cis-1,2,3,4-tetrahydro-1,3-naphthalenediamine (V) was prepared by Schmidt reaction of *cis*-4-amino-1,2,3,4-tetrahydro-2-naphthoic acid (Ⅳ) which was obtained by catalytic reduction of methyl 4-hydroximino-1,2,3,4-tetrahydro-2-naphthoate (I), followed by cyclization and hydrolysis.

Reduction of N,N′-diacetyl- (Ⅵa) and N,N′-diformyl- (Ⅵb) derivatives of V with lithium aluminum hydride afforded N,N′-diethyl- (Ⅶa) and N,N′-dimethyl- (Ⅶb) derivatives, respectively. Condensation of Ⅶa with formaldehyde and benzaldehyde gave 2,4-diethyl- (Ⅷa) and 2,4-dimethyl-3-phenyl-1,2,3,4,5,6-hexahydro-1,5-methanobenzo [*e*] [1,3]-diazocine (Ⅷc). Similarly, 2,4-dimethyl derivatives (Ⅷb) and (Ⅷd) were prepared.

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46. **Hisashi Nogami, Tsuneji Nagai, and Akira Suzuki**[*1] : Studies on Powdered Preparations. XVII.[*2] Dissolution Rate of Sulfonamides by Rotating Disk Method.[*3,*4]

(*Faculty of Pharmaceutical Sciences, University of Tokyo*[*5])

When solid preparations are administered orally, the rate-determining step of an appearance of the medicinal effect has been often observed in the dissolution process in digestive tract.1~3) Even in the manufacturing of various kinds of liquid preparations, the dissolution is a very important process. Therefore, it is considered to be significant to investigate pharmaceutically what kinds of factors give an influence on the dissolution rate of drugs.

Two types of dissolution, transport controlled dissolution and chemically controlled one,4~6) have been taken into consideration. Dissolution of medicinal preparations is usually a transport controlled reaction, except a few cases7,8) and its rate is generally represented by the Noyes-Nernst equation (1).

$$\frac{dC}{dt}=k(C_0-C)=\frac{S}{V}K_T(C_0-C)=\frac{S}{V}\,\frac{D}{\delta}(C_0-C) \qquad (1)$$

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[*2] Part XVI. H. Nogami, T. Nagai, T. Kasai, T. Kajima : This Bulletin, **14**, 125 (1966).

[*3] Presented at the 85th Annual Meeting of Pharmaceutical Society of Japan, Fukuoka, April 1965.

[*4] Taken in part from the thesis of Akira Suzuki for the degree of Doctor of Pharmaceutical Sciences, University of Tokyo, 1965.

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where C is the concentration at the time t, C_0 the saturated concentration,[*6] k the rate constant, S the surface area of solid, V the volume of solution, K_T the dissolution rate constant, D the diffusion coefficient, and δ the diffusion layer thickness.

The dissolution rate of medicinal preparations have been measured by beaker method,[9,10] oscillating tube method,[11~13] hanging disk method,[14~16] static disk method,[17~18] suspending disk method,[20~22] fixed disk method,[23,24] and rotating disk method,[25~28] and they are classified to the measurement of apparent dissolution rate and to that of intrinsic dissolution rate. In the measurement of intrinsic dissolution rate, experiments have been usually carried out under the condition of $C \fallingdotseq 0$ in equation (1), hence equation (2) is derived as

$$C=\frac{S}{V}K_TC_0t=\frac{S}{V}bt \tag{2}$$

and according to the value of b, obtained from the plot of C *vs.* t, the dissolution rate has been represented. The condition of $C \fallingdotseq 0$ is said to be satisfied by the dissolution of solid preparations in digestive tracts,[23] and so the value b is considered to be meaningful pharmaceutically. However, as K_T and C_0 contained in b are influenced by the respective factors, it is considered to give more basic consideration, with respect to the dissolution rate, to obtain these two values separately and to examine individual changes.

For obtaining the values of K_T and C_0 separately, rotating disk method is considered to be superior. The reason is that, according to the rotating disk method, the factors having influence upon K_T are theoretically presented by Levich.[29,30] But, studies by this method were on metal,[6] single crystal,[31] and sintered material[32] so far and no fundamental investigations on compressed powder disk, being polycrystalline mass, have been found.

In this study, a method of analysis was examined to obtain K_T and C_0 separately from the concentration-time curve obtained by rotating disk method, and consequently a fundamental investigation concerning the reliability of this experimental method

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[*6] This is the value estimated kinetically as described later and not always equal to the solubility.

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was carried out with sulfadiazine. Furthermore, as to the other four kinds of sulfonamides, K_T and C_0 were obtained and were examined whether they were coincident with the values anticipated. From all the results obtained, the measurements according to this method could be concluded to give an effective method for the study of dissolution rate.

Theory and Fundamental Concepts

Principle and Benefit of Dissolution Rate Measurement by Rotating Disk Method

The simplest experimental method of obtaining dissolution rate is to measure the dissolution from the static solid in the static liquid. But according to this method, because of the free convection of liquid⁶⁾ caused by an influence of the gradient of temperature, density of liquid, or gravity, the transport of the substance dissolved does not depend on diffusion only, and the second law of Fick[33,34] becomes inapplicable. One method to cover an influence of the free convection is to give a forced convection to the solid-liquid interface.

A flow of the liquid, produced with the disk which rotates at a constant angular velocity, follows the Navier-Stokes and continuity equation,[30] the solution of which has been obtained by Cochran.[35] Using the solution, the thickness of diffusion layer, δ, has been given by Levich[29,30] as

$$\delta = 1.612 \times D^{1/3} \times \nu^{1/6} \times \omega^{-1/2} \tag{3}$$

where D is the diffusion coefficient, ν the kinematic viscosity and ω the angular velocity of rotation.

Therefore, the dissolution rate constant, K_T, becomes

$$K_T = 0.620 \times D^{2/3} \times \nu^{-1/6} \times \omega^{1/2} \tag{4}$$

Measurements of dissolution rate by the rotating disk method attempted in this study were based upon the principle mentioned above, and the benefit of this method was that the surface area of solid, S, was kept constant in the progress of dissolution, and that it took shorter time for the experiments.

Method for Analyzing Concentration-Time Curve of Dissolution

On the concentration-time curve, as shown typically in Fig. 1, the concentration C_1 at time t_1 is shifted to C_2 after Δt min., then the following equations are obtained according to equation (1):

$$C_2 = \exp(-k \cdot \Delta t) \cdot C_1 + \{1 - \exp(-k \cdot \Delta t)\} \cdot C_0 \tag{5}$$

$$\ln(C_2 - C_1) = -kt_1 + \ln[\{1 - \exp(-k \cdot \Delta t)\} \cdot C_0] \tag{6}$$

When Δt is maintained constant, C_2 at respective C_1 is obtained from the concentration-

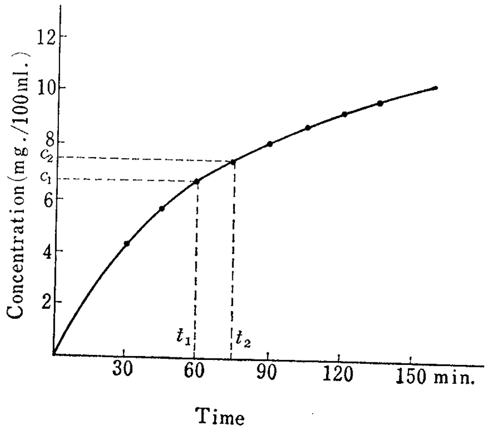

Fig. 1. Dissolution of Sulfadiazine in Water of 100 ml. at 37° from a Disk of 3 cm. Diameter Rotating at a Velocity of 600 r.p.m.

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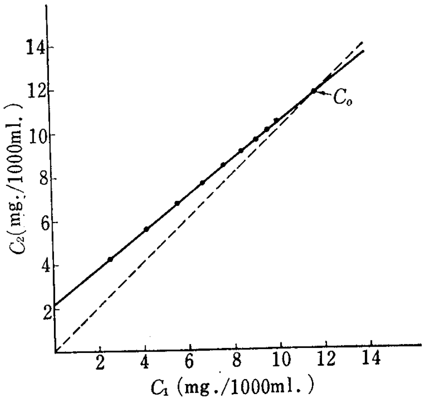


Fig. 2. Finite Differences Diagram of the Dissolution of Sulfadiazine in Water of 100 ml. at 37° from a Disk of 3 cm. Diameter Rotating at a Velocity of 600 r.p.m.

C_1: concentration at time t_1
C_2: concentration at time $t_2=t_1+15$ min.
—●— according to equation (5)
– – – $C_1=C_2$

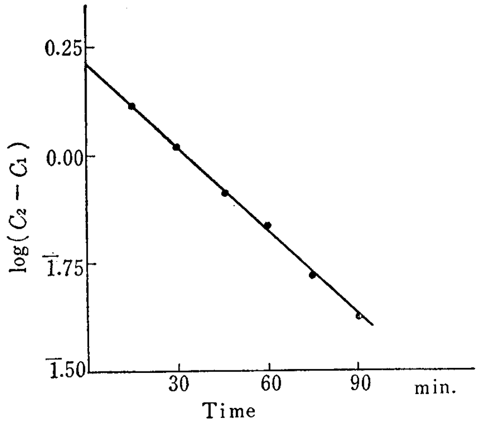


Fig. 3. Relationship between $\log(C_2-C_1)$ and Time on the Dissolution of Sulfadiazine in Water of 100 ml. at 37° from a Disk of 3 cm. Diameter Rotating at a Velocity of 600 r.p.m.

C_1: concentration at time t_1
C_2: concentration at time $t_2=t_1+15$ min.

time curve and the plot of C_2 *vs.* C_1 gives a straight line according to equation (5), as shown by the finite differences diagram in Fig. 2. The slope of this plot gives the rate constant, k, and the intersection between this plot and the line of $C_2=C_1$ gives C_0.

Similarly, when Δt is maintained constant, the plot of $\ln(C_2-C_1)$ *vs.* t_1 gives a straight line according to equation (6), as shown in Fig. 3. The slope of this plot gives k directly and the ordinate intercept gives C_0.

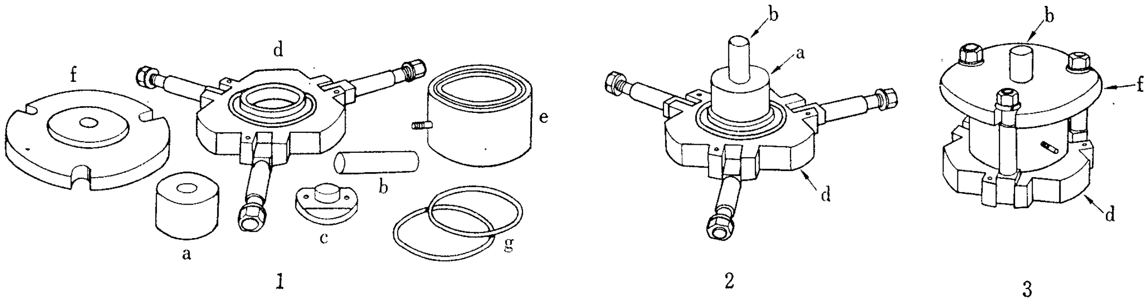
When the two methods are compared, *i.e.*, one method to get k and C_0 according to equation (5) and the other to get k and C_0 according to equation (6), the former is suitable for getting C_0, but not for k. The reason is that the error in reading of the slope of the plot C_2 *vs.* C_1 gives a great influence on the value of k as follows: Representing the reading of the slope by α, $k=-\ln\alpha/\Delta t$ from equation (5) and thus $\left|\frac{\Delta k}{k}\right|=\left|\frac{\Delta\alpha}{\alpha\ln\alpha}\right|$, where Δk and $\Delta\alpha$ are the error of k and α, respectively. If α is near to 1, even if $\Delta\alpha$ is small, k changes greatly. On the other hand, the latter method is suitable for getting k, but not for C_0, because k is obtainable easily according to equation (6), but so many calculations are needed to obtain C_0 and moreover an error of k will have influence on C_0.

Therefore, in this study, the saturated concentration, C_0, was obtained from such the line as in Fig. 2, according to equation (5), and also the rate constant, k, was from such the line as in Fig. 3, according to equation (6).

Experimental

Samples——Commercial sulfadiazine J.P., sulfisomezole, sulfaguanidine J.P., sulfisoxazole J.P. and sulfapyridine were used.

Making of Compressed Disk of Sample——A specially designed metal mold to make a compressed disk is shown in Fig. 4. It is consisted of a die, *a*, upper punch, *b*, lower punch, *c*, base with three levers and nuts, *d*, ring with a tap for exhaustion, *e*, adaptor with two small plastic O-rings in center hole, *f*, and two plastic O-rings, *g*. The O-rings in the center hole of *f* were installed to make airtight when *b* was inserted in the hole, and two O-rings, *g*, were used to make airtight between *d* and *e* and *e* and *f* respectively. After *c* and *a* were attached to *d*, a given amount of sample was put in *d*, and then *b* was inserted into *d*, as shown in Fig. 4-2. Finally, the mold was assembled as in Fig. 4-3,



1 2 3

Fig. 4. Metal Mold to Make a Compressed Disk

a: die b: upper punch c: lower punch d: base e: ring f: adaptor g: plastic O-rings

and put on an oil press. The inside of the mold was exhausted under the reduced pressure of about 2 mm. Hg for 15 min. Continuing the exhaustion, the powder sample was compressed gradually by upper punch, *b*, until the compression arrived at a certain pressure. Furthermore, compression was continued for 30 min. in that state, and later the compressed disk was taken out from the mold. If the disk was easily breakable, it was firstly broken into the particles of about $420\sim840\,\mu$ and later they were recompressed. Only at final compression, the saturated solution of magnesium stearate in benzene was painted over die and punch for lubrication to prevent capping and/or sticking. The thickness of the disk, thus obtained in 3 cm., 2 cm., or 1.5 cm. diameter, was measured by micrometer caliper and the apparent density of disk was obtained.

Apparatus and Procedure for Measurement of the Amount Dissolved——For the measurement of dissolution rate, the apparatus, shown in Fig. 5, was used. The compressed disk, *q*, was sticked to the holder of matched size, *p*, with chlorovinyl adhesives, and so as to contact only the bottom face of the disk with the liquid, the rest part of the disk was covered with epoxide resine. The epoxide resine has been known to have anti-chemical properties.[36] Its covering properties were certificated to be so excellent that no dissolution of sulfadiazine was recognized from the completely covered sulfadiazine disk even when it was suspended in water for 72 hr. As magnesium stearate used as lubricant is said to decrease the dissolution rate,[19] so in this experiment, in order to get rid of the magnesium stearate which might adhere over the surface of the disk at the final compression described before, the surface of the disk was polished with a very fine mesh of hone. A stainless steel shaft, *n*, which rotated at a certain rotating velocity by gear-box connected to induction motor, *m*, was made less trembling with brass sleeve, *o*. The holder, *p*, with disk, *q*, was attached to the shaft, *n*, and was set in the flask, *u*, which contained a given amount of liquid, adjusting the disk not to touch with the liquid, and they were placed in a constant temperature bath at a given temperature. In the case of alkaline solution in flask, *u*, nitrogen gas was streamed into *u* through the scrubbing bottle, *v*, which contained the solution of the same component and of the same temperature as that in *u*. When the temperature in flask, *u*, arrived at an equilibrium after about 60 min., the disk was rotated, and *u* was moved up to immerse the disk in the solution to have it begin to dissolve. At that time, a careful attention should be paid on the surface of the disk in order that bubbles would not attach.

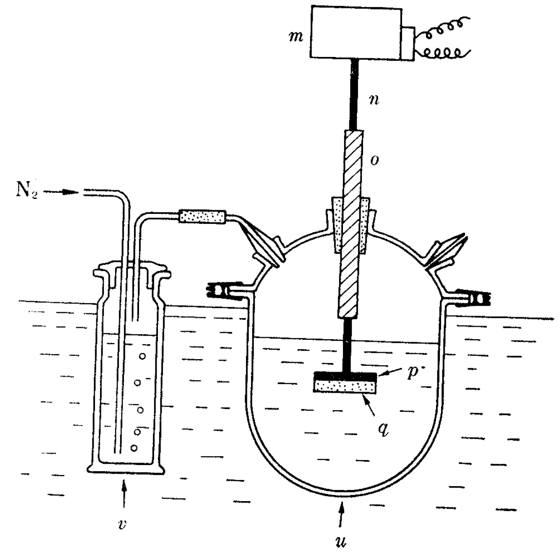


Fig. 5. Apparatus for Measurement of the Amount Dissolved

m: induction motor and gear-box
n: stainless steel shaft
o: brass sleeve
p: stainless steel disk holder
q: disk
u: flask
v: scrubbing bottle

At a certain appropriate interval, 0.5 ml. of the solution was sampled out from the flask, *u*, and the amount dissolved was measured photometrically as described later.

Immediately after every sampling, 0.5 ml. of the solution of the same component and of the same temperature as that before the beginning of the dissolution was added in the flask, *u*, in order to keep

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36) R. L. Deffoff: Corrosion, **17**, 83 (1961).

the total volume of the solution constant. As the total volume of the solution in the minimum scale of the experiment was 50 ml., an error caused by sampling was considered to be about 1/100 at the largest. The samplings were made until the concentration in bulk liquid arrived around more than 85% of the solubility.

After measuring dissolution rate, rotation of the disk was stopped, kept standing for 24～48 hr. and the solubility was measured.

Quantitative Determination of the Amount of Sulfonamide Dissolved——0.5 ml. of sample solution described above was diluted at a constant ratio according to the respective sulfonamide with 0.1M $NaHCO_3$ and the concentration was determined by colorimetric method or UV absorption method, using Hitachi Perkin-Elmer 139 UV-VS Spectrophotometer. In the case of colorimetric method, the sample solution was colored with Tsuda's reagent[37] and the optical density was determined at 524 mμ. In the case of UV absorption method, the optical density of sulfadiazine was determined at 240 mμ, sulfisomezole at 256 mμ, sulfaguanidine at 260 mμ, sulfisoxazole at 253 mμ, and sulfapyridine at 242 mμ.

Measurement of Viscosity——Kinematic viscosity, ν, was measured by Ubellode viscometer and viscosity, η, was obtained according to equation $\eta=\nu\rho$, where ρ is the density of solution.

Measurement of Density of Solution——This was measured by pycnometer.

Results and Discussion

Concentration-Time Curve of Dissolution

Typical concentration-time curve in the case of dissolution of sulfadiazine in water is shown in Fig. 1. Each point in the figure shows the mean of two determinations, which has a good reproducibility, and the experimental error was not more than 5%. The thickness of the disk was usually about 3 mm. and even if it would be changed, *e.g.*, 1 mm. or 8 mm., no difference was observed on the concentration-time curve. Even-though the size and the shape of the flask, *u*, were changed, no difference of concentration-time curve was observed. The position of bottom face of the disk, where the dissolution took place, was varied, *e.g.*, 1 cm. below the water-level, or 3 cm. below, but no change of concentration-time curve was observed.

Dependence of Rate Constant on Surface Area of the Disk and Volume of the solution

On the dissolution of sulfadiazine in water, the dependence of rate constant, k, on the surface area of the disk, S, and the volume of the solution, V, is shown in Table I. In the last column in Table I, the values of dissolution rate constant, K_T, calculated from k are shown and these are understood to be constant.

Table I. Dependence of Dissolution Rate Constant of Sulfadiazine in Water on the Surface Area of the Disk, S, and the Volume of the Solution, V, at 37°, 600 r.p.m.

S (cm^2)	V (cm^3)	$k\times10^3$ (min.$^{-1}$)	$K_T\times10$ (cm./min.)
7.07	200	8.26	2.32
3.14	200	3.60	2.29
1.77	200	2.10	2.36
7.07	100	16.60	2.35
7.07	50	32.03	2.34

When dissolution from the disk is of transport controlled reaction and diameter of the disk is pretty larger compared with the thickness of diffusion layer, edge effect can be neglected and the rate constant can be said to be proportional to the apparent surface area.[6] The results shown in Table I do not contradict this fact.

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[37] K. Tsuda, T. Nakamura: Yakugaku Zasshi, **67**, 239 (1947).

If the disintegration of the disk may be taken place together with the dissolution from the disk, as the sampling of solution is carried out with pipette, the measured concentration is expected to be higher by such an amount of particles produced by disintegration of disk and apparently K_T will be larger. As the disintegration of the disk is considered independent on the volume of the solution, if the disintegration may happen, K_T can be changed by changing the volume of the solution. However, since K_T was constant as shown in Table I, the disintegration was not taken place, or it was understood that the disintegration might be neglected if it would happen. This was confirmed by the fact that, when sampling was carried out with the pipette, at the tip which a #3 glass-filter was installed, no slight difference was observed in the concentration-time curve.

Dependence of Rate Constant on Compressional Pressure to Make Disk

If the compressional pressure to make disk was changed, the apparent density of the disk was varied, as shown in Table II. This fact suggests that porosity of the disk varies with compressional pressure and intrinsic surface area of the disk is considered to vary as well. However, as shown in Table II, no difference of K_T by compressional pressure was found, and thus the dissolution rate was concluded to depend not on the intrinsic surface area but on the apparent geometrical surface area of disk. This is quite coincident with the fact on the transport controlled dissolution.[6]

Table II. Influence of the Compressional Pressure to Make Disk on the Dissolution Rate Constant of Sulfadiazine in Water at 37°, 600 r.p.m.

Pressure (ton/cm^2)	Density (g./cm^3)	$K_T \times 10$ (cm./min.)
1	1.40	2.39
2	1.43	2.34
3	1.44	2.34
4	1.46	2.34
5	1.44	2.34

Concerning such a substance having polymorphism as sulfathiazole, it has been reported that, when it was compressed in unlubricated die wall, the dissolution rate of the disk varied depending on the compressional pressure.[24] This fact is supposed to be caused by a change of crystalline form, not caused by the difference of an apparent geometrical surface area mentioned above.

Dependence of Rate Constant on Rotating Velocity of the Disk

When the flow of liquid is of laminar flow around the disk, the dissolution rate constant, K_T, is considered to be proportional to the square root of the rotating velocity of the disk according to equation (4). If r is the radius of the disk, the Reynolds number, Re, with respect to the rotating disk is given by

$$Re=r^2\omega/\nu \qquad (7)$$

where ω is the angular velocity and ν the kinematic viscosity, and the critical Reynolds number in the circumstances is said to be 10^5.[38] When a disk of 3 cm. diameter rotates in the liquid of kinematic viscosity of 1 centi-stokes, the flow of liquid around

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38) S. I. Pai : "Viscous Flow Theory II—Turbulent Flow," chap. IV, (1957), D. Van Nostrand Co., Inc., Princeton.

the disk can be of laminar flow at the rotating velocity of less than 10^3 r.p.m., from the calculation according to equation (7). In Fig. 6, the dependence of K_T on the rotating velocity of disk at various temperatures was shown. The values measured at 600, 300, and 120 r.p.m. are on the straight lines which pass through the original point and equation (4) is established. This result also verifies that the disintegration is not taken place. The value at 60 r.p.m. has a tendency to deviate a little to the upper part from each straight line. As described by Riddiford,[6] at a slow rotating, free convection of the liquid can not be negligible and so an increase of K_T was considered to be taken place.

Temperature Dependence of Rate Constant

Temperature dependence of dissolution rate constant, K_T, are shown in Fig. 7. The activation energy calculated from the slope of the straight line in Fig. 7 was about 3.5 Kcal./mole as shown in Table Ⅲ. This is the value which is expected when the dissolution is transport controlled.[4,39]

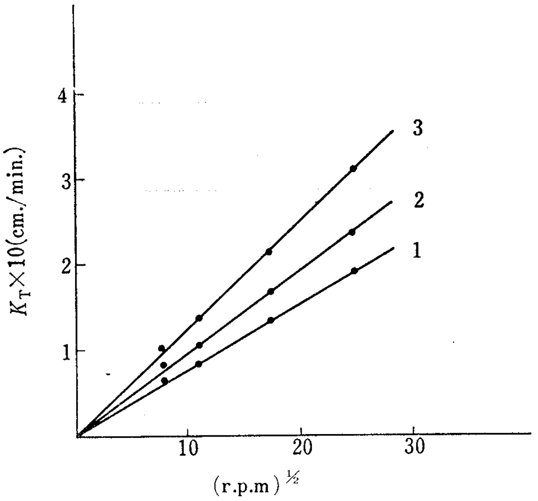

Fig. 6. Dependence of Dissolution Rate Constant, K_T, of Sulfadiazine in Water on the Rotating Velocity of Disk at Various Temperatures

1: at 25° 2: at 37°
3: at 50°

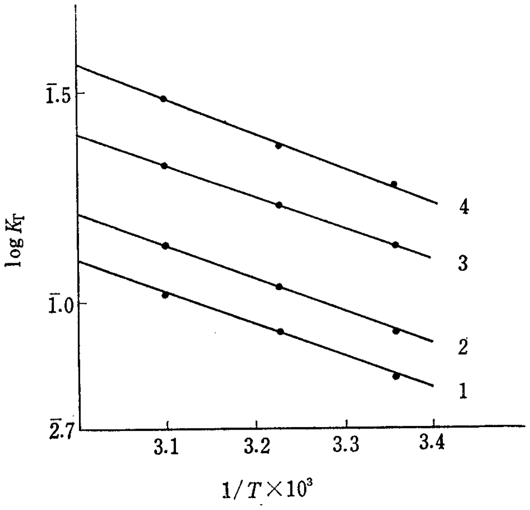

Fig. 7. Temperature Dependence of the Dissolution Rate Constant, K_T, of Sulfadiazine in Water at Various Rotating Velocities of Disk

1: 60 r.p.m. 2: 120 r.p.m.
3: 300 r.p.m. 4: 600 r.p.m.

Table Ⅲ. Activation Energy, E_A, of Dissolution of Sulfadiazine in Water

Rotating Velocity of the Disk(r.p.m.)	E_A (cal/mole)	Rotating Velocity of the Disk(r.p.m.)	E_A (cal/mole)
600	3,660	120	3,540
300	3,420	60	3,440

Dissolution of Five Kinds of Sulfonamides in Water

Five kinds of sulfonamides were compressed under 3 tons/cm^2 to make a disk of 3 cm. diameter, and dissolution rate constant, K_T, and saturated concentration, C_0 were obtained at a rotating velocity of 600 r.p.m. in water at 37°. The results are shown in Table Ⅳ. The values of C_0 were coincident with the values of solubility, C_s, observed experimentally.

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39) E. A. Moelwyn-Hughes: "The Kinetics of Reaction in Solution," (1947), The Clarendon Press, Oxford.

Table IV. Dissolution Rate Constant, K_T, Saturated Concentration, C_0, and Solubility, C_s, on the Dissolution of Sulfonamides in Water at 37°, 600 r.p.m.

Sulfonamide	$K_{T\,obs.}\times 10$ (cm./min.)	$K_{T\,calc.}\times 10$ (cm./min.)	C_0 (mg./100 ml.)	C_s (mg./100 ml.)
Sulfisomezole	2.42	2.44	62.5	62.6
Sulfaguanidine	2.58	2.47	190	194
Sulfisoxazole	2.40	2.38	142	138
Sulfapyridine	2.52	2.43	58.9	60.2
Sulfadiazine	2.34	2.33	12.0	12.9

$K_{T\,obs.}$: observed. $K_{T\,calc.}$: calculated from the values in Table V.

If the dissolution would be transport controlled, K_T should be according to equation (4). That is, the value of K_T observed is coincident with the values calculated from equation (4) by using diffusion coefficient, kinematic viscosity and angular velocity of rotation.

As the diffusion coefficients of sulfonamides have not been obtained, the values at 20°, D_{20°, were estimated according to the Arnold equation (8).[40)]

$$D_{20^\circ}=\frac{0.0100\times\left(\frac{1}{M_1}+\frac{1}{M_2}\right)^{1/2}}{A_1A_2\eta_2^{1/2}(V_1^{1/3}+V_2^{1/3})^2} \qquad (8)$$

where M_1 and M_2 are the molecular weight of solute and solvent, V_1 and V_2 the molecular volume of solute and solvent at the standard boiling point, A_1 and A_2 the correction coefficient atributed to the abnormality of solute and solvent, respectively, and η_2 is the viscosity of solvent at 20°. V_1 and V_2 can be obtained by adding the respective atomic volumes.[41)] The diffusion coefficient D_{t° at temperature $t°$ is obtained from D_{20° by the following equation : [42)]

$$D_{t^\circ}=\frac{D_{20^\circ}}{1.6}(1+0.03t) \qquad (9)$$

When the solvent is water, $M_2=18$, $V_2=18.4$, $\eta_2=1.0$, and $A_2=4.70$ at 20°.[42)] Though the value of A_1 for sulfaonamide was not known, the fitting one was found to 1.25 experimentally, which was considered to be rational compared with the values for other organic substances.[42)] Putting the values of M_1 and V_1 of each sulfonamide in equation (8), the diffusion coefficients were calculated from equations (8) and (9), as shown in Table V. Then, in equation (4), putting the diffusion coefficient mentioned

Table V. Calculation of Diffusion Coefficients of Sulfonamides According to Equations (8) and (9)

Sulfonamide	M_1	V_1	$D_{20^\circ}\times 10^6$ (cm²/sec.)	$D_{37^\circ}\times 10^6$ (cm²/sec.)
Sulfisomezole	253.3	250	5.21	6.87
Sulfaguanidine	232.3	241	5.43	7.02
Sulfisoxazole	267.3	272	5.00	6.61
Sulfapyridine	249.3	253	5.18	6.84
Sulfadiazine	250.3	286	4.88	6.45

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40) J.H. Arnold : J. Am. Chem. Soc., **52**, 2937 (1930).
41) L. Bas : Proc. Chem. Soc., **22**, 322 (1906).
42) K. Satō : "Bussei-Teisū Suisanhō," p. 306 (1957), Maruzen, Tokyo.

above, kinematic viscosity of water of 6.99×10^{-3} cm²/sec. at 37°,[*7] and angular velocity of 20π/sec., the values of dissolution rate constant, K_T, were calculated, as shown in Table Ⅳ and these agreed quite well with the values observed.

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Summary

The disk of sulfonamide was made by compression of the powder and the dissolution rate was measured by rotating it in water under various conditions. The results obtained are :

1. The concentration-time curve of dissolution was obtained with a good reproducibility and it did not depend on the thickness of disk, the size and shape of the flask which contained the liquid, and the depth of the disk from water level.
2. The dissolution rate constant, K_T, did not depend on the surface area of the disk and the volume of the liquid of 50 to 200 ml. During the dissolution experiment, disintegration of disk could not be considered to occur.
3. K_T did not depend on the compressional pressure to make disk under 1 to 5 tons/cm². This showed that the dissolution depended on the apparent geometrical surface area, not on the intrinsic surface area of solid.
4. K_T was proportional to the square root of rotating velocity of the disk.
5. The activation energy of dissolution of sulfadiazine was about 3.5 Kcal./mole.
6. The values of K_T of five kinds of sulfaonamides were quite coincident with the values calculated according to the Arnold equation. The values of saturated concentration, C_0, were coincident with the values of solubility, C_s, observed.
7. From the results obtained, it would be possible to give the following conclusions : i) From the measurement of dissolution rate by the rotating disk method, K_T and C_0 can be obtained separately with a high confidence on the value. ii) The dissolution of sulfonamide is in accordance with the Noyes-Nernst equation concerning the transport controlled dissolution. The Levich equation is also established.

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[*7] Calculated from the viscosity of 0.6947 centi-poise and the density of 0.99336 g./cm³ of water at 37°, which are listed in the reference : "Kagaku-Binran" by Nippon Kagaku-kai (1958), Maruzen, Tokyo.