration in the gastrointestinal tract becomes negligible. Thus, a plot of ln C_p *vs.* time is constructed and the linear portion is extrapolated back to time zero, and the difference between the experimental values and the extrapolated line values are then determined. These differences are plotted as ln (difference) *vs.* time and this plot will be linear with slope of $-k_a$.

This plot of sulfisoxazole No. 1 was made and is shown in Fig. 2, in which the lines had

16) E. Nelson, *J. Pharm. Sci.*, **50**, 187 (1961).

an inflexion about 3 hr for larger particle size. The result was quite similar to that obtained by percentage unabsorbed-time plots, as shown below. The estimates of k_e and k_a were made by the least squares method, and k_a of larger particle size was obtained from the initial linear portions and shown in Table III, where the values of k_a/k_e decreased with an increase in particle size.

Table III. Comparison of the Values of Apparent Absorption Rate Constant estimated by Various Methods

Sulfisoxazole	Particle size (μm)	Elimination rate constant (hr^{-1})	Apparent absorption rate constant (hr^{-1})			Ratio of ka_1/ka_2
			Residuals method	One-compt. method (ka_1)	Two-compt. method (ka_2)	
SIX-1	Soln.	0.245	6.07 (0.615)	6.15 (1.10)	2.79 (0.280)	—
	Ball-milled	0.253	1.19 (0.389)	0.977 (0.171)	0.832 (0.214)	—
	81	0.273	0.445	0.368	0.303	1.22
	163	0.251	0.364	0.208	0.162	1.28
	324	0.253	0.336	0.180	0.139	1.29
	650	0.268	0.311	0.119	0.0954	1.25
	nth power of particle size		(−0.167)	(−0.510)	(−0.522)	
SIX-3	Soln.	0.126	—	1.96 (0.462)	1.91 (0.422)	—
	Ball-milled	0.144	—	5.54 (0.239)	7.52 (0.243)	—
	81	0.144	—	0.597	0.455	1.31
	163	0.138[a]	—	0.338	0.270	1.25
	324	0.138[a]	—	0.165	0.138	1.20
	545	0.138[a]	—	0.0933	0.0793	1.18
	nth power of particle size			(−0.978)	(−0.919)	

Figures in parentheses show the values of slower absorption rate constant by a bi-exponential equation and the dependence of nth power of particle size of four grades on absorption rate constant,
a) Averaged value was used when the elimination rate constant was not obtained correctly.
—, Not calculated. Parameters used to calculate absorption rate constant for two-compartment open method: k_2, k_{12}, k_{21}=0.413, 0.204, 0.676 for SIX-1 and 0.235, 0.290, 0.637 for SIX-3 and slow disposition rate constant (β) was 0.274, 0.147 respectively. k_{12} and k_{21} are the first-order distribution rate constants out of and back into the central compartment from the peripheral compartment, and k_2 is the sum of the first-order elimination rate constants for the simultaneous process of metabolism and excretion from the central compartment.

Since k_e must be determined when the amount of a drug in the gastrointestinal tract has approached zero, the method is not applicable to cases where $k_a < k_e$. In other words, there must be a time period during which a significant amount of a drug exists in the body after absorption of the drug is completed. The estimate of k_e will therefore increase in accuracy as the value of k_a/k_e increases. However, the estimates are not as good at smaller ratios. In addition, the value for k_a is based on the slope and intercept of this ln C_p plot in both methods and the error in k_a then results in part from the plot used for k_e. When the ratio of k_a/k_e approaches nearly one, the error in k_e will be around −20% and in k_a also around +30%.[14b,c] Therefore, application of this method for larger particle size may lead to a significant error.

Subsequently, compartmental analysis was made of the estimates of k_a and the plots of percentage unabsorbed *vs.* time for sulfisoxazole No. 1 and No. 3 are shown in Fig. 3, which was obtained by the Loo-Riegelman method[17] and in Fig. 4, by the Wagner-Nelson[18] method. When comparing Fig. 3 and 4, it appears that the absorption rates were small in the Loo-Riegelman method as reported earlier.[17] In these graphs, the plots were linear and lines for larger particle size had necessarily an inflexion at about 3 hr after administration of the drug. This fact indicated that absorption of sulfisoxazole was apparently first order

17) J.C. Loo and S. Riegelman, *J. Pharm. Sci.*, **57**, 918 (1968).
18) J.G. Wagner and E. Nelson, *J. Pharm. Sci.*, **52**, 610 (1963); *idem*, *ibid.*, **53**, 1392 (1964).

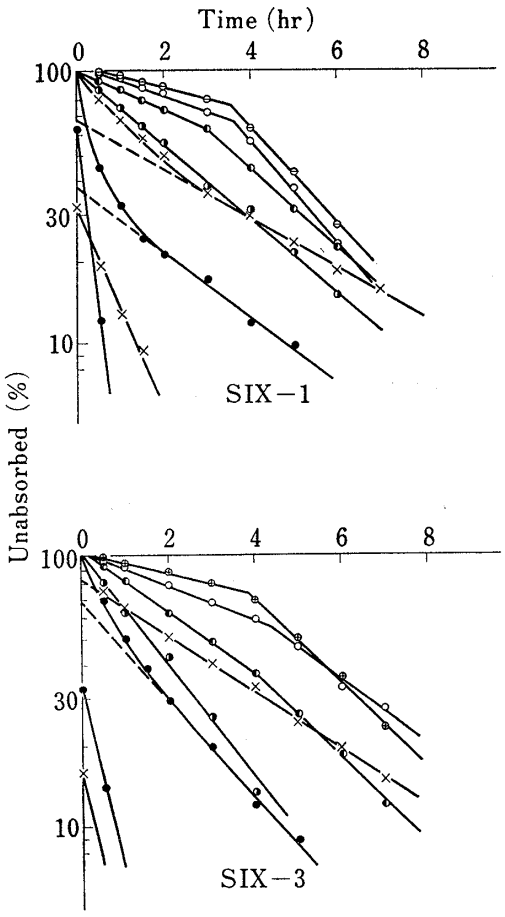

Fig. 3. Plot of Percentage Unabsorbed *vs.* Time by Applying Two-Compartment Open Model, Particle Size in diameter (μm)

●: solution, ×: ball-milled, ◑: 81, ◐: 163, ○: 324, ⊕: 545, ⊖: 650.

and an inflexion for larger particle size might be considered due to the simultaneous loss of the drug having a lag time to extravascular compartment at the site of administration, as reported already.[19] However, as seen in the section of the extent of bioavailability, the total amount excreted during 48 hr and the AUC of the drug were constant irrespective of particle size and no difference was found for the extent of availability of various dosage forms in other sulfonamides. This phenomenon was therefore considered to indicate that movement of the drug down the gastrointestinal tract[20] resulted in the change of dissolution environment; increase in pH[21] resulted in increase of dissolution rate and thereby increased absorption rate of the drug, because these drugs are weak acids. It is further considered that the time of an inflexion appearing about 3 hr after oral administration of the drug corresponded to the gastric emptying time.[22]

The percentage unabsorbed-time plots for aqueous solution and ball-milled sample became concave descending-type curves and the plot may be described by a bi-exponential equation. Thus the method of residuals was used to separate the fast absorption component from the slower step. This phenomenon of aqueous solution supported the observation that the free acid of sulfisoxazole would be precipitated at pH of the stomach and dissolved again to be absorbed, because the aqueous solution was administered orally in the form of an acid salt which was prepared with equivalent sodium hydroxide. In the case of a ground sample, it was considered due to the imcompleted dispersion of agglomerated ball-milled sample before the administration of these drugs.

The estimate of k_a was then made by the least squares method and k_a for larger particle size was also obtained from the initial linear portions and shown in Table III, in which the ratio of k_2/k_e was around 1.5 in both sulfisoxazoles and corresponded to the values reported already.[23]

As the blood concentration *vs.* time course curve for sulfisoxazole was clearly described by a bi-exponential equation after rapid *i.v.* injection, absolute values for absorption rate must be estimated by the two-compartment open model.[17] However, as shown by Wagner,[24] when we wish to correlate the apparent absorption rate constants estimated by applying the one-compartment open model with *in vitro* rates of drug dissolution from dosage forms, it

19) R.E. Notari, J.L. DeYoung, and R.H. Reuning, *J. Pharm. Sci.*, **61**, 135 (1972); D. Perrier and M. Gibaldi, *ibid.*, **62**, 225 (1973); L.J. Leeson and H. Weintraub, *ibid.*, **62**, 1936 (1973).
20) S. Grevsten, H. Johansson, and G. Nylander, *Acta Chir. Scand.*, **133**, 563 (1967).
21) W.G. Crouthamel, C.R. Abolin, J. Hsieh, and J.K. Lim, *J. Pharm. Sci.*, **64**, 1726 (1975).
22) E. Nelson, *Clin. Pharmacol. Therap.*, **4**, 283 (1963).
23) S. Riegelman, J.C. Loo, and M. Rowland, *J. Pharm. Sci.*, **57**, 117 (1968).
24) J.G. Wagner, *J. Pharm. Sci.*, **59**, 1049 (1970).

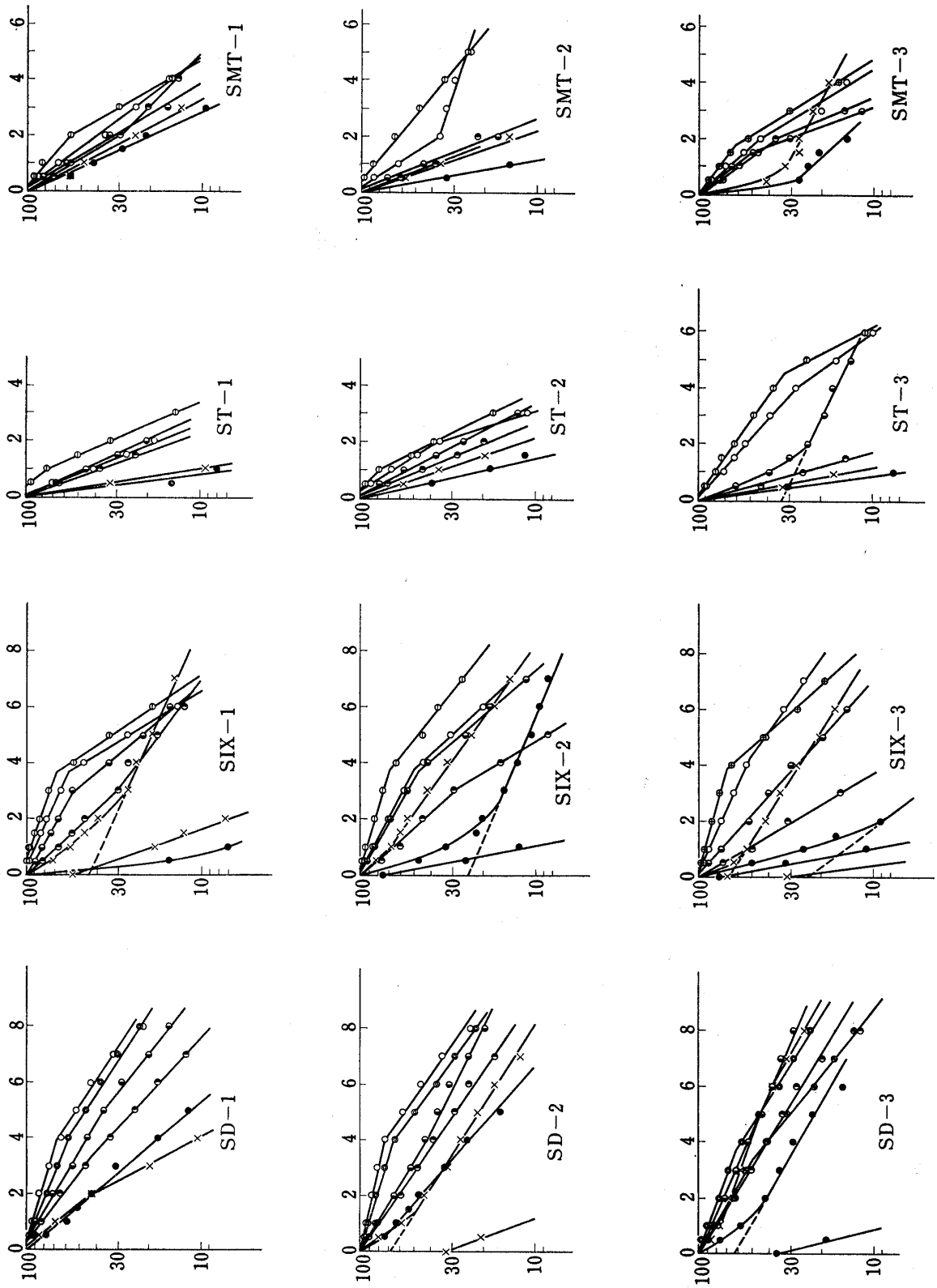

Fig. 4. Semilogarithmic Plot of Percentage Unabsorbed *vs.* Time after orally Administered Sulfonamides by Applying the One-Compartment Open Model

Ordinates show the percentage unabsorbed and abscisas the time in hour, particle size in diameter (μm), ●: solution, ×: ball-milled, ◑: 81, ◔: 115, ◐: 163, ◎: 230, ○: 324, ⊕: 545, ⊖: 650.

may be reasonably safe to utilize the ratios of the absorption rate constants and correlate these with ratios of dissolution rates of dosage forms from an *in vitro* test.

The dependence of *n*th power of particle size on apparent absorption rate constants obtained from the slope of a line plotting absorption rate constant *vs.* particle size of four grades on a logarithmic graph was calculated. The difference for the values of *n* in both compartment methods was hardly found. In addition, the ratio of absorption rate constant obtained by one-compartment open method to that by two-compartment open method, as shown in the last column in Table III, was constant irrespective of dosage forms, as reported earlier.[24]

Dependence of *n*th Power of Particle Size on Absorption Rate Constant and *in Vitro* Dissolution Rate Constant, and Their Relation to Solubility

As we wish to correlate absorption rate derived from drug concentration in the blood with *in vitro* rate of drug dissolution from dosage forms, we are interested in relative values or ratios and not wish absolute individual values. Therefore, in the present work, estimates of k_a were made by applying one-compartment open model and percentage unabsorbed was plotted *vs.* time and shown in Fig. 4, which revealed that absorption of sulfonamides was apparently first order and the lines of larger particle size had an inflexion about 3 hr after administration of the drugs. Appearance of these inflexions strongly supported the earlier observation that passage of the drug in the gastrointestinal tract resulted in the change of dissolution environment. Further, percentage unabsorbed-time plots for aqueous solution and ball-milled sample became a concave descending-type curve in some cases and this tendency was marked with decrease in solubility of the drug such as sulfadiazine and sulfisoxazole. It was obvious in the case of aqueous solution that the free acids of sulfonamide would be precipitated by pH of the stomach and dissolved again to be absorbed because of its administration as an acid salt. In the case of ball-milled sample, this phenomenon was also considered as described in the above section.

As shown in Fig. 4, absorption from solution proceeded much more rapidly than from other powdered dosage forms in each sulfonamide and this result indicated obviously that absorption of these sulfonamide dosage forms was rate-limited by the dissolution process.

Drug absorption from solution may be governed by the principles embodied in the pH-partition theory of Brodie and his group.[25] Gibaldi[26] said that very weak bases ($pK_a < 2.5$) may be absorbed to some extent in the stomach because they are significantly un-ionized even in this strongly acidic environment and the absorption of weak acids with pK_a values >3 in the small intestine is quite rapid due to the large surface area available for absorption. As shown in Table I, sulfonamides being very weak bases and weak acids used in the present work belong to the class of above drugs. Furthermore, Crouthamel, *et al.*[27] reported that the ionized form of sulfaethizole was significantly absorbed from the stomach and intestine. These facts supported the observation that the absorption of larger particle size after 3 hr of medication was quite rapid.

The apparent absorption rate constants were then calculated in the same manner described above and are shown in Table IV. Dependence of *n*th power of particle size on apparent absorption rate constants was also calculated and is shown in Tables IV and V.

In the present work, as dissolution is the rate-limiting step in the absorption process, the kinetics of absorption are not governed by the pH-partition theory, but by the physicochemical factors which govern the rate of dissolution of the drugs in aqueous media. *In vitro* drug dissolution test was therefore conducted with postulating that the amount of the drug dissolved in the gastrointestinal tract was rapidly absorbed into the body and the drug

25) B.B. Brodie and C.A.M. Hogben, *J. Pharm. Pharmacol*, **9**, 345 (1957).
26) M. Gibaldi, "Introduction to Biopharmaceutics," Lea and Febiger, Philadelphia, 1971, p. 18.
27) W.G. Crouthamel, G.H. Tan, L.W. Dittert, and J.T. Dolluisio, *J. Pharm. Sci.*, **60**, 1160 (1971).

TABLE IV. Apparent Absorption Rate Constant of Aqueous Suspension of Sulfonamide estimated by Applying the One-Compartment Open Model

Sulfonamide	Number of rabitt								
	No. 1			No. 2			No. 3		
	Particle size (μm)	Elimination rate const. (hr^{-1})	Absorption rate const. (hr^{-1})	Particle size (μm)	Elimination rate const. (hr^{-1})	Absorption rate const. (hr^{-1})	Particle size (μm)	Elimination rate const. (hr^{-1})	Absorption rate const. (hr^{-1})
SD	Soln.	0.415	0.417	Soln.	0.409	— (0.310)	Soln.	0.328	1.33 (0.204)
	Ball-milled	0.413[a]	0.654	Ball-milled	0.433	0.906 (0.220)	Ball-milled	0.364	2.69 (0.133)
	81	0.402	0.281	81	0.403	0.271	81	0.335[a]	0.227
	163	0.430	0.229	163	0.422[a]	0.221	115	0.335[a]	0.218
	230	0.405	0.138	230	0.422[a]	0.105	163	0.327	0.170
	324	0.413[a]	0.103	324	0.444	0.0724	230	0.320	0.133
	*n*th power of particle size		(−0.737)			(−0.977)			(−0.532)
SIX	Soln.	0.245	6.15 (1.10)	Soln.	0.272	1.81 (0.152)	Soln.	0.126	1.96 (0.462)
	Ball-milled	0.253	0.977 (0.171)	Ball-milled	0.279	1.86 (0.255)	Ball-milled	0.144	5.54 (0.239)
	81	0.273	0.368	81	0.262[a]	0.370	81	0.144	0.597
	163	0.251	0.208	163	0.254	0.223	163	0.138[a]	0.338
	324	0.253	0.180	324	0.253	0.202	324	0.138[a]	0.165
	650	0.268	0.119	650	0.254	0.104	545	0.138[a]	0.0933
	*n*th power of particle size		(−0.501)			(−0.564)			(−0.978)
ST	Soln.	0.495	2.51	Soln.	0.366	1.71	Soln.	0.458	1.92
	Ball-milled	0.487	2.42	Ball-milled	0.354	1.06	Ball-milled	0.460	1.79
	81	0.478[a]	1.06	81	0.345	0.839	81	0.451	1.11
	163	0.478[a]	0.771	163	0.349[a]	0.754	163	0.456[a]	0.804
	324	0.459	0.988	324	0.331	0.603	324	0.456[a]	0.392
	650	0.472	0.407	650	0.349[a]	0.460	650	0.456[a]	0.257
	*n*th power of particle size		(−0.379)			(−0.346)			(−0.736)
SMT	Soln.	0.486	0.712	Soln.	0.332	1.67	Soln.	0.291[a]	0.962
	Ball-milled	0.515	0.622	Ball-milled	0.346	0.903	Ball-milled	0.279	0.838
	81	0.580	0.601	81	0.334[a]	0.643	81	0.299	0.465
	163	0.504[a]	0.571	163	0.310	0.591	163	0.291[a]	0.464
	324	0.504[a]	0.497	324	0.334[a]	0.576	324	0.299	0.444
	650	0.505	0.342	650	0.349	0.308	545	0.286	0.277
	*n*th power of particle size		(−0.264)			(−0.322)			(−0.237)

Figures in parentheses show the values of slower absorption rate constant described by a bi-exponential equation, and dependence of particle size of four grades on its absorption rate constants.

a) Averaged values were used when the elimination rate constants were not obtained correctly.

—, Not calculated.

dissolution in the gastrointestinal fluid would proceed under sink conditions because of dissolution rate-limited absorption.

The dissolution rate of a solid is described by the Noyes–Whitney equation:[28]

$$\frac{dc}{dt} = KS(C_s - C) \tag{1}$$

where dc/dt is the dissolution rate, K, the apparent dissolution rate constant, S, the surface area of the solid, C_s, the saturated concentration, and C is the solute concentration in the bulk medium. Under the conditions postulated above, the equation is reduced to

$$\frac{dc}{dt} = KSC_s \tag{2}$$

When W_0 mg of powder particles was used, the surface area (S) was then replaced with total surface area of the particles assuming that powder particles are all spherical and the following equation was obtained at initial stage of dissolution.

$$\frac{dc}{dt} = 6KW_0C_s/\rho d_0 \tag{3}$$

where d_0 is the mean diameter of the particles, ρ, the density of the particles, and $6/\rho d_0$ is the specific surface area of the powder. An equation, the so-called Hixson–Crowell cube root law,[11,29] was then derived for the dissolution of particles in which the surface area was allowed to change with time from this equation and gives

$$W_0^{1/3} - W^{1/3} = kt \tag{4}$$

where W is the weight of the particles at time t and $k=2KW_0^{1/3}C_s/\rho d_0$ is the apparent dissolution rate constant.

With respect to the dissolution medium and agitation speed, as we are interest in relative values or ratios of dissolution rate constants, distilled water was used instead of artificial gastric juice and agitation speed used was 700 rpm in spite of 50 rpm pointed out by Levy, *et al.*[30] Because sulfonamide solubility as a function of pH is not marked below the pH of distilled water[31] and the surface tension of gastric juice[32d] was significantly low in the presence of physiological surfactants,[32] and an increase in agitation speed resulted in a similar effect where addition of a surfactant to the dissolution media increased the dissolution rate according to improved wetting of the solid by the liquid.[33]

Considering the above facts, each sample grade of powder particles was well wetted and prepared as an aqueous suspension before the administration of these drugs.

The logarithmic plots of apparent dissolution rate constants obtained from Eq. (4) under sink conditions *vs.* particle size are shown in Fig. 5. The dependence of nth power of particle size on dissolution rate constant was then calculated and shown in Table V. Comparison of the dependence of particle size on dissolution rate constant and absorption rate constant showed the strongest correlation in the case of the lowest solubility drug of sulfadiazine and this relation decreased with an increase in solubility as in sulfathiazole and sulfamethizole.

As shown in Table V, the solubility of sulfadiazine was less than one-half of that of sulfisoxazole and the dependence of particle size on absorption rate for sulfadiazine was

28) A.A. Noyes and W.R. Whitney, *J. Am. Chem. Soc.*, **19**, 930 (1897).
29) A.W. Hixson and J.H. Crowell, *Ind. Eng. Chem.*, **23**, 923 (1931).
30) G. Levy, J.R. Leonards, and J.A. Procknal, *J. Pharm. Sci.*, **54**, 1719 (1965).
31) F.A. Svec, P.S. Rhoads, and J.H. Rohr, *Arch. Intern. Med.*, **85**, 83 (1950); S.A. Kaplan, R.E. Weinfeld, C.W. Abruzzo, and M. Lewis, *J. Pharm. Sci.*, **61**, 773 (1972).
32) *a*) T.R. Bates, M. Gibaldi, and J.L. Kanig, *Nature* (London), **210**, 1331 (1966); *b*) T.R. Bates, S-L. Lin, and M. Gibaldi, *J. Pharm. Sci.*, **56**, 1492 (1967); *c*) S-L. Lin, J. Menig, and L. Lachman, *ibid.*, **57**, 2143 (1968); *d*) P. Finholt and S. Solvang, *ibid.*, **57**, 1322 (1968); *e*) H. Weintraub and M. Gibaldi, *ibid.*, **58**, 1368 (1969).
33) N. Watari and N. Kaneniwa, *Chem. Pharm. Bull.* (Tokyo), **24**, 2577 (1976).

Table V. Dependence of Particle Size on Apparent Absorption Rate Constant and Apparent Dissolution Rate Constant

Sulfonamide	nth power of particle size		Solubility (mg/100 ml)
	Absorption rate constant	Dissolution rate constant	
SD	−0.737, −0.977, −0.532	−0.882	12.8
SIX	−0.510, −0.564, −0.978	−0.929	29.2
ST	−0.379, −0.346, −0.736	−0.857	87.9
SMT	−0.264, −0.322, −0.237	−0.962	88.4

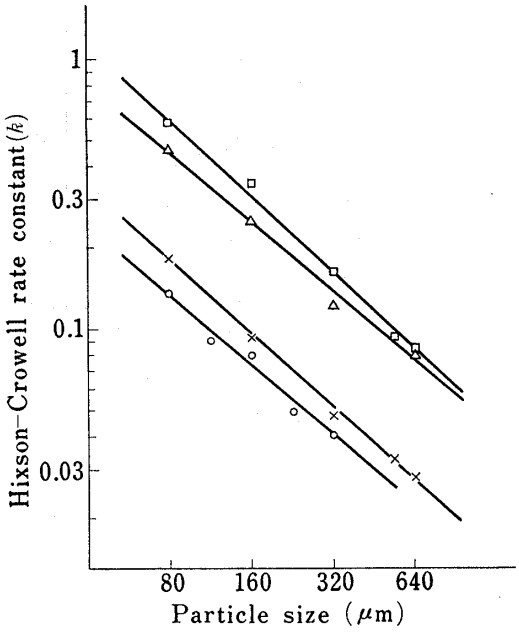

Fig. 5. Dependence of log Dissolution Rate Constant on log Particle Size

○: SD, ×: SIX, △: ST, □: SMT.

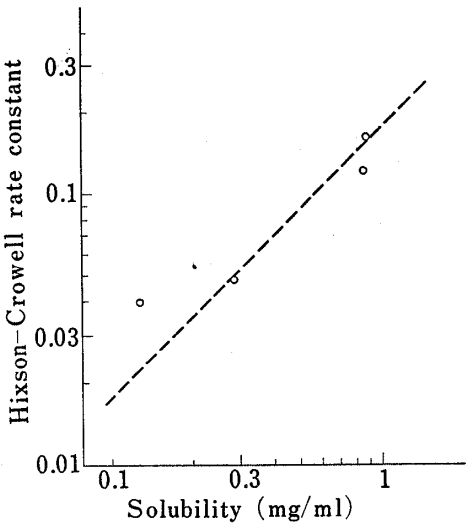

Fig. 6. Plot of Dissolution Rate Constant with a Particle Size of 324 μm *vs.* Solubility

more than that of sulfisoxazole. Apparent dissolution rate constant with a sample size of 324 μm *vs.* solubility was plotted and shown in Fig. 6, in which the line with a slope of 1 was appropriately drawn considering that the dissolution rate depended on the first power of the solubility, if the apparent dissolution rate constant for each sulfonamide was approximately all the same. Because the diffusion coefficient, which is included the apparent dissolution rate constant, depending on molecular weight for sulfonamide is hardly variable and the densities of sulfonamide were almost constant as shown in Table I.

The point for the dissolution rate constant of sulfadiazine was far from this line. The particle shape with a sample size of 324 μm was then examined by a microscope and photomicrographs are shown in Fig. 7, in which the crystal shape of sulfadiazine was needles. It was therefore considered that the specific surface area of sulfadiazine increased compared with those of other sulfonamides and resulted in increase of the dissolution rate of sulfadiazine. This fact would explain the fact that a large difference was not found as was found for the dependence of particle size on absorption rate constant of sulfadiazine compared with that of sulfisoxazole.

These results supported the observation that, in the case of low solubility drug such as sulfadiazine, amount of the drug dissolved in the gastrointestinal tract was rapidly absorbed

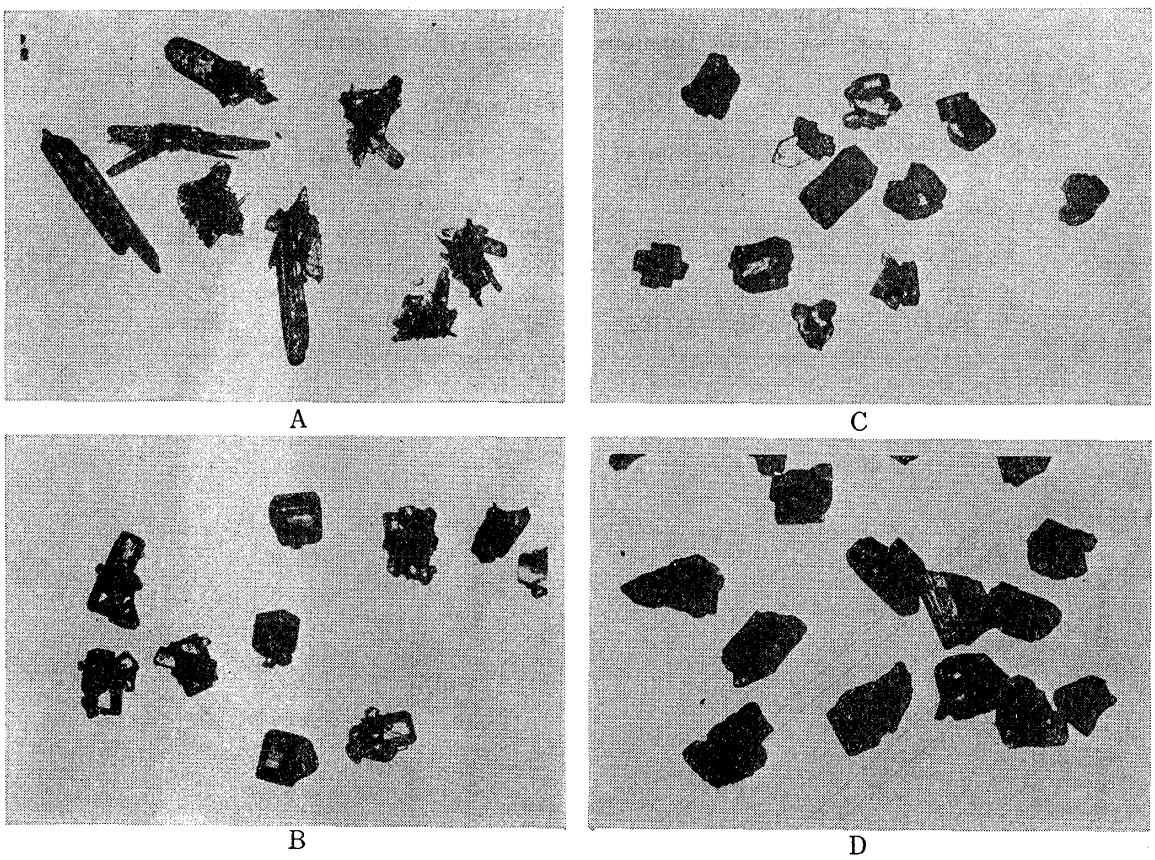

Fig. 7. Photomicrographs of Sulfonamides with a Particle Size of 324 μm, ×20
A: SD, B; SIX, C; ST, D: SMT.

into the body and dissolution of the drug in the gastrointestinal fluid would approximately proceed under sink conditions, as shown in Eq. (2). Furthermore, with an increase in drug solubility, the dissolution rate increased compared with absorption rate of the drug and consequently, the solute concentration of the bulk medium (C) in Eq. (1) was not negligible in the gastrointestinal fluid and the dependence of particle size on dissolution rate in the gastrointestinal tract would decrease. It was therefore considered that the correlation between *in vitro* and *in vivo* decreased as in sulfathiazole and sulfamethizole.