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Dissolution of slightly Soluble Drugs. V.[1] Effect of Particle Size on Gastrointestinal Drug Absorption and Its Relation to Solubility[2]

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Experiments were made on the effect of particle size on gastrointestinal drug absorption in the rabbit and its relation to solubility using powder drugs, in a series of solubility ranging from 1 to 25 mg/ml at 37° in suspension, and a consideration was made on the relationship between solubility and bioavailability on the basis of particle size, with following results.

1) The blood concentration-time curves at the particle size up to some sizes showed a similar time course curve obtained with an aqueous solution of each drug. Provided that the maximum particle size limit which described a time course curve similar to that of solution was the critical particle size (CPS), effect of particle size on the blood level appeared above the CPS of a drug. The CPS depended mainly on the solubility with slight relation of individual absorption rate of each drug solution and increased linearly with an increase in solubility. The extent of availability for different particle size grades was almost constant in each powder drug.

2) General consideration was made on the relationship between solubility and bioavailability on the basis of a particle size. This relation may vary with other factors, especially, dosage forms such as tablet, capsule, *etc.*, physiological factors, and individual properties of the drugs. However, this relation would be useful as a temporary standard as for considering the relationship between solubility and bioavailability on the basis of particle size.

Keywords——critical particle size in absorption; particle size; solubility; bioavailability; powder drug absorption

In our previous studies,[1] it became obvious, in the case of the absorption of a very slightly soluble drug such as sulfadiazine, that the dissolution rate in the gastrointestinal fluid was a rate-limiting step and the dependence of particle size on the *in vivo* absorption rate and *in vitro* dissolution rate obtained with sink conditions was well correlated and that the correlation between *in vivo* and *in vitro* decreased with an increase in solubility. This result supported the observation that the amount of a drug dissolved in the gastrointestinal tract was rapidly absorbed into the body and drug dissolution in the gastrointestinal fluid would approximately proceed under sink conditions, when drug solubility was as low as or less than that of sulfadiazine. With an increase in solubility, the dissolution rate increased compared

1) Part IV: N. Kaneniwa and N. Watari, *Chem. Pharm. Bull.* (Tokyo), **26**, 813 (1978).
2) Presented at the 97th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 1977.
3) Location: *Hatanodai, Shinagawa-ku, Tokyo, 142, Japan.*

with absorption rate of the drug and drug dissolution in the gastrointestinal fluid would not proceed under sink conditions. Consequently, the dependence of particle size on dissolution rate in the gastrointestinal fluid would decrease and thereby the correlation between *in vivo* and *in vitro* decreased.

As drug solubility increases further, the blood level of different particle size grades of a drug after oral administration may show a blood concentration–time curve similar to that obtained with the solution of a drug. Thus in this case, absorption rate would become the rate-limiting step in the transport from the gastrointestinal tract to the systemic circulation in the body. Therefore, the maximum limit of a particle size, which indicated a similar blood concentration–time curve as that of aqueous solution, was defined as the critical particle size (CPS) in absorption. The effect of particle size on blood level is not found below CPS and its effect on blood level would appear above CPS.

If powder drugs were appropriately used considering their solubility, this phenomenon would be found. Kakemi *et al.* reported that the CPS was about 200 μm in the absorption of chloramphenicol powder in the rabbit.[4]

In the present work, we examined to clarify the presence of CPS in absorption of a drug in the rabbit and its relation to solubility, and attempted to consider what degree of drug solubility corresponded exactly to the term of "water-insoluble drugs" on the basis of particle size in relation to bioavailability.

Experimental

Materials——Powder Drugs: Sulfisomidine (SIM), aspirin (AP), sulfacetamide (SAA), sulfanilamide (SA), and acetaminophen (AAP) used were J.P. grade and different particle size grades were obtained by sieving through a Ro-Tap testing shaker using Japan Industrial Standard (JIS) sieves. The arithmetic mean diameter of sieved samples was taken as the diameter of the drug particles. The ground sample of sulfisomidine was obtained by ball-milling as described previously,[5] and the surface mean diameter (D_{sp}) was about 1.96 μm, which was determined by the air permeability method.[6] The densities were measured by the use of a helium densitometer and shown in Table I.

Table I. Abbreviation and Physicochemical Properties of Powder Drugs

Substance	Abbreviation	Density ρ	Solubility[a] (mg/ml)
Sulfisomidine	SIM	1.49	1.91
Aspirin	AP	1.50	6.43
Sulfacetamide	SAA	1.46	12.0
Sulfanilamide	SA	1.61	14.9
Acetaminophen	AAP	1.38	21.8

a) Measured in distilled water at 37°.

Study Conditions and Drug Administration——Male albino rabbits weighing around 2.5 kg were used and fasted for 48 hr before the experiments to minimize the influence of admixture in the stomach but water was given freely. Experiments for 1 rabbit were repeated every 7 days for different particle size grades of a drug. Under these conditions, rabbit weight was almost constant at the maximum limit within 10% and, if necessary, food was controlled.

In some cases, the study of elimination of a drug for *i.v.* injection was conducted twice at before and after the experiments under above conditions and the same half-life was obtained. Similar results were

4) K. Kakemi, T. Arita, and S. Ohashi, *Yakugaku Zasshi*, **82**, 1468 (1962); N. Kaneniwa, *Funsai*, **15**, 48 (1970).
5) N. Kaneniwa and N. Watari, *Chem. Pharm. Bull.* (Tokyo), **25**, 867 (1977).
6) E. Suito, M. Arakawa, and M. Takahashi, *Kogyo Kagaku Zasshi*, **59**, 307 (1956).

also observed for sulfonamides administered intravenously[7] and orally[1] to rabbits. Therefore, the intra-subject variability through the experimental period of a drug for elimination may be negligible.

Aqueous solution of the drugs (200 mg/20 ml) was prepared by dissolving in distilled water and, in the case of sulfisomidine and aspirin, their acid salt forms prepared with equivalent NaOH were used for the aqueous solution for lack of their solubility and administered orally. When given intravenously, the volume of solution was appropriately controlled. Each particle size grade was rapidly prepared to minimize the dissolution of the sample 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 relative surface area of powder particles effective in the dissolution in a 30 ml syringe, which was connected with a catheter inserted into the stomach, and immediately administered.

Blood specimens were taken from the aural vein at certain intervals and urine was collected by inserting the Nelaton's catheter to the bladdar. Food was withheld during 10 hr after the experiments but water was given freely. In the case of acetaminophen, water was given by passing a catheter to the stomach to keep constant urine flow at 4 hr after the experiment.

Analytical Methods——Sulfonamide in blood was determined as total sulfonamide, and as free and total sulfonamides in urine by the Bratton-Marshall method.[8] Aspirin in plasma was determined as total salicylic acid after hydrolysis of aspirin, modifying the method of Harris–Riegelman,[9] and acetaminophen in urine as total acetaminophen after hydrolysis of conjugated acetaminophens using glusulase (Boehringer Mannheim GmbH, Catalogue number 15427) by the method of Thomas–Coldwell.[10]

***In Vitro* Dissolution Rate and Solubility**——The same apparatus and procedure, as reported earlier,[11] were used for the determination of the amount of the drug dissolved in distilled water and the dissolution rate was determined by applying the Hixson–Crowell cube root law[1,12] under sink conditions. Solubility of the drugs was also determined in the same manner as described previously.[11] The drug assays were made by spectrophotometry.

Results and Discussion

Blood Concentration-Time Curves of Different Particle Size Grades of Drugs of Various Solubility

As shown in Table I, powder drugs of various solubility were used to investigate the CPS in absorption in the rabbit. Each drug was tested with three rabbits and the blood concentration–time curves of two examples of different particle sizes of the drugs are shown in Fig. 1, in which the blood concentration–time curves of these drugs of some particle size grades showed a similar time course curve as obtained with the aqueous solution of each drug, and the CPS was then found. Above the CPS, the effect of particle size on the blood level appeared. In the case of cumulative amount excreted-time curve in the urine, similar results were also obtained with acetaminophen and shown in Fig. 2.

The determination of CPS from the blood level or urine level data was adequately made as follows: The blood concentration–time curves or cumulative amount excreted–time curves, which showed a similar curve obtained with an aqueous solution, were attracted and the maximum particle size among their group was used as the CPS of a drug considering the drug level peak time in the blood especially.

In the case of sufisomidine, the fastest drug level peak time was about at 1 hr after the medications, and an aqueous solution, ball-milled sample, and a sample size of 81 μm belonged to this group. As shown in the following section, the result of percentage unabsorbed–time plots for sulfisomidine approximately agreed with the above facts except for ball-milled sample of No. 1. Slow absorption for ball-milled sample of sulfisomidine No. 1 might be considered

7) *a*) J.W. Frymoyer and R.F. Jacox, *J. Lab. Clin. Med.*, **62**, 891 (1963); *b*) M. Yamazaki, M. Aoki, and A. Kamada, *Chem. Pharm. Bull.* (Tokyo), **16**, 707 (1968).
8) A.C. Bratton and E.K. Marshall, *J. Biol. Chem.*, **128**, 537 (1939).
9) P.A. Harris and S. Riegelman, *J. Pharm. Sci.*, **56**, 713 (1967).
10) B.H. Thomas and B.B. Coldwell, *J. Pharm. Pharmacol.*, **24**, 243 (1972).
11) N. Kaneniwa and N. Watari, *Chem. Pharm. Bull.* (Tokyo), **22**, 1699 (1974).
12) A.W. Hixson and J.H. Crowell, *Ind. Eng. Chem.*, **23**, 923 (1931).

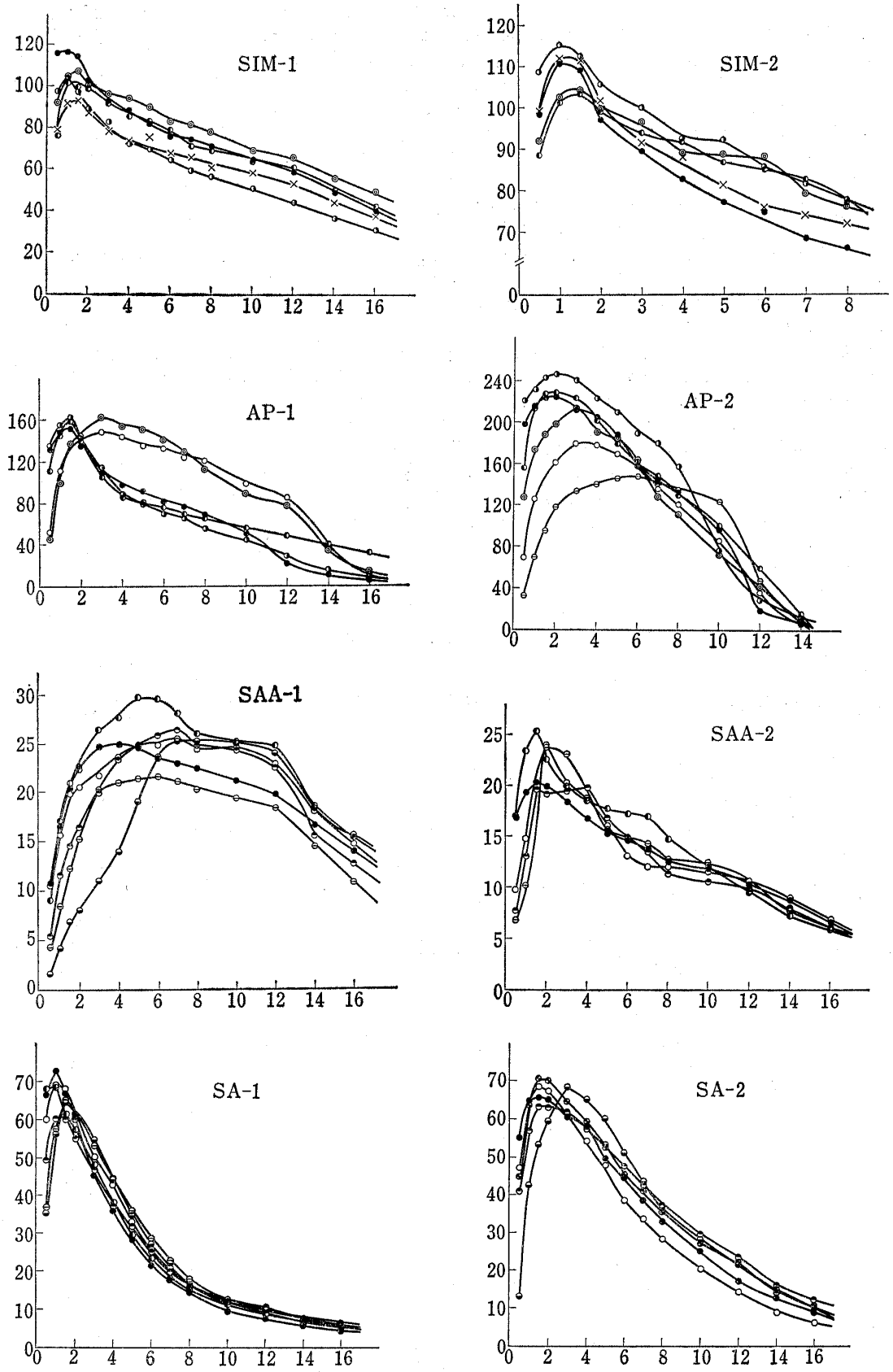

Fig. 1. Plot of Blood Concentration *vs.* Time after Oral Administration of Different Particle Size Grades

Ordinates show the blood concentration of drugs in μg/ml and abscisas the time in hour after orally administered drugs, particle size in diameter (μm),
●: soln., ×: 1.96, ◑: 81, ◐: 163, ◎: 230, ○: 324, ◔: 385, ◓: 460, ⊖: 650, ⊙: 775, ◒: 920.

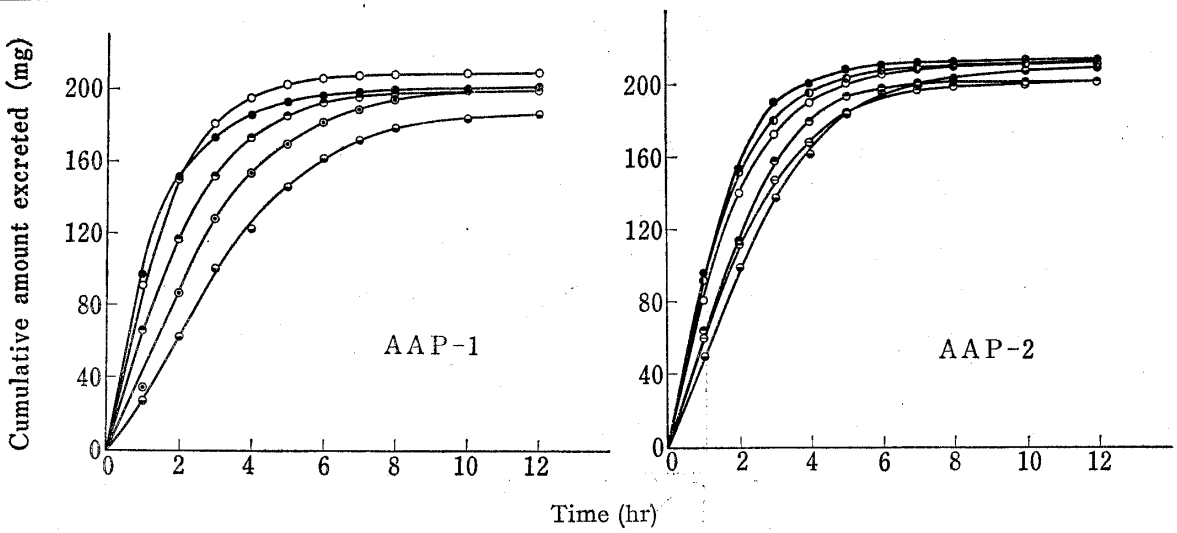

Fig. 2. Plot of Cumulative Amount excreted *vs.* Time after Oral Administration of Different Particle Size Grades of Acetaminophen

Particle size in diameter (μm),
●: soln., ◐: 163, ○: 324, ◓: 460, ⊖: 650, ⊙: 775, ◒: 920.

due to large agglomerated ball-milled sample being incompletely dispersed before the administration. Thus, the CPS of sulfisomidine was approximately determined around at 81 μm.

The CPS of other drugs was also determined in the same manner as in sulfisomidine. The CPS for aspirin was around 163 μm, 324 μm for sulfanilamide, and 460 μm or less for acetaminophen, which are shown in Table III. In the case of sulfacetamide, this phenomenon was not clear but the initial stage of absorption showed that the CPS was about 324 μm. These results showed a tendency that CPS increased with an increase in drug solubility.

Below the CPS of these drugs, the drug level peak time for different particle size grades approximately corresponded to those of aqueous solutions. No matter how complicated the ingestion and disposition process for a drug, it may generally be assumed that relative order of peak time following the administration of different dosage forms of the drug corresponds to the rank order of the rates of availability of the drug from various dosage forms. Thus, the rate of availability for these dosage forms of different particle sizes may be the same for all and this result may indicate that absorption rate was a rate-limiting step in the drug transport from the gastrointestinal tract to the systemic circulation in the body.

Above the CPS of these drugs, the drug level peak time increased from that of a group of those below the CPS and the values of peak time increased with an increase in particle size for each drug. Consequently, the rate of availability decreased with an increase in particle size and, in this case, it might be considered that dissolution rate in the gastrointestinal fluid became the rate-limiting step.

Determination of Absorption Rate Constant of Drugs from Observed Data

Compartmental analysis was made on the estimates of apparent absorption rate constant. The two-compartment open model was applied to determine the absorption rate as described earlier,[1,13] because the blood concentration–time curve of these drugs after *i.v.* injection was appropriately described by a bi-exponential equation. In the case of acetaminophen, absorption rates were obtained from urinary excretion data by applying the one-compartment open model[14] for lack of *i.v.* injection data, and percentage unabsorbed-time plots of two examples of each drug are shown in Fig. 3, in which the plots were approximately linear and

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

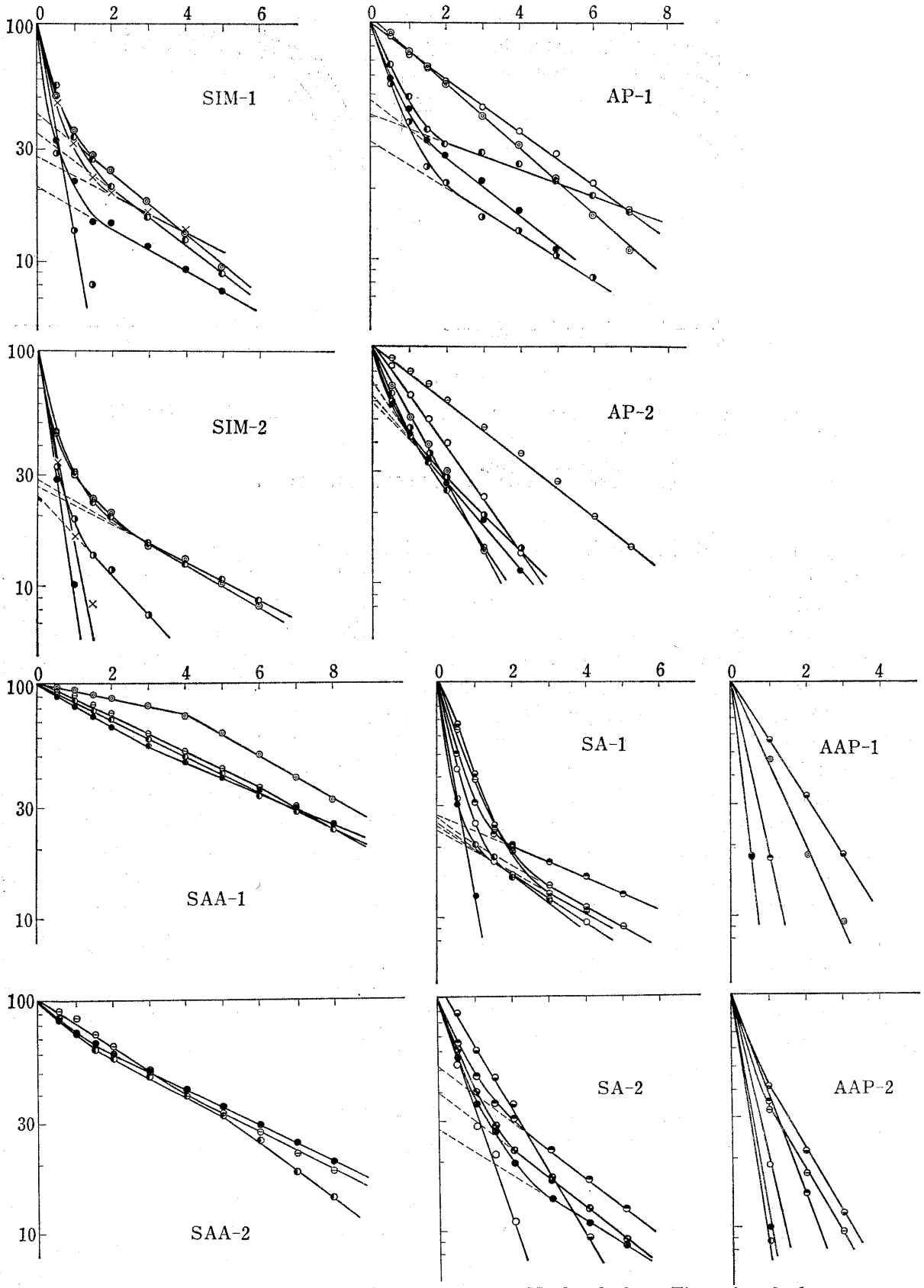

Fig. 3. Semilogarithmic Plot of Percentage Unabsorbed *vs.* Time after Oral Administration of Different Particle Size Grades

In the case of sulfacetamide, the plots of particle sizes of 324 and 460 μm were omitted because of their complicated plots, Ordinates show the percentage unabsorbed and abscisas the time in hour, particle size in diameter (μm),
●: soln., ×: 1.96, ◑: 81, ◐: 163, ◎: 230, ○: 324, ◔: 385, ◓: 460, ⊖: 650, ⊙: 775, ◒: 920.

in some cases resulted in concave descending-type curves which consisted of the fast absorption component and the slower one. This result indicated that absorption of these drugs was of first order and the concave descending-type curves might be described by the appropriate bi-exponential equation.

The method of residuals was then used to separate the fast component from the slower step. The dashed line in Fig. 3 was drawn to extrapolate the line of slower absorption step

Table II-a. Apparent Absorption Rate Constants and Extent of Bioavailability

Substance		Particle size (μm)	Parameter k_2 k_{12} (hr^{-1}) k_{21}	Absorption rate const. (hr^{-1})	Amount excreted for 48 hr (%) Free	Total	AUC × 10^{-2} (μg·hr/ml)	Metabolized ratio (%) (Total-free)/Total
SIM	No. 1	soln.	0.100	2.78(0.211)	79.6	85.9	18.5	7.4
		ball-milled	0.317	2.20(0.174)	76.0	84.8	16.6	10.4
		81	0.585	2.02	80.5	88.4	15.1	9.0
		163		1.92(0.268)	71.0	76.2	18.9	6.9
		230		2.42(0.275)	77.2	83.1	21.4	7.0
	No. 2	soln.	0.0649	2.28	60.4	80.2	24.5	24.6
		ball-milled	0.311	1.81	69.5	80.1	26.5	13.2
		81	0.617	3.52(0.406)	76.3	86.2	27.2	11.4
		163		1.80(0.177)	67.6	81.4	26.9	16.9
		230		2.13(0.221)	48.6	73.9	28.2	34.2
	No. 3	soln.			57.4	75.3	23.6	23.7
		ball-milled			60.1	80.7	24.0	25.6
		81			55.6	73.1	21.8	23.9
		137			67.5	78.9	23.3	14.4
		230			62.0	82.4	20.3	24.8
		324			75.7	85.3	23.4	11.2
SAA	No. 1	soln.	0.336	0.202	60.2	86.5	4.22	30.4
		163	0.723	0.177	44.5	84.3	4.98	47.2
		324	0.687	0.178	38.1	89.7	4.68	57.5
		460		0.147	37.3	105.4	4.11	64.6
		650		0.157	48.8	79.1	3.49	38.3
		920		0.0711	33.1	75.3	4.02	56.1
	No. 2	soln.	0.497	0.211	63.3	88.2	2.69	28.2
		163	0.517	0.259	62.8	94.4	2.83	33.5
		324	0.268	0.198	62.9	86.7	2.71	27.4
		460		0.178	51.5	80.2	2.57	35.7
		650		0.131	59.0	90.8	2.67	35.0
	No. 3	soln.	0.225	0.190	66.3	79.8	5.04	16.9
		163	0.815	0.189	61.9	72.9	5.38	15.1
		324	0.464	0.182	65.8	82.9	5.50	20.6
		460		0.113	61.9	75.9	5.03	18.4
		650		0.149	58.8	73.1	5.05	19.6
SA	No. 1	soln.	0.318	2.10	44.1	91.4	3.89	51.8
		163	0.831	4.26(0.269)	52.8	94.4	4.06	44.0
		324	3.04	2.57(0.235)	53.4	91.7	4.30	41.7
		460		2.31(0.162)	56.7	87.9	4.06	35.5
		650		1.40(0.196)	26.4	91.2	4.26	71.1
		920		1.24(0.153)	54.7	87.4	4.22	37.3
	No. 2	soln.	0.229	1.53(0.234)	37.4	89.2	5.93	58.1
		324	0.800	1.04	14.1	81.0	5.47	82.5
		385	2.71	1.80(0.310)	14.9	84.0	6.77	82.3
		460		1.97(0.302)	23.2	79.6	6.65	70.8
		920		0.649	9.7	59.6	6.44	83.7
	No. 3	soln.	0.222	1.60(0.370)	28.4	84.4	5.63	66.4
		324	0.553	1.40(0.308)	38.4	70.7	5.22	45.7
		460	2.85	0.632	48.7	86.3	5.05	43.6
		920		0.795	51.6	86.7	4.55	40.5

beyond the experimental data, and the slope and the y intercept show absorption rate constant and percentage of the drug absorbed where slower absorption step occurred. In most cases, percentage of the drug absorbed of slower absorption step was small. Therefore, it might be said in the case of the concave descending-type absorption, that the initial fast absorption occured due to its large solubility and the following slower absorption might be influenced by physiological factors of the gastrointestinal tract, for example, movement of the stomach by admixture because of imcomplete emptying of the stomach under the conditions where the rabbits were fasted for 48 hr before the experiments. This idea further receives a support from the fact that this phenomenon appeared independent of different particle size grades.

As shown in Fig. 3, percentage unabsorbed-time plots for below the CPS of the drug showed approximately a similar line for each drug and above the CPS, absorption rates decreased with an increase in particle size, namely, the effect of particle size on absorption rate

Table II-b. Apparent Absorption Rate Constants and Extent of Bioavailability

Substance		Particle size (μm)	Paramater k_2 k_{12} (hr^{-1}) k_{21}	Absorption rate const. (hr^{-1})	Total amount excreted for 12 hr (%)	AUC × 10^{-2} (μg·hr/ml)
AP	No. 1	soln.	0.291	1.70 (0.269)		11.0
		81	0.343	1.62 (0.219)		10.9
		163	0.445	1.60 (0.135)		14.4
		324		0.255		16.6
		775		0.302		16.8
	No. 2	soln.	0.265	3.19 (0.426)		18.9
		81	1.01	2.36 (0.369)		20.8
		163	1.57	2.12 (0.482)		19.7
		230		0.641		17.2
		324		0.519		15.6
		650		0.283		14.8
	No. 3[a]	soln.	0.232	2.01		8.23
		81	0.752	2.08		7.39
		163	3.22	3.62 (0.693)		11.5
		324		0.669		9.52
		650		0.702		9.21
AAP	No. 1	soln.	0.568	3.44	101.0	
		324	0.586	3.44	105.2	
		460	0.579	1.64	99.7	
		775	0.575	0.806	101.7	
		920	0.565	0.561	93.6	
	No. 2	soln.	0.773	2.01	106.5	
		163	0.745	2.46	104.7	
		324	0.760	1.46	105.4	
		460	0.759	0.976	100.2	
		650	0.759	0.886	99.7	
		920	0.759	0.807	104.3	
	No. 3	soln.	0.685	2.49	90.1	
		324	0.685	2.56	94.0	
		460	0.685	2.44	89.9	
		650	0.686	1.24	105.1	
		920	0.685	1.56	98.3	

a) 100 mg was administered.

Figures in parenthese show the values of slower absorption rate constant by a bi-exponential equation. Parameters used to calculate absorption rate constant for two-compartment open method: 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. In the case of acetaminophen, absorption rate constant was estimated by applying one-compartment open model and the elimination rate constants (k_e) are given in parameters.

appeared. Furthermore, absorption rates of sulfacetamide were smaller than those of other drugs and this results may explain that the CPS did not appear clearly.

The apparent absorption rate constants were then calculated by the least-squares method and shown in Table II, in which the value for those below the CPS was near to that of the aqueous solution for each drug. The absorption rate constant of acetaminophen was comparable with those of other drugs and this is considered due to the estimates of applying the one-compartment open model as described earlier.[1,13]

These facts therefore supported the observation that the CPS in absorption of a drug in the rabbit appeared and the CPS increased with an increase in solubility.

Extent of Bioavailability after Oral Administration of Different Particle Size Grades

The extent of availability may be measured either using a drug concentration in the blood or amount of a drug in the urine. The area under the blood or plasma concentration–time curve (AUC) for the drugs in different dosage forms is a measure for the extent of availability.

The AUC and amount of a drug excreted in the urine were then measured and are shown in Table II, which revealed that the difference among different particle size grades for each drug was hardly seen in both methods of AUC and amount of a drug excreted. In the case of sulfonamide, individual difference among rabbits was found in relation to the ability for metabolism, and the ratio of metabolized product excreted to total amount excreted was in close agreement with previous experimental data.[7b]

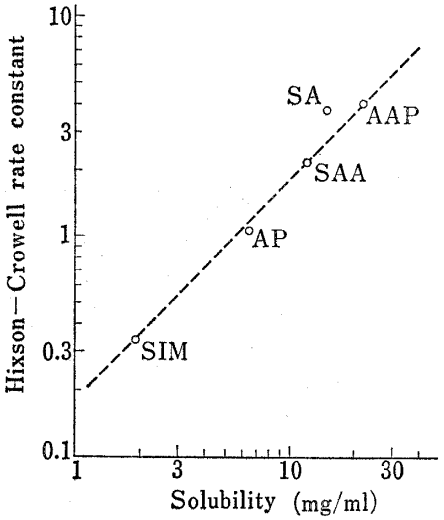

Fig. 4. Plot of Dissolution Rate Constant with a Particle Size of 324 μm *vs.* Solubility

Dependence of CPS on Solubility and General Consideration with the Relationship between Solubility and Bioavailability on the Basis of Particle Size

CPS in absorption in rabbits and solubility of the drug are shown in Table III. *In vitro* dissolution tests were then examined to clarify the relationship between solubility and dissolution rate with a sample size of 324 μm and shown in Fig. 4, in which dashed 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 drug was approximately all the same as described earlier.[1] In this graph, the point of sulfanilamide

Table III. Dependence of the CPS on Solubility, and Its Absorption Rate Constant

Substance	Solubility[a] (g/100 ml)	CPS (μm)	Apparent absorption rate constant (hr^{-1})[b]
SIM	0.191	81, 81, 137	2.02, 3.52
Chloramphenicol[4]	0.556	200	
AP	0.643	163, 163, 81	1.60, 2.12, 2.08
SAA	1.20	324, 163, 324	0.178, 0.259, 0.182
SA	1.49	324, 324, 324	2.57, 1.04, 1.40
AAP	2.18	324, 324, 460	3.44, 1.46, 2.44

a) Measured in distilled water at 37°.
b) Each value corresponds to the CPS respectively and the initial fast absorption rate constants are given.

was far from this line and crystal shape was then examined by a microscope and shown in Fig. 5, in which the size of sieved sample grade of each drug was approximately uniform.

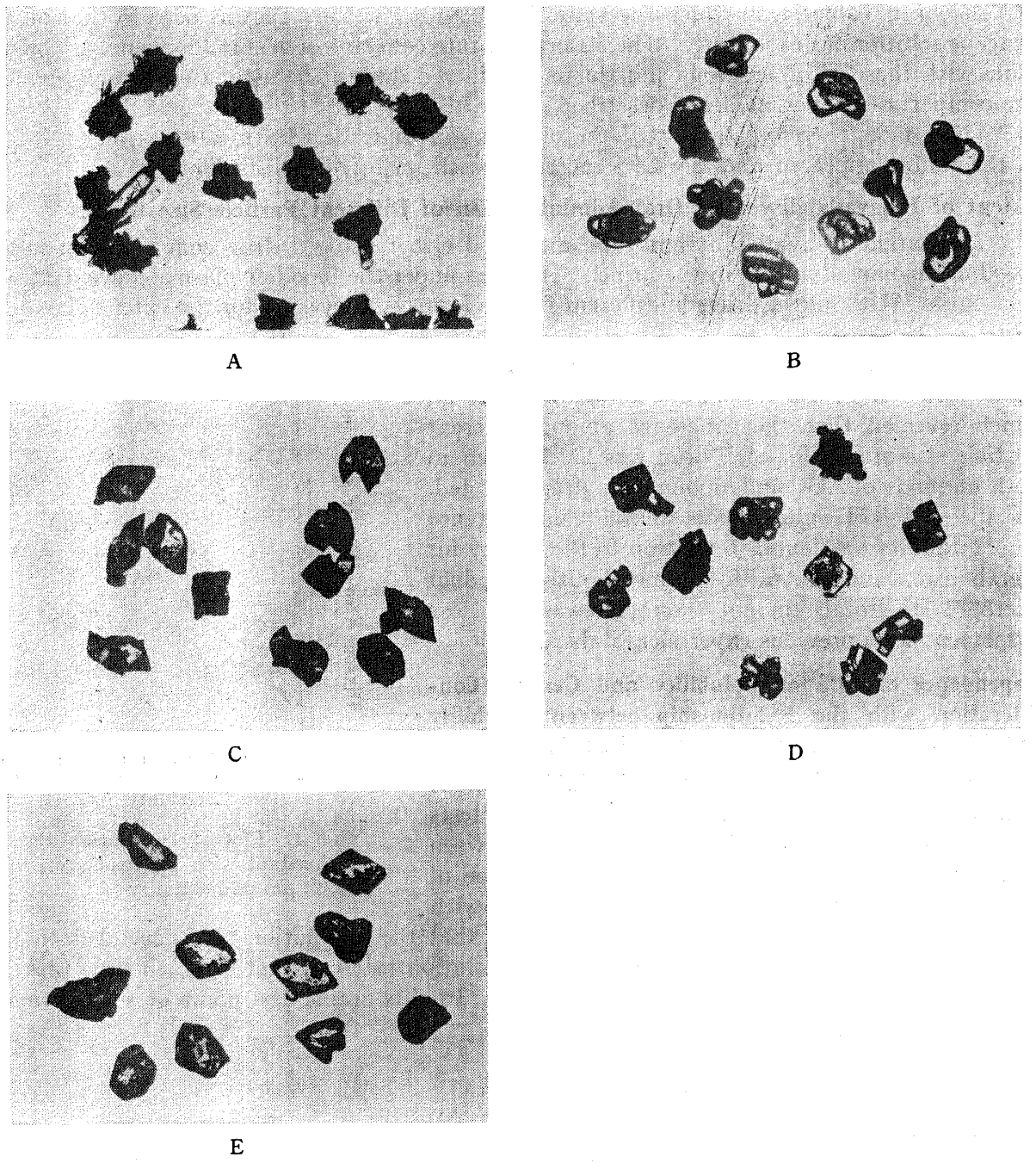

Fig. 5. Photomicrographs of Powder Drugs with a Particle Size of 324 μm, ×20
A: SIM, B: AP, C: SAA, D: SA, E: AAP.

With respect to the relationship between the CPS and solubility, the CPS of acetaminophen was small compared with that of sulfanilamide as far as considering their solubility, but the dissolution rate with *in vitro* test for sulfanilamide and acetaminophen was almost the same. It was therefore considered that a large difference was not found for the values of CPS between sulfanilamide and acetaminophen. Furthermore, it was revealed that the CPS was approximately proportional to the solubility, that is, the CPS depended mainly on

the drug solubility and it might be said that individual apparent absorption rates of these drugs in aqueous solutions could be neglected except for sulfacetamide as shown in Table III.

Our previous experiments[1] on the effect of particle size on bioavailability using sulfonamide powder drugs with the solubility ranging from 0.1 to 1 mg/ml at 37° revealed that the effect of particle size on the rate of bioavailability was marked but its effect on the extent of bioavailability was approximately the same. Furthermore, in the case of low solubility drugs such as sulfadiazine, the strongest correlation was found between *in vitro* dissolution rate obtained under sink conditions and *in vivo* absorption rate, and the correlation decreased with an increase in solubility.

Table IV. General Consideration with the Relationship between Solubility and Bioavailability on the Basis of Particle Size

Definition in Japan Pharmacopoeia	Solubility (%)	Substance	Bioavailability	
			Rate	Extent
	— 0.001			
Practically insoluble or Insoluble		Griseofulvin[16]	+	+
	— 0.01			
Very slightly soluble		Sulfadiazine, Sulfisoxazole, Sulfathiazole, Sulfamethizole 1)	+	±
	— 0.1			
Slightly soluble		Sulfisomidine, Chloramphenicol[4], Aspirin	±	—
	— 1			
Sparingly soluble		Sulfacetamide, Sulfanilamide, Acetaminophen	—	—
	— 3.3			
Soluble				
	— 10			

+, Effect of particle size on the rate or the extent of bioavailability would appear evidently
±, its effect may appear slightly, —, its effect is hardly found.

These relations were then applied to the terms of the solubility defined by Japan Pharmacopoeia[15] and are shown in Table IV, and the general consideration was made on the relationship between solubility and bioavailability on the basis of particle size. Thus, it may be said that in the case of drugs belonging to the very slightly soluble class, the effect of particle size on the rate of bioavailability was marked and low solubility drugs such as sulfadiazine showed that the dependence of particle size on *in vivo* absorption rate and *in vitro* dissolution rate would correlate well, and this relation decreased with an increase in solubility. In other words, the effect of particle size on the rate of availability decreased with an increase in solubility, while the effect of particle size on the extent of bioavailability was approximately the same.

In the case of drugs belonging to the slightly soluble and sparingly soluble classes, the CPS in absorption may be found and the CPS is approximately proportional to their solubility, but the effect of particle size on the extent of bioavailability is almost the same as described above for sulfisomidine, aspirin, sulfacetamide, sulfanilamide, and acetaminophen.

15) N. Kaneniwa, *Funtaikogaku Kenkyukaishi*, **14**, 83 (1977).

In the case of drugs such as griseofulvin belonging to the practically insoluble class, the effect of particle size on the rate of bioavailability would be marked and its effect on the extent of bioavailability is also marked. Further, good correlation would be seen between *in vitro* dissolution rate and *in vivo* absorption rate, as reported earlier.[16]

These relations would apply in the case of an ideal example, that is, in the conditions of powder particles of drugs wetted well and completely dispersed. In addition, these relations may vary with other fractors such as dosage forms (tablet, capsule, *etc.*), physiological factors, and individual properties of the drugs. However, these relations would be useful as a temporary standard as for considering the relationship between solubility and bioavailability on the basis of particle size.

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16) R.M. Atkinson, C. Bedford, K.J. Child, and E.G. Tomich, *Antibiot. Chemother.*, **12**, 232 (1962); *idem*, *Nature* (London), **193**, 588 (1962); B. Katchen and S. Symchowicz, *J. Pharm. Sci.*, **56**, 1108 (1967); *idem*, *ibid.*, **57**, 1383 (1968).