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48. Hisashi Nogami, Tsuneji Nagai,*1 and Koji Ito*2 : Studies on Powdered Preparations. XIX.*3 Dissolution Kinetics of Benzoic Acid Derivatives.*4

(*Faculty of Pharmaceutical Sciences, University of Tokyo**1 *and Research Laboratory of Pharmaceutics, Daiichi Seiyaku Co., Ltd.**2)

Studies of the dissolution rate of drug are considered to give useful informations on the mechanism of mass transport which may be related with the dissolution and absorption in body fluid. Many works have been reported from a biopharmaceutical viewpoint on the drug release from solid and its effect on the absorption in body. The dissolution kinetics in non-reactive medium has been relatively well understood, while that in reactive medium has not been analyzed sufficiently.

In the previous paper,*3,1) the dissolution of sulfonamides by rotating disk method was discussed.

The present paper is concerned with the study of dissolution of benzoic acid derivatives in water and in urea solution.

On the dissolution of sulfadiazine in urea solution,*3 the theory of transport controlled or chemically controlled process could not explain the distinct difference between the saturated concentration, C_0, and the solubility, C_s. It was suggested that there was some reaction between sulfadiazine and urea and that the observed dissolution rate was determined by both processes, namely an intermediate type.

The similar phenomena were observed in the case of the dissolution of benzoic acid and salicylic acid in urea solution.

An attempt was made in this study to explain the drug release in urea solution and the results obtained were explained qualitatively.

Experimental

Materials——Benzoic acid, *o*-, *m*-, *p*-hydroxybenzoic acid, *o*-, *m*-, *p*-aminobenzoic acid and urea used were of the purest reagent grade.

Apparatus and Procedure——Rotating disk method, as was described in the previous paper,1) was employed. Every experiment was carried out under the following conditions : the solution of 100 ml. at 30°; the disk of 3 cm. diameter compressed under 3 tons/cm^2; the rotating velocity of disk at 100 r.p.m. The concentration of each benzoic acid derivative was determined according to UV absorption method, using Hitachi Perkin-Elmer 139 UV-VS spectrophotometer. The optical density of benzoic acid was determined at 227 mμ and 272 mμ, *o*-hydroxybenzoic acid at 232 mμ and 296 mμ, *m*-hydroxybenzoic acid at 231 mμ and 290 mμ, *p*-hydroxybenzoic acid at 250 mμ, *o*-aminobenzoic acid at 324 mμ, *m*-aminobenzoic acid at 310 mμ and *p*-aminobenzoic acid at 274 mμ. The viscosity of urea solution was determined by Ubellohde viscometer, as was described in the previous paper.1)

Results and Discussion

Dissolution of Benzoic Acid Derivatives in Water

The results obtained on the dissolution of benzoic acid derivatives in water are summarized in Table I. The dissolution rate was in accordance with equation (1), and

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*1 Hongo, Tokyo (野上 寿, 永井恒司).

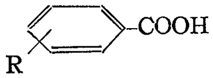
*2 Hirakawa-bashi, Sumida-ku, Tokyo (伊藤孝治).

*3 Part XVIII. H. Nogami, T. Nagai, A. Suzuki : This Bulletin, 14, 339 (1966).

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

1) Part XVII. H. Nogami, T. Nagai, A. Suzuki : This Bulletin, 14, 329 (1966).

TABLE I. Dissolution of Benzoic Acid Derivatives in Water



R	Solubility observed (%)	$K_T \times 10$ (cm./min.)
H	0.407	1.30
o-OH	0.261	1.22
m-OH	0.768	1.23
p-OH	0.735	1.01
o-NH_2	0.576	1.17
m-NH_2	0.667	1.11
p-NH_2	0.572	1.10

was explained with the same model as described on the dissolution of sulfonamides in water.[1] The Noyes-Nernst equation (1) is generally accepted to represent the rate of dissolution process in non-reactive medium.

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

where C is the concentration at the time t, C_0 the saturated concentration,[*5] 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 solubilities observed were almost equal to the values of C_0, and the values of K_T were $1.1 \sim 1.3 \times 10^{-1}$ cm./min.

Ortho substituted substance, *e.g.*, salicylic acid, is known to show a remarkable feature in physico-chemical properties, due to the intramolecular hydrogen bonding. For example, the solubility of salicylic acid is remarkably different from those of other substituted derivatives, as shown in Table I. However, such an ortho effect on K_T or D was not found, as shown in Table I. This indicates that the diffusion coefficient is dependent mainly on the molecular volume, and it is supported by the theories of Arnold,[2] Wilke,[3] and other workers.

Dissolution of Benzoic Acid and Salicylic Acid in Urea Solution

Analyzing the concentration-time curve according to the method in the previous paper,[1] a non-linear relationship was found on the dissolution of benzoic acid and salicylic acid in urea solution, as shown in Figs. 1 and 2 to cite one example. Here, C_1 is the concentration at time t, C_2 the concentration at time $t+20$ min., and ΔC the difference between C_1 and C_2 at time t. A point of intersection between the tangential line of the plot C_2 *vs.* C_1 and the line $C_2=C_1$ in Fig. 1 corresponds to the saturated concentration, C_0.

If there are no reaction and the dissolution rate is controlled by transport process in this case, the slopes of Figs. 1 and 2 must be constant.

Urea has the great ability to undergo hydrogen bonding with solute and solvent owing to the presence of three potential bonding centers on each molecule. The formation of complex, clathrate or inclusion compound with urea has been reported, and pharmaceutically, urea is useful to improve stability and solubility of drug.

[*5] This is the value estimated kinetically[1] and not always equal to the solubility.

2) J.H. Arnold: J. Am. Chem. Soc., **52**, 3937 (1930).

3) C.R. Wilke: Chem. Eng. Progress, **45**, 218 (1949).

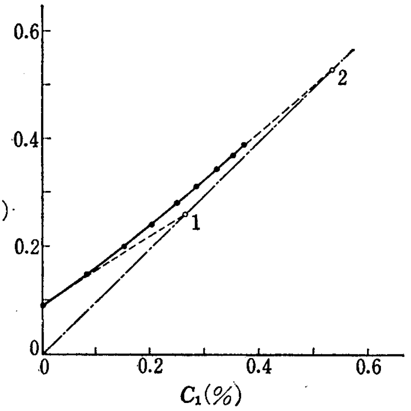


Fig. 1. Finite Differences Diagram of the Dissolution of Salicylic Acid in 2*M* Urea Solution

C_1: concentration at time *t*
C_2: concentration at time $t+20$ min.
1: solubility in water, *i.e.*, 0.261%
2: solubility observed in 2*M* urea solution, *i.e.*, 0.528% chain line: $C_1=C_2$

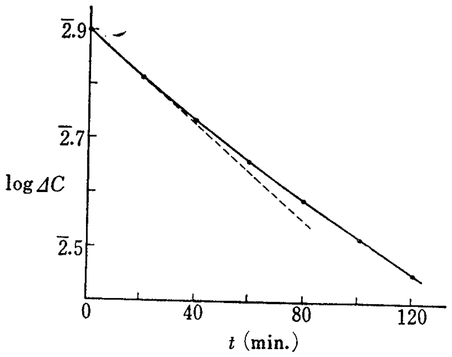


Fig. 2. Relationship between log ΔC and Time of the Dissolution of Salicylic Acid in 2*M* Urea Solution

ΔC: difference between the concentration at time *t* and that at $t+20$ min.

Solubilities of benzoic acid, salicylic acid,[4] terramycin[5] and benzocaine[6] in water were shown to be increased in the presence of urea. Complex formation of sulfonamides with urea[7] has also been described.

On the cases of sulfonamide and benzoic acid derivatives with urea, some reaction such as complex formation may be assumed during the dissolution process.

In the field of chemical engineering, many works[8,9] have been reported on the process involving mass transport and chemical reaction, and reaction rate has been explained using mainly film theory. But in general fundamental equation can be solved only on special cases.

Higuchi, *et al.*,[10] presented a theory on the dissolution rate of solid weak acid in basic and buffered media and they assumed all chemical equilibria to be rapidly reached compared to diffusion. However, it seems the above assumption may not always available in any case. On the dissolution of sulfadiazine in urea solution,*3 for example, it is expected that the equilibrium is reached rather slowly in the diffusion layer and so the solutes may be transferred into the bulk solution under non-equilibrium state.

Here, it is assumed that i) there is a thin diffusion layer of solution adhering to the solid surface of substance A; ii) each diffusion co efficient is independent on concentration : and

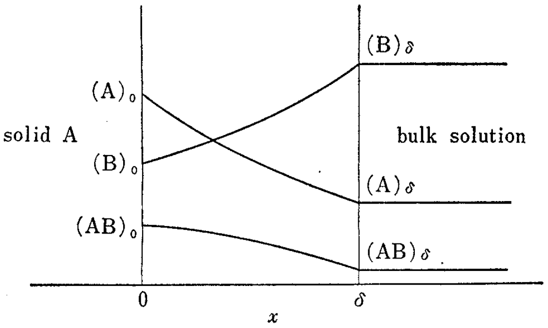


Fig. 3. Schematic Illustration of Concentration Profiles during the Dissolution of Solid A in Reactive Medium

x: the distance from the solid surface
δ: the diffusion layer thickness

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4) S. Bolton : J. Pharm. Sci., **52**, 1071 (1963).
5) T. Higuchi, S. Bolton : *Ibid.*, **48**, 557 (1959).
6) J.L. Lach, W.A. Pauli : Drug Std., **27**, 104 (1959).
7) R. Dolique, J. Foucault : Trav. Soc. Pharm. Montpellier, **12**, 145 (1952).
8) S. Hatta : Kagaku to Kōgyō (Chemistry and Chemical Industry), **14**, 120 (1961).
9) "Symposium on Fundamentals of Diffusional Operations." Kagaku Kōgaku (Chemical Engineering), **82**, 429~566 (1964).
10) W.I. Higuchi, E.L. Parrott, D.E. Wurster, T. Higuchi : J. Am. Pharm. Assoc., Sci. Ed., **47**, 376 (1958).

iii) the chemical reaction such as a complex formation is expressed by equation (2):

$$\mathrm{A} + \mathrm{B(urea)} \rightleftarrows \mathrm{AB} \tag{2}$$

where these solutes are not in equilibrium with each other during the dissolution process.

The concentration profiles in a diffusion layer are shown schematically in Fig. 3.

For the steady state, the following equations are led for each species in a unit volume at the distance from solid surface, x, considering the Fick law and the reaction described above.

$$\left.\begin{aligned}\frac{d(\mathrm{A})}{dt} &= D_{\mathrm{A}}\frac{d^2(\mathrm{A})}{dx^2}+\phi_{\mathrm{A}}=0\\ \frac{d(\mathrm{B})}{dt} &= D_{\mathrm{B}}\frac{d^2(\mathrm{B})}{dx^2}+\phi_{\mathrm{B}}=0\\ \frac{d(\mathrm{AB})}{dt} &= D_{\mathrm{AB}}\frac{d^2(\mathrm{AB})}{dx^2}+\phi_{\mathrm{AB}}=0\end{aligned}\right\} \tag{3}$$

where D_{A}, D_{B}, and D_{AB} are the diffusion coefficients of A, B, and AB respectively, and ϕ_{A}, ϕ_{B}, and ϕ_{AB} the source or sink functions owing to the reaction. By material balance and $\phi_{\mathrm{A}}=\phi_{\mathrm{B}}=-\phi_{\mathrm{AB}}$.

$$D_{\mathrm{A}}\frac{d^2(\mathrm{A})}{dx^2}=D_{\mathrm{B}}\frac{d^2(\mathrm{B})}{dx^2}=-D_{\mathrm{AB}}\frac{d^2(\mathrm{AB})}{dx^2} \tag{4}$$

Integrating equation (4)

$$D_{\mathrm{A}}\frac{d(\mathrm{A})}{dx}+E_1=D_{\mathrm{B}}\frac{d(\mathrm{B})}{dx}+E_2=-D_{\mathrm{AB}}\frac{d(\mathrm{AB})}{dx} \tag{5}$$

where E_1 and E_2 are the integration constants. Again by material balance

$$D_{\mathrm{B}}\frac{d(\mathrm{B})}{dx}=-D_{\mathrm{AB}}\frac{d(\mathrm{AB})}{dx}$$

Therefore,

$$E_1=-\left\{D_{\mathrm{A}}\frac{d(\mathrm{A})}{dx}+D_{\mathrm{AB}}\frac{d(\mathrm{AB})}{dx}\right\} \tag{6}$$

Equation (6) is the sum of the diffusion rates of A and AB in medium, namely it means the dissolution rate of solid A. Integrating equation (5),

$$D_{\mathrm{A}}(\mathrm{A})+E_1x+F_1=D_{\mathrm{B}}(\mathrm{B})+F_2=-D_{\mathrm{AB}}(\mathrm{AB}) \tag{7}$$

where F_1 and F_2 are the integration constants. Denoting that, at $x=0$, $(\mathrm{A})=(\mathrm{A})_0$, $(\mathrm{B})=(\mathrm{B})_0$ and $(\mathrm{AB})=(\mathrm{AB})_0$,

$$\left.\begin{aligned}F_1&=-D_{\mathrm{AB}}(\mathrm{AB})_0-D_{\mathrm{A}}(\mathrm{A})_0\\ F_2&=-D_{\mathrm{AB}}(\mathrm{AB})_0-D_{\mathrm{B}}(\mathrm{B})_0\end{aligned}\right\} \tag{8}$$

Combining equations (7) and (8), and putting $x=\delta$, the dissolution rate per unit area is expressed as

$$E_1=\frac{1}{\delta}[D_{\mathrm{A}}\{(\mathrm{A})_0-(\mathrm{A})_\delta\}+D_{\mathrm{AB}}\{(\mathrm{AB})_0-(\mathrm{AB})_\delta\}] \tag{9}$$

where $(\mathrm{A})_\delta$ and $(\mathrm{AB})_\delta$ are the concentrations at $x=\delta$, *i.e.*, the concentrations in bulk solution. Taking the effective surface area, S, and the volume of solution, V, into consideration, equation (9) becomes

$$\frac{dC_\delta}{dt}=\frac{S}{V}\frac{1}{\delta}[D_A\{(A)_0-(A)_\delta\}+D_{AB}\{(AB)_0-(AB)_\delta\}] \tag{10}$$

where $C_\delta=(A)_\delta+(AB)_\delta$.

On the other hand, the apparent dissolution rate of A is given according to equation (1) as

$$\frac{dC_\delta}{dt}=\frac{S}{V}\frac{D}{\delta}(C_0-C_\delta) \tag{11}$$

where the diffusion constant, D, and the saturated concentration, C_0, are not constant and are variable, as described in the following. Combining equations (10) and (11), and putting $C_0=(A)_0+(AB)_0$ and $C_\delta=(A)_\delta+(AB)_\delta$,

$$D=D_A-\frac{D_A-D_{AB}}{\dfrac{(A)_0-(A)_\delta}{(AB)_0-(AB)_\delta}+1} \tag{12}$$

Then apparent dissolution rate of solid A is given by the following equation.

$$\frac{dC}{dt}=\frac{S}{V}\frac{1}{\delta}\left[D_A-\frac{D_A-D_{AB}}{\dfrac{(A)_0-(A)_\delta}{(AB)_0-(AB)_\delta}+1}\right][(A_0)+(AB)_0-C] \tag{13}$$

According to equation (12), the diffusion coefficient $D=D_A-(D_A-D_{AB})\Big/\left[\dfrac{(A)_0-(A)_\delta}{(AB)_0-(AB)_\delta}+1\right]$ is expected to decrease as the concentration of B increases in the diffusion layer with the progress of dissolution. For example, D may be equal to D_A at the beginning of the process, because $(AB)_0$, $(A)_\delta$ and $(AB)_\delta$ are considered to be zero at $t=0$. These are illustrated schematically in Fig. 4. The dissolution rate constant, K_T may be shown by a similar graph since $K_T=D/\delta$. The saturated concentration $C_0=(A)_0+(AB)_0$ is expected to increase as the concentration of B increases in the diffusion layer with progress of dissolution, starting from $C_0=(A)_0$ at $t=0$, as shown in Fig. 5.

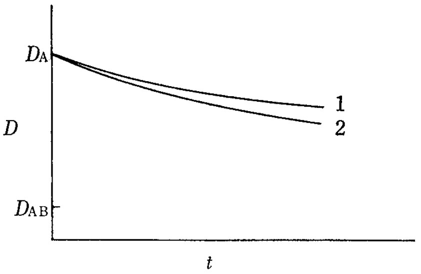

Fig. 4. Estimated Dependence of D on the Urea Concentration and the Lapse of Time

1: the urea concentration is lower than that of the case 2
2: the urea concentration is higher than that of the case 1

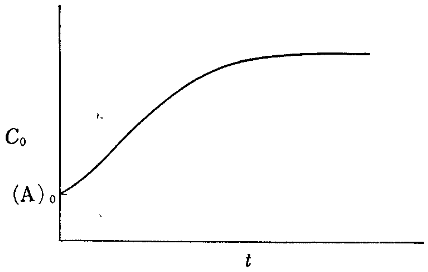

Fig. 5. Estimated Dependence of C_0 on the Lapse of Time

In order to explain the distinctive trends of the values of K_T and C_0 according to equation (13), comparisons will be made with those values of the following two processes in which the circumstances are supposed to arrive at the limit :

Process (a)—in which the chemical reaction is so rapid compared to diffusion that the chemical equilibrium is reached everywhere in a diffusion layer.

Process (b)—in which the reaction is so slow that scarecely any reaction is taken place in a diffusion layer.

In the process (a), as shown in Figs. 6 and 7, the values of D and C_0 at the beginning of the process are expected to be not the same as D_A and $(A)_0$, respectively.

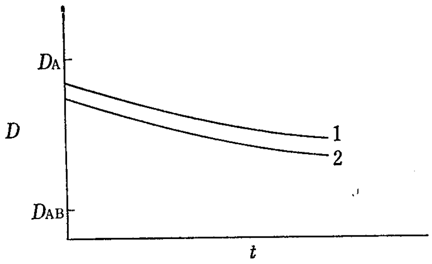

Fig. 6. Apparent D *vs.* Time Curve in the Process (a)

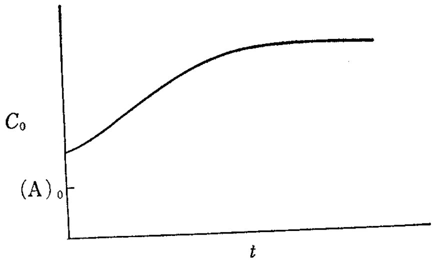

Fig. 7. C_0 *vs.* Time Curve in the Process (a)

In the process (b), in the diffusion layer, a transfer may be taken place concerning only A. Then, the dissolution rate is given by

$$\frac{d(A)_\delta}{dt}=\frac{D_A}{\delta}\{(A)_0-(A)_\delta\} \tag{14}$$

In the bulk solution, an equilibrium is reached as follows : $A+B\rightleftarrows AB$, and $K_\delta=(AB)_\delta/(A)_\delta(B)_\delta$, where K_δ is the equilibrium constant. As $C=(A)_\delta+(AB)_\delta$,

$$C=(A)_\delta+\frac{K_\delta(A)_\delta(B)_{\delta i}}{K_\delta(A)_\delta+1} \tag{15}$$

where $(B)_{\delta i}$ is the initial concentration of B in the bulk solution, *i.e.*, $(B)_{\delta i}=(AB)_\delta+(B)_\delta$. Practically, $K_\delta(A)_\delta \ll 1$ and accordingly,

$$C=(A)_\delta\{1+K_\delta(B)_{\delta i}\} \tag{16}$$

Combining equations (14) and (16),

$$\frac{1}{1+K_\delta(B)_{\delta i}}\frac{dC}{dt}=\frac{S}{V}\frac{D_A}{\delta}\left\{(A)_0-\frac{C}{1+K_\delta(B)_{\delta i}}\right\} \tag{17}$$

Equation (17) is in accordance with the Noyes-Nernst equation, and D and C_0 become D_A and $(A)_0$, respectively.

Above discussion give an explanation of the non-linear relationship of Figs. 1 and 2.

As the dissolution proceeded, the value of C_0 increased, starting from a point very near to the solubility in water, to approach to the solubility observed in urea solution, as was expected. A slope of the plot of log $\varDelta C$ *vs.* t, which gives the dissolution rate constant, is found to be independent on the lapse of time in non-reactive medium. But, in the present case the slope changed with the progress of dissolution as was expected from equation (12). It was rather difficult to find an accurate experimental relationship between the dissolution rate constant, K_T, and the progress of dissolution, because the further the dissolution proceeded, the greater the experimental error became. Accordingly, it was considered to be convenient to discuss the dissolution rate constant by means of the initial dissolution rate constant, $K_T(t\rightarrow 0)$, and the graphical average of dissolution rate constant, $K_T(av.)$, during the time that the concentration C arrived two thirds of the solubility. Tables II and III show the data of the dissolution of benzoic acid and salicylic acid in urea solution. Diffusion coefficients

TABLE II. Dissolution of Benzoic Acid in Urea Solution

Urea concn. (M)	Solubility observed (%)	$K_T(t\to 0)\times 10$ (cm./min.)	$K_T(av.)\times 10$ (cm./min.)
0	0.407	1.30	1.30
1	0.550	1.30	1.14
2	0.688	1.30	1.10

TABLE III. Dissolution of Salicylic Acid in Urea Solution

Urea concn. (M)	Viscosity $\times 10^3$ (stokes)	Solubility observed (%)	$K_T(t\to 0)\times 10$ (cm./min.)	$K_T(av.)\times 10$ (cm./min.)	$D\times 10^6$ (cm^2/sec.)
0	8.04	0.261	1.22	1.22	9.74
0.5	8.13	0.316	1.25	1.22	9.77
1	8.26	0.374	1.23	1.18	9.23
1.5	8.39	0.434	1.25	1.17	9.20
2	8.53	0.528	1.23	1.14	8.82

of these acids in urea solution, as listed in the last column of Table III, were calculated according to the Levich equation,*3 considering the viscosity of the solution.

The value of $K_T(t\to 0)$ showed a good agreement with the value of K_T observed on the dissolution in water. The value of $K_T(av.)$ decreased as the urea concentration increased. These results may indicate that the dissolution process is different from both processes (a) and (b) described before and is in accordance with the process in which the equilibrium is reached rather slowly in the diffusion layer and the solutes are transferred into the bulk solution under non-equilibrium state.

In this study, the existence of ionic species of benzoic acid derivatives in solution was neglected, because the concentration of ionic species was very low compared to that of molecular one and moreover the transfer rate of ionic one was considered to be almost the same as that of molecular one.

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Summary

The dissolution rates of benzoic acid derivatives in water and in urea solution were measured by rotating disk method. The data of the dissolution in urea solution showed a good agreement qualitatively with the process in which there exist some reaction and the equilibrium is reached rather slowly in the diffusion layer and the solutes are transferred into the bulk solution under non-equilibrium state. That is, the dissolution rate constant, K_T, and the saturated concentration, C_0, showed the dependence on the lapse of time, and the initial dissolution rate constant, $K_T(t\to 0)$, was almost the same as the value of K_T observed on the dissolution in water.

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