[Chem. Pharm. Bull. 14(4) 339~350 (1966)]

UDC 615.412.1-011 : 615.778.25

47. Hisashi Nogami, Tsuneji Nagai, and Akira Suzuki[*1] : Studies on Powdered Preparations. XVIII.[*2] Dissolution Rate of Sulfadiazine in Various Aqueous Solutions.[*3,*4]

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In the previous paper,[*2] fundamental investigations on the experiment of dissolution rate by rotating disk method were made and a method was established to obtain the dissolution rate constant, K_T, and saturated concentration, C_0, separately.

In this study, sulfadiazine, which is determined easily and has been used frequently for a long period of years, was chosen to examine how K_T and C_0 would change on the dissolution by the addition of substance in the solution, and moreover, the mechanism of dissolution was studied. The conclusions obtained here are not limited to sulfadiazine only, but are in general for the other sulfonamides, and also it may be considered to be in common, even on the other kinds of medicinal preparations.

As to the transport controlled dissolution, its rate is generally represented by the Noyes-Nernst equation (1).

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

where C is the concentration at the time t, C_0 the saturated concontration,[*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 mechanism of transport controlled dissolution are classified into the following three models : i) Noyes-Nernst model,[1)] ii) Nernst-Brünner model,[2)] and iii) Higuchi model.[3)] Among them, i) is subdivided into two : i-a) abdiffusion controlled case and i-b) zudiffusion controlled case. These models are shown in Table I.

i-a) is the case when diffusion from solid A is the rate-determining step and the dissolution rate is represented by

$$\frac{dC}{dt}=\frac{S}{V}\,\frac{D_A}{\delta}(C_s-C) \qquad (2)$$

where D_A is the diffusion coefficient of A, C_s the solubility. Therefore, $K_T=D_A/\delta$ and $C_0=C_s$.

i-b) is the case when a reaction is taken place between the solid A and the solute B in the solid-liquid interface, and the diffusion of the solute B is the rate determining step. The dissolution rate is represented by

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[*2] Part XVII. H. Nogami, T. Nagai, A. Suzuki : This Bulletin, 14, 329 (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 Science, University of Tokyo, 1965.

[*5] Hongo, Tokyo (野上 寿, 永井恒司, 鈴木 章).

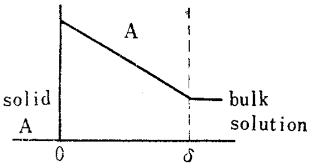
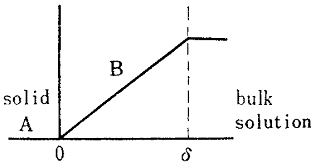
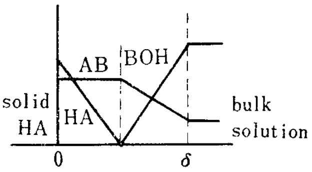
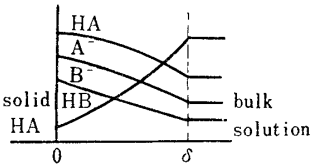
[*6] This is the value estimated kinetically[*2] and not always equal to the solubility.

1) W. Nernst : Z. physik. Chem., **47**, 52 (1904).

2) E. Brünner, St. Tolloczko : *Ibid.*, **47**, 56 (1904).

3) W.I. Higuchi, E.L. Parrott, D.E. Wurster, T. Higuchi : J. Am. Pharm. Assoc., Sci. Ed., **47**, 376 (1958).

Table I. Models for Transport Controlled Dissolution

Model		Concentration profile[a)]	K_T	C_0
i) Noyes–Nernst model	a) No chemical reaction in diffusion layer (abdiffusion)		$\frac{D_A}{\delta}$	C_s
	b) No chemical reaction in diffusion layer (zudiffusion)		$\frac{D_B}{\delta}$	C_{BO}
ii) Nernst–Brunner model	Simultaneous chemical reaction in diffusion layer		$\frac{D_B}{\delta}$	C_{BO}
iii) Higuchi model	Simultaneous chemical reaction in diffusion layer		$\frac{D^*}{\delta}$	C_s

a) ordinate: concentration. abscissa: distance from the solid surface.

$$\frac{dC^{*7}}{dt}=\frac{S}{V}\frac{D_B}{\delta}C_B \tag{3}$$

where D_B is the diffusion coefficient of B, C_B is the concentration of B at time t. If the reaction is taken place at a ratio of 1:1 between A and B, equation (3) becomes

$$\frac{dC}{dt}=\frac{S}{V}\frac{D_B}{\delta}(C_{BO}-C) \tag{4}$$

where C_{BO} is the initial concentration of B. Therefore, $K_T=D_B/\delta$ and $C_0=C_{BO}$.

ii) is the case when a neutralization between the acid HA dissolved from the solid and the base BOH in the solution is taken place in the diffusion layer where "total effective thickness" is δ, on the place situated at a certain distance from the surface of the solid, and the dissolution rate is represented by

$$\frac{dC}{dt}=\frac{S}{V}\left(\frac{D_AC_s+D_BC_B}{\delta}\right) \tag{5}$$

where D_A and D_B are the diffusion coefficients of HA and BOH respectively, C_s the solubility of HA, C_B the concentration of BOH at time t. The reaction between HA and BOH is considered to be taken place at a ratio of 1:1 and so equation (5) becomes

$$\frac{dC}{dt}=\frac{S}{V}\frac{D_B}{\delta}\left(\frac{D_AC_s+D_BC_{BO}}{D_B}-C\right) \tag{6}$$

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[7] Dissolved amount of solid A is represented by C in concentration unit, and C did not mean the concentration of A in the solution, but AB in this case.

where C_{BO} is the initial concentration of BOH. Therefore, $K_T = D_B/\delta$ and $C_0 = (D_A C_s + D_B C_{BO})/D_B$. If $D_B C_{BO}$ is larger than $D_A C_s$, C_0 may become almost C_{BO}. After a completion of consumption of BOH, the solid HA can dissolve in the presence of the reaction product AB. Therefore, the process of dissolution is divided into two stages, the former stage accompanying the neutralization and the latter stage not accompanying the neutralization. Here the value of C_0 in the latter stage of dissolution becomes different from C_{BO} described above.

iii) is the case when an equilibrium is established during the dissolution of a solid weak acid HA in a solution of an ionic base B^-, in the diffusion layer, as follows :

$$HA + B^- \rightleftharpoons A^- + HB$$

and the equilibrium constant, K, is given by

$$K = \frac{(A^-)(HB)}{(HA)(B^-)} \qquad (7)$$

where ( ) denotes the concentration of the respective component. Then, the dissolution rate is represented by

$$\frac{dC}{dt} = \frac{S}{V}\left[\frac{D_{B^-}C_{B^-} - D_{HA}C_{HA} + D_{HA}C_{SO}}{\delta} - \frac{D_{B^-}(L_1+L_2) + D_{HB}D_{A^-} - KC_{SO} \pm [\{D_{B^-}(L_1+L_2) + D_{HB}D_{A^-} - KC_{SO}\}^2 - 4L_1L_2D_{B^-}^2]^{1/2}}{2D_{B^-}\delta}\right] \qquad (8)$$

where D_{HA}, D_{HB}, D_{A^-}, and D_{B^-} are the diffusion coefficients of HA, HB, A^-, and B^- respectively; C_{SO} the solubility of HA in the solvent; C_{HA}, C_{HB}, C_{A^-}, and C_{B^-} the concentrations in bulk liquid at time t of HA, HB, A^-, and B^- respectively; $L_1 = D_{B^-}C_{B^-} + D_{A^-}C_{A^-}$; and $L_2 = D_{B^-}C_{B^-} + D_{HB}C_{HB}$. If $K \rightarrow \infty$, then equation (8) becomes coincident with equation (5). That is, the dissolution is expected to be in accordance with the Nernst-Brünner equation. Here, for equation (5) to approximate equation (8), the following conditions are necessary :

$$\left.\begin{array}{ll} K > 10^2, & \text{if } C_{SO} = C_{B^-} \\ K > 2\times 10^3, & \text{if } 10C_{SO} = C_{B^-} \\ K > 2\times 10^4, & \text{if } 100C_{SO} = C_{B^-} \end{array}\right\} \qquad (9)$$

It has been reported[4] that, when every diffusion coefficient is almost equal, equation (8) becomes

$$\frac{dC}{dt} = \frac{S}{V}\frac{D^*}{\delta}(C_s - C) \qquad (10)$$

where C_s is the total solubility in the solution and $D^* \fallingdotseq D_{HA} \fallingdotseq D_{HB} \fallingdotseq D_{A^-} \fallingdotseq D_{B^-}$. Therefore, $K_T = D^*/\delta$ and $C_0 = C_s$.

Experimental

Sample——Commercial sulfadiazine J. P. was used.

Apparatus and Procedure——Rotating disk method, as was described in the previous paper,*2 was employed. Every experiment was carried out under the following conditions : the solution of 100 ml. at 37°; the disk of 3 cm. diameter compressed under 3 tons/cm^2; the rotating velocity of disk at 600 r.p.m.

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4) W. I. Higuchi, E. Nelson, J. G. Wagner : J. Pharm. Sci., 53, 333 (1964).

Results and Discussion

Dissolution in Sucrose Solution——Influence of Viscosity

Sucrose solution is pretty viscous, and it is supposed to be suitable to examine an influence of viscosity on the dissolution rate. As it is known, sucrose solution is important as syrups pharmaceutically. The results obtained are shown in Table II. The saturated concentration, C_0, was increased a little as the concentration of sucrose was increased. This phenomenon was considered to be adequate from the fact that, as an increase of sucrose concentration, the solubilities of phenobarbital and sulfanilamide are increased as a result of the decrease of dielectric constant of the solution.5) As shown in Table II, the values of C_0 estimated were almost coincident with the values of solubility observed.

Table II. Values Obtained on the Dissolution of Sulfadiazine in Sucrose Solution at 37°

C_{sucrose} (M)	$K_T \times 10$ (cm./min.)	$\nu \times 10^3$ (cm²/sec.)	$D \times 10^6$ (cm²/sec.)	D_{H_2O}/D	η/η_{H_2O}	C_0 (mg./100 ml.)	C_s (mg./100 ml.)
10^{-3}	2.34	7.01	6.55	0.99	1.005	10.5	10.9
10^{-2}	2.26	7.04	6.27	1.03	1.012	10.6	11.0
10^{-1}	2.03	7.50	5.35	1.21	1.14	11.8	12.0
1	0.868	17.60	2.12	3.03	2.87	12.2	12.9

C_{sucrose}: Concentration of sucrose
K_T: dissolution rate constant
ν: kinematic viscosity
D: diffusion coefficient of sulfadiazine obtained according to equation (11)
D_{H_2O}: diffusion coefficient of sulfadiazine in water[*2]
η: viscosity of the solution
η_{H_2O}: viscosity of water
C_0: saturated concentration of sulfadiazine estimated kinetically
C_s: solubility of sulfadiazine

On the other hand, the dissolution rate constant, K_T, became smaller, as the concentration of sucrose was increased, as shown in Table II, and the dissolution rate by practical representation,[*2] $K_T \times C_0$, became smaller. For the decrease of K_T mentioned above, two reasons were considered : one was an increase of kinematic viscosity and the other is a decrease of diffusion coefficient as an increase of viscosity,6) according to the following equation (11).

As shown in the previous paper,[*2] the dissolution rate constant, K_T, is given by the Levich equation7,8) as

$$K_T = 0.620 \times D^{2/3} \times \nu^{-1/6} \times \omega^{1/2} \qquad (11)$$

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

According to equation (11), the kinematic viscosity, ν, gives an influence on K_T by $-1/6$ power. Therefore, even if the kinematic viscosity becomes 2.5 times, K_T is expected to be decreased simply 10% or more.

The diffusion coefficient, D, of sulfadiazine, obtained by putting K_T and ν in equation (11), was decreased as an increase of the concentration of sucrose, as shown in

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5) A.N. Paruta : J. Pharm. Sci., **53**, 1252 (1964).
6) C.R. Wilke : Chem. Eng. Progress, **45**, 218 (1949).
7) V.G. Levich : Acta Physicochim., U.S.S.S., **17**, 257 (1942).
8) *Idem* : "Physicochemical Hydrodynamics," (1962), Prentice-Hall, Inc., Englewood Cliffs, N.J.

Table II. When the ratio of the diffusion coefficient of sulfadiazine in water[*8] to that obtained above, D_{H_2O}/D, was compared with the relative viscosity, η/η_{H_2O}, they indicated the similar tendency. This seemed to be reasonable from the fact that, in sucrose solution, the diffusion ccefficient is inversely proportional to the viscosity, though not completely.[9,10]

The results obtained concerning C_0 and D in K_T showed that the dissolution was in accrodance with the Noyes-Nernst model.

Dissolution in Sodium Chloride Solution——Influence of Neutral Electrolyte

NaCl is one of the most typical neutral electrolyte, and it exists in body fluid in a pretty higher concentration. The results obtained are shown in Table III. As an increase of NaCl concentration, both C_0 and K_T were decreased. The decrease of C_0 was considered to be taken by salting out.[11,12]

TABLE III. Values Obtained on the Dissolution of Sulfadiazine in Sodium Chloride Solution at 37°

C_{NaCl} (M)	$K_T\times 10$ (cm./min.)	$\nu\times 10^3$ (cm²/sec.)	$D\times 10^6$ (cm²/sec.)	D_{H_2O}/D	η/η_{H_2O}	C_0 (mg./100 ml.)	C_s (mg./100 ml.)
10^{-3}	2.34	6.99	6.49	1.00	1.00	11.7	12.1
10^{-2}	2.23	6.99	6.02	1.07	1.00	10.8	11.3
10^{-1}	1.86	7.04	4.59	1.41	1.02	10.2	10.2
1	1.73	7.46	4.19	1.55	1.19	8.8	9.0

Denotions: refer to the footnote of Table II.

As shown in Table III, C_0 was almost coincident with C_s, and K_T was quite near to the value obtained on the dissolution of sulfadiazine in water, 2.34×10^{-1} cm./min.[*2] Therefore, it is concluded that the dissolution is in accordance with the Noyes-Nernst model.

D_{H_2O}/D calculated from K_T was not so coincident with the relative viscosity, η/η_{H_2O}, as was shown in the case of sucrose solution described above. This can not be explained only from the decrease of diffusion coefficient as an increase of viscosity. From the standpoint of irreversible thermodynamics,[13] for example, it may be possible to explain that, owing to the flow of sulfadiazine into bulk liquid, the concentration gradient of sodium chloride may exist in the opposite direction and this may interfere with the flow of sulfadiazine.

Dissolution in Strong Base Solution——Dissolution According to the Nernst-Brünner Model

Sulfonamide is often dissolved in aqueous solution of strong basic substance in manufacturing the injections.[14] The results obtained will be described separately in two: 1) dissolution in sodium hydroxide and 2) dissolution in the other strong base solution.

1) **Dissolution in Sodium Hydroxide Solution**——As shown in Fig. 1, a flexion point was observed on the finite differences diagram,[*2] where C_1 is the concentration at time

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[*8] Calculated as 6.45×10^{-6} cm²/sec. at 37° in the previous paper.[*2]

9) C.V. King, S.S. Brodie: J. Am. Chem. Soc., **59**, 1375 (1937).

10) A.R. Cooper, Jr., W.D. Kingery: J. Phys. Chem., **66**, 665 (1962).

11) E.L. Parrott, D.E. Wurster, T. Higuchi: J. Am. Pharm. Assoc., Sci., Ed., **44**, 269 (1955).

12) H. Owen: "The Physical Chemistry of Electrolytic Solution," 2nd Ed., (1950), Reinhold Publishing Corp., New York.

13) M. Senoo: "Fukagyakukatei no Netsurikigaku Joron," (1964), Tokyo-Kagaku-Dojin, Tokyo.

14) F.S. Hom, J. Austin: J. Am. Pharm. Assoc., Sci. Ed., **45**, 608 (1956).

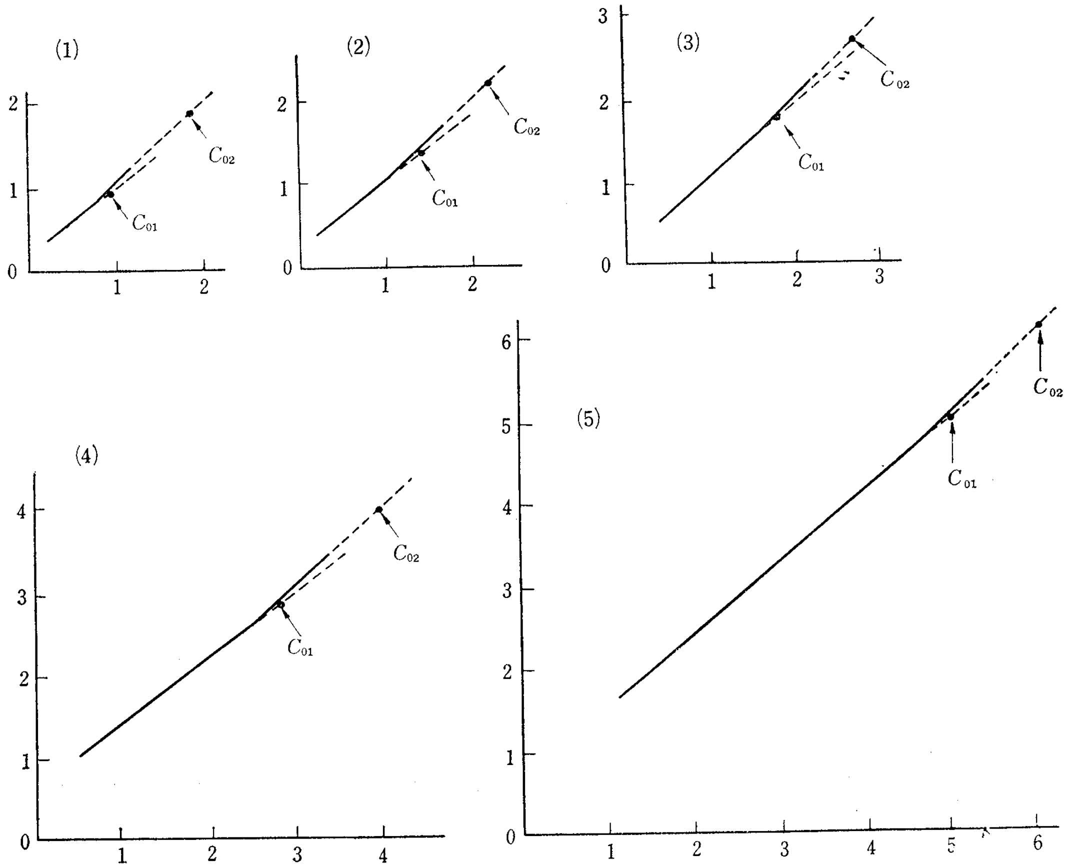

Fig. 1. Finite Differences Diagrams of the Dissolution of Sulfadiazine in Sodium Hydroxide Solution at 37°

ordinate: $C_2 \times 10^{+3}$ (M)
abscissa: $C_1 \times 10^{+3}$ (M)

(1): $C_{NaOH}=10^{-3}M$
(2): $C_{NaOH}=1.4 \times 10^{-3}M$
(3): $C_{NaOH}=2 \times 10^{-3}M$
(4): $C_{NaOH}=3 \times 10^{-3}M$
(5): $C_{NaOH}=5 \times 10^{-3}M$

t and C_2 the concentration at $t+5$ minutes. Therefore, the dissolution can be divided into two stages, *i.e.* the former stage and the latter, according to before and after the flexion point, respectively. C_{01} is the saturated concentration for the former stage, estimated kinetically, and C_{02} for the latter stage.

When the initial concentration of sodium hydroxide, C_{NaOH}, was made larger, C_{01} and C_{02} were increased, but the difference between C_{01} and C_{02} was not changed remarkably. Therefore, as an increase of C_{NaOH}, the ratio $(C_{02}-C_{01})/C_{01}$ became smaller, and

TABLE IV. Values Obtained on the Dissolution of Sulfadiazine in Sodium Hydroxide Solution at 37°

C_{NaOH} (M)	$K_T \times 10$ (cm./min.)	C_{01} (mg./100 ml.)	C_{02} (mg./100 ml.)	C_s (mg./100 ml.)
1×10^{-3}	4.56	23.4 ($0.94 \times 10^{-3}M$)	32.9 ($1.32 \times 10^{-3}M$)	35.2 ($1.41 \times 10^{-3}M$)
1.4×10^{-3}	4.65	34.6 ($1.38 \times 10^{-3}M$)	46.8 ($1.87 \times 10^{-3}M$)	46.9 ($1.88 \times 10^{-3}M$)
2×10^{-3}	6.15	43.6 ($1.75 \times 10^{-3}M$)	67.8 ($2.71 \times 10^{-3}M$)	68.1 ($2.72 \times 10^{-3}M$)
3×10^{-3}	6.32	71.8 ($2.88 \times 10^{-3}M$)	95.0 ($3.80 \times 10^{-3}M$)	96.0 ($3.84 \times 10^{-3}M$)
4×10^{-3}	7.08	95.4 ($3.82 \times 10^{-3}M$)	115. ($4.61 \times 10^{-3}M$)	118. ($4.72 \times 10^{-3}M$)
5×10^{-3}	7.55	126. ($5.02 \times 10^{-3}M$)	151. ($6.05 \times 10^{-3}M$)	153. ($6.12 \times 10^{-3}M$)
10×10^{-3}	8.39	252. ($10.0 \times 10^{-3}M$)	270. ($10.8 \times 10^{-3}M$)	272. ($10.9 \times 10^{-3}M$)
3×10^{-2}	7.76	765. ($3.06 \times 10^{-2}M$)	—	760. ($3.04 \times 10^{-2}M$)
5×10^{-2}	8.12	1160. ($4.61 \times 10^{-2}M$)	—	1270. ($5.08 \times 10^{-2}M$)
10×10^{-2}	8.75	2380. ($9.54 \times 10^{-2}M$)	—	2520. ($10.08 \times 10^{-2}M$)

in the case when C_{NaOH} was made more than $10^{-1}M$, the difference between C_{01} and C_{02} became undiscriminative on the finite differences diagram and thus the values of C_{02} in such cases are not listed in Table Ⅳ.

The plot of C_{01} and C_{NaOH} is shown in Fig. 2. It is almost a straight line having a slope of 45°. This means that the saturated concentration in the former stage of dissolution was coincident with the initial concentration of sodium hydroxide. On the other hand, the saturated concentration in the latter stage was almost coincident with the solubility, C_s, in each solution, as shown in Table Ⅳ. From the existence of flexion point on the finite differences diagram and the coincidence of C_{01} with C_{NaOH}, it is concluded that the dissolution is in accordance with the Nernst-Brünner model.

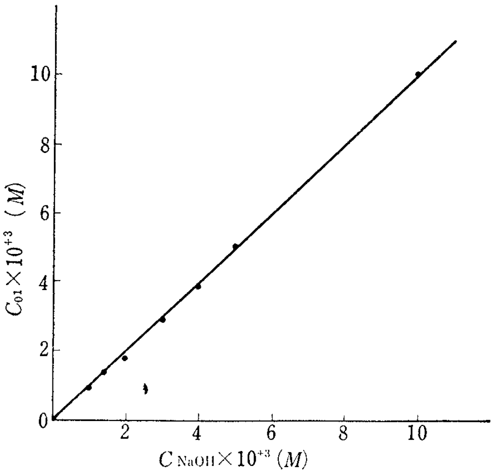

Fig. 2. Relationship between the Saturated Concentration for the Former Stage, C_{01}, and the Initial Concentration of Sodium Hydroxide, C_{NaOH}, on the Dissolution of Sulfadiazine in Sodium Hydroxide Solution at 37°

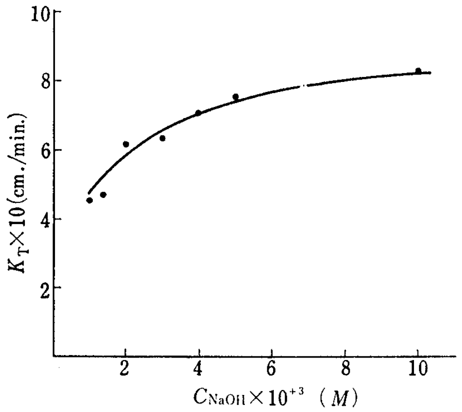

Fig. 3. Effect of Sodium Hydroxide on the Dissolution Rate Constant, K_T, of Sulfadiazine in Sodium Hydroxide Solution at 37° from a Disk Rotating at a Velocity of 600 r.p.m.

As shown in Fig. 3, K_T was found to become larger with an increase of C_{NaOH}. When C_{NaOH} was less than $10^{-1}M$, the kinematic viscosity of the solution was recognized to be almost equal to that of water, and therefore the increase of K_T can be attributed to an increase of diffusion coefficient. For this increase of diffusion coefficient, the following interpretation seems possible. As the dissolution is considered to be according to the Nernst-Brünner model, the diffusion coefficient having influence on K_T is that of sodium hydroxide as shown by equation (6) and furthermore sodium hydroxide diffuses in the presence of sodium salt of sulfadiazine produced by the neutralization. The diffusion coefficient of sodium hydroxide, if this salt is present, is said to be increased because of the drop of diffusion potential.15) As an experimental fact for this phenomenon, it has been reported that the diffusion coefficient of sodium hydroxide is increased in the presence of sodium benzoate.16) The result shown in Fig. 3 is similar to this fact, and thus the increase of K_T can be attributed to an increase of diffusion coefficient of sodium hydroxide because of a drop of diffusion potential.

On the dissolution in $10^{-2}M$ sodium hydroxide solution, dependence of dissolution rate on the rotating velocity of the disk was examined, and the results obtained are shown in Fig. 4. In the same way as in water,[*2] K_T was proportional to $\omega^{1/2}$. The value of K_T, calculated by putting the diffusion coefficient of sodium hydroxide in water

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15) J.R. Vinograd, J.W. McBain: J. Am. Chem. Soc., **63**, 2008 (1941).
16) C.V. King, S.S. Brodie: *Ibid.*, **59**, 1375 (1937).

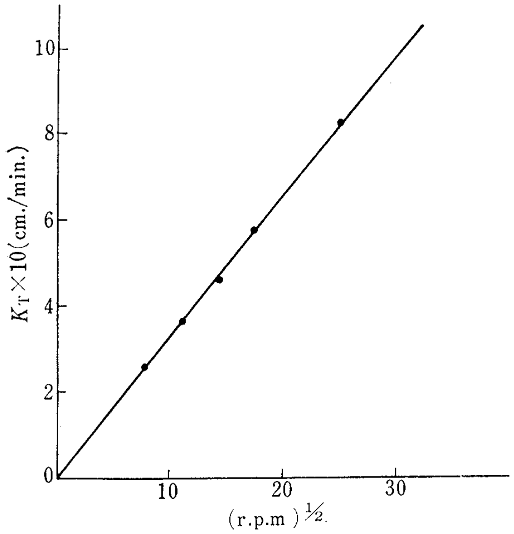

Fig. 4. Dependence of Dissolution Rate Constant, K_T, of Sulfadiazine in $10^{-2}M$ Sodium Hydroxide Solution on the Rotating Velocity of Disk at 37°

of 2.11×10^{-5} cm²/sec.*8 in equation (11), was 4.76×10^{-1}cm./min., which was almost equal to the value of K_T in $10^{-3}M$ sodium hydroxide solution, as shown in Table IV. From htis result and the proportionality of K_T to the rotating velocity described above, the Levich theory was supposed to be established.

2) **Dissolution in Strong Base Solution Other Than Sodium Hydroxide**——On the dissolution in potassium hydroxide, triethanolamine, or diethanolamine solution, a flexion point was observed on the finite differences diagram in the same way as in sodium hydroxide solution.

The changes of K_T, with change of concentration of each substance added, are shown in Tables V to VII. K_T was increased with an increase of concentration. As to the saturated concentration in every case, C_{01} and C_{02} were found to be in accordance with the initial concentration of the base and the solubility, C_s, respectively, as shown in Tables V to VII. The value of K_T, calculated by putting the diffusion coefficient of potassium hyd-

Table V. Values Obtained on the Dissolution of Sulfadiazine in Potassium Hydroxide Solution at 37°

C_{KOH} (M)	$K_T\times10$ (cm./min.)	C_{01} (mg./100 ml.)	C_{02} (mg./100 ml.)	C_s (mg./100 ml.)
1×10^{-3}	5.46	23.6($0.94\times10^{-3}M$)	34.7($1.38\times10^{-3}M$)	35.2($1.41\times10^{-3}M$)
5×10^{-3}	6.65	125. ($4.99\times10^{-3}M$)	130. ($5.20\times10^{-3}M$)	131. ($5.24\times10^{-3}M$)
1×10^{-2}	7.42	228. ($0.91\times10^{-2}M$)	—	326. ($1.30\times10^{-2}M$)
5×10^{-2}	7.96	1210. ($4.84\times10^{-2}M$)	—	1350. ($5.40\times10^{-2}M$)
10×10^{-2}	8.10	2420. ($0.97\times10^{-2}M$)	—	2710. ($1.08\times10^{-2}M$)

Table VI. Values Obtained on the Dissolution of Sulfadiazine in Triethanolamine (TEA) at 37°

C_{TEA} (M)	$K_T\times10$ (cm./min.)	C_{01} (mg./100 ml.)	C_{02} (mg./100 ml.)	C_s (mg./100 ml.)
10^{-3}	1.99	24.4($0.98\times10^{-3}M$)	31.2($1.25\times10^{-3}M$)	31.4($1.3\times10^{-3}M$)
10^{-2}	2.20	282. ($1.1\times10^{-2}M$)	—	286. ($1.1\times10^{-2}M$)
10^{-1}	2.53	2540. ($1.0\times10^{-1}M$)	—	2550. ($1.0\times10^{-1}M$)

Table VII. Values Obtained on the Dissolution of Sulfadiazine in Diethanolamine (DEA) at 37°

C_{DEA} (M)	$K_T\times10$ (cm./min.)	C_{01} (mg./100 ml.)	C_{02} (mg./100 ml.)	C_s (mg./100 ml.)
10^{-3}	1.97	28.4($1.14\times10^{-3}M$)	32.2($1.29\times10^{-3}M$)	33.8($1.35\times10^{-3}M$)
10^{-2}	2.66	250. ($1.00\times10^{-2}M$)	—	266. ($1.06\times10^{-2}M$)
10^{-1}	2.74	2250. ($0.90\times10^{-1}M$)	—	2510. ($1.00\times10^{-1}M$)

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*9 Calculated according to equation, $D\eta/T$=constant, where D is the diffusion coefficient, η the viscosity and T the temperature in °K, using the values listed in the reference : 17).

17) Nippon Kagaku-kai : "Kagaku-Binran," (1958), Maruzen, Tokyo.

roxide in water of 3.32×10^{-5} cm^2/sec.*9 in equation (11), was 6.32×10^{-1} cm./min., which was almost equal to the value of K_T observed in $10^{-3}M$ potassium hydroxide solution, as shown in Table V.

These results mentioned above may offer the conclusion that the dissolution is in accordance with the Nernst-Brünner model.

Dissolution in Buffer Solution and in Dilute Mineral Acid——Dissolution According to the Higuchi Model

As sulfadiazine is an ampholite having $pK_1=2.0$ and $pK_2=6.48$,18) in buffer solution or dilute mineral acid solution, it exists in both ionic form and molecular form, between which an equilibrium is considered to be established. The results obtained on the dissolutions in Na_2HPO_4 solution, in Mc'Ilvaine buffer solution and in hydrochloric acid solution will be described and discussed.

1) **Dissolution in Na_2HPO_4 Solution**——Representing the molecular form of sulfadiazine by HSD, the following equilibrium may exist in Na_2HPO_4 solution :

$$HSD + HPO_4^{2-} \rightleftharpoons SD^- + H_2PO_4^-$$

According to the theory given by Higuchi,3) the equilibrium constant, K, is represented from equation (7) as

$$K=\frac{(SD^-)(H_2PO_4^-)}{(HSD)(HPO_4^{2-})}=\frac{Ka_2}{K_{H_2PO_4^-}} \tag{12}$$

where Ka_2 is the dissociation constant of sulfadiazine as acid and $K_{H_2PO_4^-}$ the dissociation constant of $H_2PO_4^-$. As $Ka_2=3.31\times10^{-7}$17) and $K_{H_2PO_4^-}=5.31\times10^{-8}$17) are given, K becomes 6.85 from equation (12). When this value is compared with the conditions in equation (9), it is too small. Therefore, the dissolution is considared to be in accordance with the Higuchi model, not in accordance with the Nernst-Brünner model.

No flexion point was observed on the finite differences diagram. The saturated concentration, C_0, and the solubility, C_s, were almost in accordance each other, and they were increased as an increase of initial concentration of Na_2HPO_4, $C_{Na_2HPO_4}$, as shown in Table VIII. The increase of solubility, C_s, was considered to follow the decrease of hydrogen ion concentration in the same way as in the case of theophylline.19) The change of K_T with an increase of $C_{Na_2HPO_4}$, on the other hand, was not remarkable and the value obtained were quite near to the value obtained on the dissolution of sulfadiazine in water, 2.34×10^{-1} cm./min.,*2 as shown in Table VIII.

Table VIII. Values Obtained on the Dissolution of Sulfadiazine in Na_2HPO_4 Solution at 37°

$C_{Na_2HPO_4}$ (M)	$K_T\times10$ (cm./min.)	C_0 (mg./100 ml.)	C_s (mg./100 ml.)
10^{-4}	2.34	15.8 ($6.3\times10^{-4}M$)	15.8 ($6.3\times10^{-4}M$)
10^{-3}	2.32	32.4 ($1.3\times10^{-3}M$)	33.1 ($1.3\times10^{-3}M$)
10^{-2}	2.32	99.0 ($4.0\times10^{-3}M$)	104. ($4.2\times10^{-3}M$)
10^{-1}	2.21	226. ($9.1\times10^{-3}M$)	242. ($9.7\times10^{-3}M$)

These results mentioned above correspond to the case when the dissolution is in accordance with the Higuchi model.

2) **Dissolution in Mc'Ilvaine Buffer Solution**——The results obtained on the dissolution in Mc'Ilvaine buffer, *i.e.*, citric acid-Na_2HPO_4 buffer solution, at a constant ionic strength

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18) T. Koizumi, T. Arita, K. Kakemi : This Bulletin, **12**, 413 (1964).

19) E. Nelson : J. Am. Pharm. Assoc., Sci. Ed., **46**, 607 (1957).

Table IX. Values Obtained on the Dissolution of Sulfadiazine in Mc'Ilvaine Buffer Solution at 37°

pH_i	pH_f	$K_T \times 10$ (cm./min.)	C_0 (mg./100 ml.)	C_s (mg./100 ml.)
4.17	4.19	2.18	9.41	10.7
5.06	5.09	2.16	9.80	11.0
6.56	6.59	2.18	90.0	93.0
7.23	7.10	2.17	172.	175.
8.14	7.30	2.17	240.	242.

pH_i: pH of the solution at the beginning of the run.
pH_f: pH of the solution at the end of the run.

of $\mu=0.35$, are shown in Table IX. Regardless of pH, K_T was constant and was near to the value observed on the dissolution in water, 2.34×10^{-1} cm./min.*2

The saturated concentration, C_0, was coincident with the value of C_s observed. These results were similar to the ones obtained on the dissolution of sulfadiazine in Na_2HPO_4 solution, and the dissolution was considered to be in accordance with the Higuchi model.

3) **Dissolution in Hydrochloric Acid Solution**——Representing the molecular form of sulfadiazine by HSD, the following equilibrium may exist in solution:

$$\text{HSD} + \text{H}^+ \rightleftharpoons \text{H}_2\text{SD}^+$$

The Equilibrium constant, K, is represented as

$$K=\frac{(\text{H}_2\text{SD}^+)}{(\text{HSD})(\text{H}^+)}=\frac{1}{Ka_1} \qquad (13)$$

where Ka_1 is the dissociation constant of H_2SD^+. If, in the same way as in equation (9), the following equation (14) is established, the dissolution can be said to accord with the Nernst-Brünner model.[3)]

$$K>\frac{10^2}{C_{SO}} \qquad (14)$$

where C_{SO} is the solubility of dissolving substance in the solvent. In this case, as the solubility of sulfadiazine in water is about $4 \times 10^{-4}M$, the right-hand side of equation (14) is calculated as 2.5×10^5. As $pKa_1=2$, K in equation (13) is 10^{-2}. Therefore, equation (14) is not established and the dissolution is expected to be in accordance with the Higuchi model.

The results obtained are shown in Table X. The saturated concentration, C_0, was nearly equal to the solubility, C_s, which became larger as an increase of the initial concentration of hydrochloric acid, C_{HCl}. But, C_0 or C_s was found to be pretty small compared with C_{HCl}. On the other hand, the value of K_T was near to the one obtained on the dissolution of sulfadiazine in water, 2.34×10^{-1} cm./min.*2

Table X. Values Obtained on the Dissolution of Sulfadiazine in Hydrochloric Acid Solution at 37°

C_{HCl} (M)	$K_T \times 10$ (cm./min.)	C_0 (mg./100 ml.)	C_s (mg./100 ml.)
10^{-1}	2.80	89.0	92.0
10^{-2}	2.91	17.2	18.0
10^{-3}	3.13	10.2	11.1

These results may indicate that the dissolution can be explained by Higuchi model.

Dissolution in Urea Solution

It is known that urea forms complexes with various substances,[20] and also forms inclusion compound.[21] In this sense, it is a very interesting substance pharmaceutically.

K_T was decreased as an increase of initial concentration of urea, C_{urea}, as shown in Table XI. The way of decreasing of K_T was found to be small compared with the case of dissolution in sodium chloride solution described before. One of the reason for this phenomenon might be explained by the smaller viscosity of urea solution.[22] The saturated solution, C_0, was increased as an increase of C_{urea}. But the value, C_0, was found to be small compared with the solubility, C_s, as shown in Table XI. This result may not fit to any of the models mentioned at the beginning.

Table XI. Values Obtained on the Dissolution of Sulfadiazine in Urea Solution at 37°

C_{urea} (M)	$K_T \times 10$ (cm./min.)	C_0 (mg./100 ml.)	C_s (mg./100 ml.)
10^{-3}	2.32	10.1	15.9
10^{-2}	2.26	10.7	20.2
10^{-1}	2.29	12.4	28.8
5×10^{-1}	2.29	13.2	31.4
1	2.21	18.7	42.3

K_T was proportional to 1/2 power of rotating velocity of the disk, as shown in Fig. 5. From the temperature dependence of K_T, as shown in Table XII, the activation energy was calculated as 3.6 kcal./mole. From these facts, the dissolution was supposed to be transport controlled one.

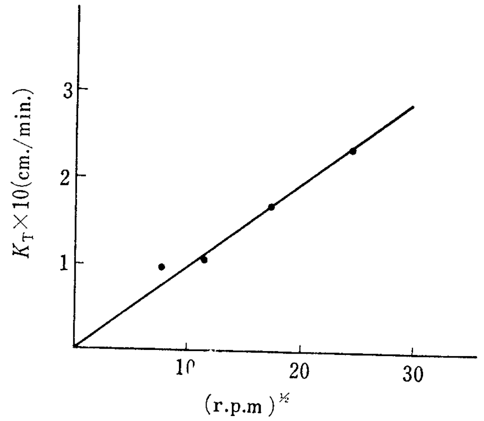

Fig. 5. Dependence of Dissolution Rate Constant, K_T, of Sulfadiazine in 0.1M Urea Solution on the Rotating Velosity of Disk at 37°

As a mechanism for the dissolution, in which the transport from solid is rate-determining and C_0 is different from C_s, the following model can be presented. That is, a reaction, which is slow compared with the transport of sulfadiazine, is

Table XII. Temperature Dependence of Dissolution Rate Constant, Saturated Concentration and Solubility of Sulfadiazine in 0.1M Urea Solution

Temperature (°C)	$K_T \times 10$ (cm./min.)	C_0 (mg./100 ml.)	C_s (mg./100 ml.)
25	1.21	8.0	10.2
37	2.29	13.2	31.4
50	3.45	27.5	34.4

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20) S. Bolton: J. Pharm. Sci., **52**, 1071 (1963).

21) T. Watanabe, H. Chihara: "Hōsetsu-kagōbutsu," Gendai-kagaku VII. H., (1956), Iwanami Shoten, Tokyo.

22) J. A. Rupley: J. Phys. Chem., **68**, 2002 (1964).

found between urea and sulfadiazine, and therefore, the dissolution may be taken place nearly in the same way as in water. Accordingly, C_0 obtained from the measurement of dissolution rate becomes near to the value of solubility of sulfadiazine in water. But, when the dissolution reaches an equilibrium state, because of the reaction product between urea and sulfadiazine, the solubility, C_s, becomes larger than C_0.

At the present, the mechanism mentioned above is only suggestive, because the reaction between urea and sulfadiazine is not ascertained. However, in the following paper,*[10] it will be presented that similar mechanism was recognized to be established on the dissolution of salicylic acid in urea solution.

This study was supported in part by a Grant in Aid for Fundamental Scientific Research from the Ministry of Education, to which the authors are grateful.

Summary

The following results were obtained on the dissolution of sulfadiazine in various aqueous solution.

1. On the dissolution in sucrose solution, with an increase of sucrose concentration, the saturated concentration, C_0, was increased a little, and the dissolution constant, K_T, was decreased with an increase of viscosity following an increase of the concentration. The dissolution rate by practical representation, $K_T \times C_0$, became smaller with an increase of sucrose concentration. The dissolution was in accordance with the Noyes-Nernst model, and C_0 was coincident with the solubility, C_s.
2. On the dissolution in sodium chloride solution, both K_T and C_0 were decreased with an increase of the concentration of sodium chloride. The dissolution was in accordance with the Noyes-Nernst model.
3. On the dissolution in sodium hydroxide solution, both K_T and C_0 were increased with an increase of the concentration of sodium hydroxide. The dissolution was in accordance with the Nernst-Brünner model. The increase of K_T was considered to be due to the increase of diffusion coefficient of sodium hydroxide in the presence of sodium salt of sulfadiazine.
4. The dissolution in Na_2HPO_4 solution, in Mc'Ilvaine buffer solution and in hydrochloric acid solution were in accordance with the Higuchi model, and as an increase of concentration of the solution, C_0 was increased by the change of hydrogen ion concentration.
5. The dissolution in urea solution did not fit to any of the model in Table I.

(Received August 26, 1965)

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*[10] Part. XIX. H. Nogami, T. Nagai, K. Ito: This Bulletin, **14**, 351 (1966).