

Dissolution Phenomena of Organic Medicinals involving Simultaneous Phase Changes^{1,2)}

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A model was proposed to analyze the dissolution phenomena involving simultaneous phase changes and its experimental demonstration was done with *p*-hydroxybenzoic acid and phenobarbital which change to the respective hydrates during dissolution. The mathematical expression for the dissolution according to this model was given by equation (3) or (4). Combining the rotating disk method with the above equations, it was possible to determine the rate constant of crystallization process, kr , and the saturated concentration of anhydrate, C_{SA} , which are hardly obtainable by other usual methods. At the same time, the rate constant of transport process, kt , and the saturated concentration of hydrate, C_{SH} , were obtained.

Analyzing the values of kt , kr , C_{SA} , and C_{SH} obtained at various temperatures, the activation energies of transport and crystallization process and the thermodynamic functions of the transition from anhydrate were determined, being reasonable compared with the past data reported on organic medicinals. The transition temperatures obtained from the intersections of the van't Hoff plots regarding anhydrate and hydrate were 84° for *p*-hydroxybenzoic acid and 37° for phenobarbital. In the case of *p*-hydroxybenzoic acid, $(C_{SA}-C_{SH})$ increased with temperature in the experimental temperature region.

It is well known that many organic compounds may exist in different crystalline modifications such as polymorphism and solvated form, as are often found in organic medicinals.⁴⁻⁷⁾ The condition of such a system of one component is completely determined by temperature and pressure.

Considering what modification is the most stable in such system as consisting of solid and liquid phase in two components, it is determined not only by the above two physical variables, but also by surrounding conditions, as is in the case of the solid phase in contact with a solvent. Then, the dissolution of a modification which is unstable or metastable in a given solvent may not be explained according to the classical diffusion controlled model only, because such phase may dissolve into the solvent accompanying a transformation to the stable phase, finally attaining to the most stable one at equilibrium. That is, the effect of the change in external conditions on the system is counterbalanced by the phase reaction.⁸⁾

Accordingly, phase specificity of the crystalline modification having influence on dissolution behavior seemed to be an important consideration in drug availability. Higuchi, *et al.* examined qualitatively the relative dissolution rates of some solvated and nonsolvated organic

- 1) This paper forms part XXVII of "Studies on Powdered Preparations." Preceding paper, Part XXIV: H. Nogami, T. Nagai, and H. Uchida, *Chem. Pharm. Bull.* (Tokyo), **17**, 176 (1969).
- 2) This work was presented at the 88th Annual Meeting of Pharmaceutical Society of Japan, Tokyo, April 1968, being taken in part from the thesis of Toshihisa Yotsuyanagi for the degree of Doctor of Pharmaceutical Sciences, University of Tokyo, 1968.
- 3) Location: *Hongo, Tokyo*; a) To whom communication should be directed.
- 4) B. Cleverley, *Analyst, Lond.*, **85**, 582 (1960).
- 5) R.J. Mesley and E.E. Houghton, *J. Pharm. Pharmacol.*, **19**, 295 (1967).
- 6) E. Shefter and T. Higuchi, *J. Pharm. Sci.*, **52**, 781 (1963).
- 7) K. Sekiguchi, K. Itoh, E. Owada, and K. Ueno, *Chem. Pharm. Bull.* (Tokyo), **12**, 1192 (1964).
- 8) A. Findlay, A. N. Campbell, and N. O. Smith, "The Phase Rule and Its Applications," Dover Pub., Inc., (1951).

medicinals, noticing the different thermodynamic activities.⁶⁾ The dissolution rates of higher energy polymorphs of sulfathiazole and methylpredonisolone have been also reported from the practical pharmaceutical standpoint.⁹⁾

In the present paper, dissolution behaviors of organic medicinals accompanying simultaneous phase change were investigated quantitatively using *p*-hydroxybenzoic acid and phenobarbital, which transformed to the respective hydrates. In addition, the thermodynamic differences between solvated and nonsolvated crystal forms were discussed.

Experimental

Materials—*p*-Hydroxybenzoic acid used was of the purest reagent grade. Phenobarbital was of J.P. VII grade, infrared (IR) spectrum being in agreement with that of anhydrate obtained by recrystallization from water.

Preparations of Anhydrate and Hydrate of both *p*-Hydroxybenzoic Acid and Phenobarbital—The hydrate of *p*-hydroxybenzoic acid was obtained by recrystallization from aqueous solution, the anhydrate being prepared by heating the hydrate at 100° for 24 hr (mp 213°).

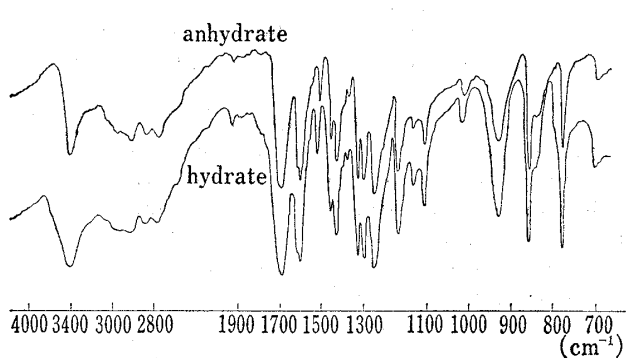


Fig. 1. Infrared Absorption Spectra of *p*-Hydroxybenzoic Acid Anhydrate and Hydrate by KBr Disk Method

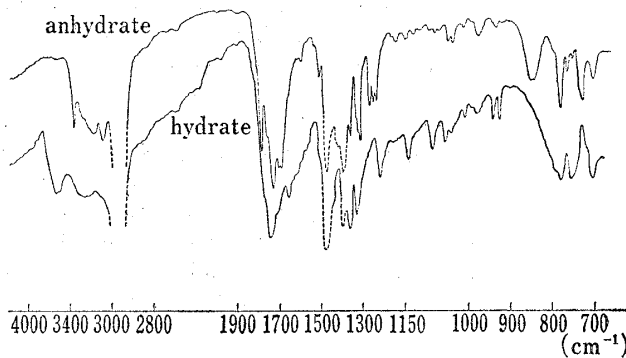


Fig. 2. Infrared Absorption Spectra of Phenobarbital Anhydrate and Hydrate by Nujol Method.

TABLE I. X-Ray Diffraction Patterns of *p*-Hydroxybenzoic Acid and Phenobarbital using Cu-K α Radiation

<i>p</i> -Hydroxybenzoic acid				Phenobarbital			
Anhydrate		Hydrate		Anhydrate		Hydrate	
<i>d</i> (Å)	<i>I</i> / <i>I</i> ₁	<i>d</i> (Å)	<i>I</i> / <i>I</i> ₁	<i>d</i> (Å)	<i>I</i> / <i>I</i> ₁	<i>d</i> (Å)	<i>I</i> / <i>I</i> ₁
4.98	81	5.94	100	11.48	100	15.23	49
4.49	28	5.06	72	7.69	41	7.76	44
3.95	20	4.23	18	6.32	69	5.82	100
3.59	100	3.70	57	6.19	82	5.57	38
3.40	16	3.24	48	5.64	47	5.45	39
3.28	53	3.16	78	5.29	63	5.27	29
2.95	60	3.00	16	5.01	18	4.70	22
		2.86	14	4.74	23	3.88	86
				4.21	24	3.60	15
				4.00	48	3.53	17
				3.90	28	3.38	11
				3.72	38	3.10	19
				3.56	24	2.97	39
				3.33	21	2.87	26
				3.18	20	2.80	38

d: interplanar distance

I/*I*₁: relative intensity

9) W.I. Higuchi, P.D. Bernardo, and S.C. Metha, *J. Pharm. Sci.*, **56**, 200 (1967).

The hydrate of phenobarbital was crystallized out in the aqueous solution below 30°, the anhydrate being done above 50° (mp 178°). Since several polymorphic forms of phenobarbital had been reported,¹⁰⁾ it was necessary to check the phase before dissolution experiments. Phenobarbital used was of the stable phase under the experimental conditions. It was difficult to determine the intrinsic melting point of this phase, because the transformation to stable phase might take place at elevated temperature. As hydrates of both *p*-hydroxybenzoic acid and phenobarbital were easy to be dehydrated, they were preserved under saturated vapour pressure in a desiccator. Determination of melting point of these hydrates were impossible because of the dehydration on heating. X-Ray diffraction patterns and IR absorption spectra of the respective phases are shown in Fig. 1 and 2 and in Table I.

Procedures for Dissolution Studies—a) Rotating Disk Method: The procedure employed was the same as described in the previous paper.¹¹⁾ Every experiment for *p*-hydroxybenzoic acid was carried out under the following conditions: 50 ml of distilled water at 40°, 35°, 30° and 25°; the rotating velocity of disk at 600, 500, 300, 200, 120, 100 and 60 rpm; the disk of 3 cm diameter compressed under 3 ton/cm². For phenobarbital: 50 ml of distilled water at 30°, 25° and 20°; the rotating velocity of disk at 600, 300 and 200 rpm; the disk of 3 cm diameter compressed under 3 ton/cm². When the samples were compressed to make the disks, the phase transition was not observed and the density of disk was not influenced by the pressure. At an appropriate interval, 50 μ l or 100 μ l of the solution were sampled out by a micro syringe (Jintan Terumo).

b) Dispersed Amount Method: 50 ml of distilled water warmed preliminarily at the same temperature as the bath were added quickly in the flask, which was the same as used for rotating disk method, containing an excess amount (about two times saturated concentration) of the sample of 60 mesh (246 μ) to 150 mesh (140 μ), and immediately a vigorous agitation was applied. The solution was sampled out periodically by a 0.5 ml cotton-filter attached pipette.

c) Analytical Method: The concentration was determined according to ultraviolet (UV) absorption method. The optical density of *p*-hydroxybenzoic acid was measured at 250 m μ after diluting with water, phenobarbital at 241 m μ after diluting with borate buffer of pH 9.6.

General Concepts

Dissolution rate depends on the diffusion coefficient and the solubility of a dissolving solid under constant physical conditions. Whether hydrate or anhydrate was in the solid state, its diffusion coefficient in water should be identical, as is in the same situation in the case of polymorphism. Therefore, it is considered that the varieties of dissolution rate among solid modifications are attributed to the difference of chemical potential among the respective modifications.

Unusual dissolution behaviors of anhydrate of some organic medicinals have been observed by Higuchi, *et al.*⁶⁾ In this connection, the apparent dissolution rates of anhydrides of *p*-hydroxybenzoic acid and phenobarbital tends to be much greater than that of the hydrates, as shown in Fig. 3, that is, the concentration in bulk liquid increases rapidly, reaching maximum in an initial stage. Then, it falls gradually, attaining to the equilibrium state. Such a characteristic dissolution behavior has been observed in the dissolution of polymorphs.¹²⁾ The convex curve described above means that the bulk liquid is supersaturated over the solubility of hydrate and solid phase of the hydrate

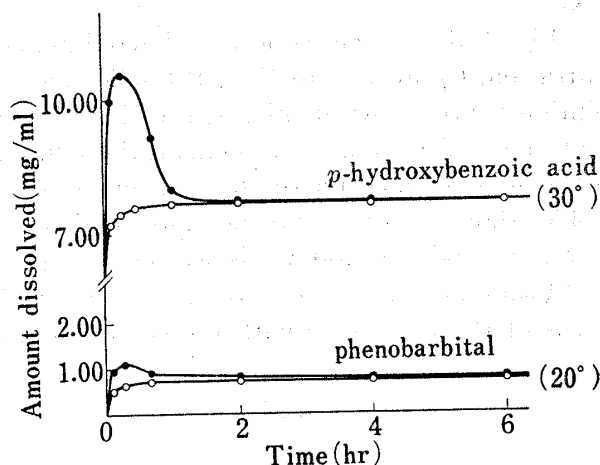


Fig. 3. Dissolution Behaviours of Anhydrate and of Its Hydrate by Dispersed Amount Method

sample amount: *p*-hydroxybenzoic acid 0.7 g
phenobarbital 0.2 g in 50 ml water
—●— : anhydrate —○— : hydrate

10) B. Cleverley and P.P. Willaims, *Tetrahedron*, **7**, 277 (1959).

11) H. Nogami, T. Nagai, and A. Suzuki, *Chem. Pharm. Bull.* (Tokyo), **14**, 329 (1966).

12) D.E. Wurster and P.W. Taylor, Jr., *J. Pharm. Sci.*, **54**, 670 (1965).

is precipitated with lapse of time. This type of curve, however, may be observed only in the experiment with multiparticulate system because of the large surface area, while it is not suitable to the quantitative treatment because the surface area is scarcely obtainable. On the other hand, the rotating disk method is suitable to the quantitative treatment, but it hardly gives such a convex dissolution curve. If the dissolution experiment is carried out with the hydrate, no phase change takes place and a typical dissolution pattern is given.

Considering the above circumstances, the following explanation will be attempted for the dissolution phenomena involving the phase change caused by hydration. The concentration profile in the dissolution is expressed schematically as shown in Fig. 4, based on the following assumptions: (1) the rate of release at the interface is much greater than the transport process; (2) as soon as the saturation layer is formed, the hydrate begins to crystallize out on the surface of solid due to the dissolution-crystallization cycle; (3) the change of the surface area of dissolving material is negligible; (4) the phase change to hydrate takes place penetrating into

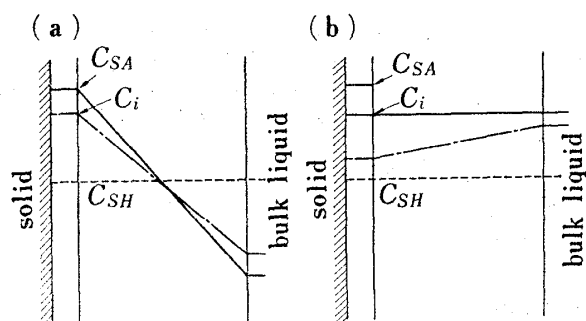


Fig. 4. Schematic Diagram of Concentration Profiles on the Dissolution Process of Solid

C_{SA} : saturated concentration of anhydrate
 C_i : effective concentration on solid surface
 C_{SH} : saturated concentration of hydrate

the interior of solid and the whole surface gets covered with the hydrate. These assumptions are evidently reasonable according to various past works,^{9,13,14} and the respective concentration profiles shown in Fig. 4 mean as follows: Fig. 4-(a)—

From assumption (2), the saturated concentration of anhydrate, C_{SA} , may not be maintained and decreases gradually, attaining to the saturated concentration of hydrate, C_{SH} ; the surface of the solid, however, is coated perfectly by the hydrate before the concentration of bulk liquid attains to C_{SH} or to some amount higher than (lower than C_{SA} , originated from the convex dissolution curve); the dotted line indicates C_{SH} .

Fig. 4-(b)—The concentration of bulk liquid is higher than C_{SH} before the effective concentration, C_i , attains to C_{SH} ; the solid line corresponds to the maximum of the convex dissolution curve shown in Fig. 3; the chain line indicates the concentration profile between the limited conditions; after a moment, the solute molecules existing in bulk liquid are transported to the solid surface for the sake of reverse concentration gradient. These two concentration profiles shown in Fig. 4 are not independent each other, and either model (a) only or model (a) which model (b) follows is available depending on the physical conditions of solid.

Assuming that the rate of crystal growth is proportional to the degree of supersaturation and is of the first order with respect to the concentration term,¹⁵ it may be expressed as

$$-\frac{dC_i}{dt} = k_r (C_i - C_{SH}) \quad (1)$$

where t and k_r are the time and the rate constant of crystallization process, respectively, and the other symbols are the same as described in Fig. 4. Considering $C_i = C_{SA}$ at $t=0$, equation (1) is integrated to yield

$$C_i = C_{SA} \cdot \exp(-k_r t) + C_{SH} [1 - \exp(-k_r t)] \quad (2)$$

13) W. Nernst, *Z. Physik. Chem.*, **47**, 52 (1904).

14) T. Yawataya, "Shin-kagakukogaku-koza, crystallization," Nikkan Kogyo Shinbunsha, 1956.

15) A. VanHook, "Crystallization, Theory and Practice," Reinhold Pub. Corp., 1961.

The concentration gradient effective as the driving force in the material transport into bulk liquid is

$$(C_t - C)/\delta$$

where C is the concentration in bulk liquid and δ the diffusion layer thickness. Then, the dissolution rate is expressed as

$$\frac{dC}{dt} = k_t \{ C_{SA} \cdot \exp(-k_r t) + C_{SH} [1 - \exp(-k_r t)] - C \} \quad (3)$$

where k_t is the rate constant of transport process. Since $C=0$ at $t=0$, equation (3) is integrated to yield

$$C = k_t (C_{SA} - C_{SH}) / (k_t - k_r) [\exp(-k_r t) - \exp(-k_t t)] + C_{SH} [1 - \exp(-k_t t)] \quad (4)$$

The second term of the right side of equation (4) corresponds to the concentration at time t in such a system that no phase change takes place during the dissolution, *i.e.*, the hydrate dissolves according to transport-controlled mechanism. Therefore, the first term functions as a deviation from the dissolution curve concerning the hydrate. Since the initial rates of the first and the second terms in equation (4) are $k_t(C_{SA} - C_{SH})$ and $k_t C_{SH}$, respectively, the dissolution curve according to equation (4) may be divided into two cases of $C_{SA} - C_{SH} > C_{SH}$ and $C_{SA} - C_{SH} < C_{SH}$, and each cases subdivided into two modes of $|k_r - k_t| = \text{large}$ and $|k_r - k_t| = \text{small}$, as shown schematically in Fig. 5.

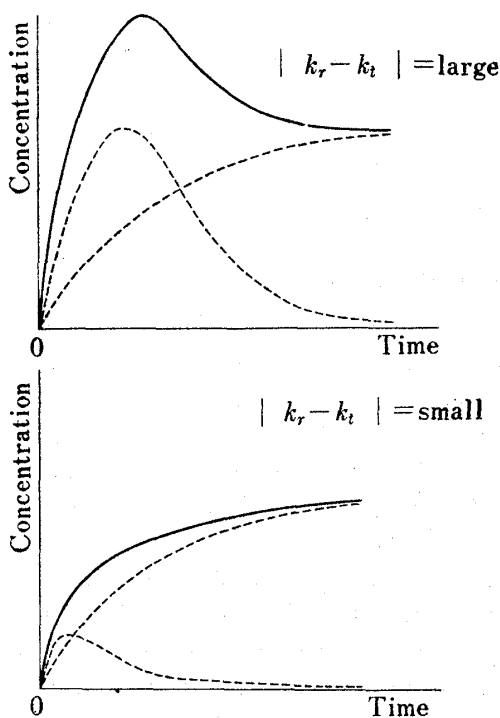


Fig. 5 (a). Schematic Illustration for Relationship between Concentration and Time according to Equation (4) in the Case of $C_{SA} - C_{SH} > C_{SH}$

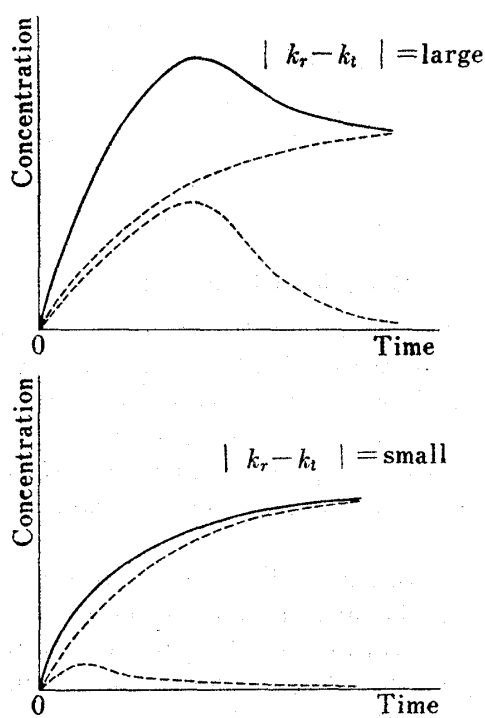


Fig. 5 (b). Schematic Illustration for Relationship between Concentration and Time according to Equation (4) in the Case of $C_{SA} - C_{SH} < C_{SH}$

Equation (4) expresses a general dissolution curve involving the phase change caused by hydration. However, the characteristic dissolution phenomena of anhydrate may appear in the extremely initial stage in the experiment by rotating disk method. Since $C_i \gg C$ in the initial stage in the present experimental condition, equation (3) is modified to

$$\frac{dC}{dt} = k_t \{ C_{SA} \cdot \exp(-k_r t) + C_{SH} [1 - \exp(-k_r t)] \} \quad (5)$$

Under the initial condition $C=0$ at $t=0$, equation (5) is integrated to yield

$$C = k_t (C_{SA} - C_{SH}) / k_r [1 - \exp(-k_r t)] + k_t C_{SH} t \quad (6)$$

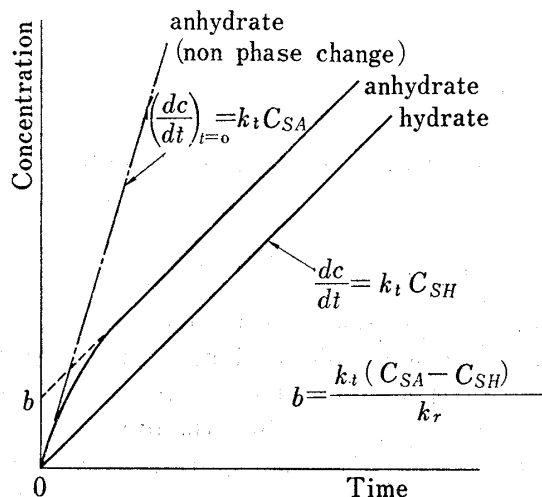


Fig. 6. Schematic Illustration for Relationship between Concentration and Time in Initial Time of Dissolution according to Equation (6) and Equation (8)

Since it is possible to consider t sufficiently long even in the initial stage, a linear relationship is given by equation (6), having the gradient of $k_t C_{SA}$. Then, extrapolating the linear portion of equation (6), the intercept, b , is

$$b = k_t (C_{SA} - C_{SH}) / k_r \quad (7)$$

Equation (7) predicts how much the dissolution data deviate from the dissolution curve expected concerning the hydrate.

The initial dissolution rate, $(dc/dt)_{t=0}$, is derived from equation (5) as

$$\left(\frac{dC}{dt} \right)_{t=0} = k_t C_{SA} \quad (8)$$

which corresponds to the rate concerning

the anhydrate with no phase change.

The general patterns of dissolution behavior according equations (6) and (8) are illustrated in Fig. 6. The concepts described in this paper may be applied also to the dissolution of polymorphs accompanying simultaneous phase change.

Results and Discussion

Dissolution Behavior Observed by Dispersed Amount Method

When the anhydrate was dispersed, a characteristic convex dissolution curve was obtained, as shown in Fig. 3. A dispersed particle of anhydrate was expected to be surrounded with a solution of higher concentration than the solubility of hydrate, C_{SH} . Moreover, the total surface area of the particles was very large. Therefore, when the sample was brought in contact with water, an abrupt transport of solute from the surface of dispersed particles might take place, resulting in a concentration higher than C_{SH} in bulk liquid in the initial stage of dissolution.

On the other hand, as described in the part of general concept, the hydrate might crystallize out on the surface of solid due to the dissolution-crystallization cycle and the transition to hydrate also might take place on the surface of solid, resulting in a reverse concentration gradient in the diffusion layer and making the maximum of concentration in bulk liquid. Accordingly, the dissolution phenomenon was considered to corresponding to the continuous process of schematic model Fig. 4-(a) which the model Fig. 4-(b) followed. The concentrations of *p*-hydroxybenzoic acid and phenobarbital at the respective maximum point in Fig. 3 were 1.5 times of the respective solubilities of hydrates. It was determined by X-ray diffraction and IR absorption that the transformation of the dispersed anhydrate to hydrate was completed when dissolution attained to equilibrium. The decreasing curve of the concentration in bulk liquid after the maximum point in Fig. 3, which was considered to be concerned with the crystallization, might not be always described by the transport mechanism only, because C_t should not attain to C_{SH} at the maximum. In other words, it was necessary to consider

the concentration change on solid surface, *i.e.*, the rate of crystallization, in addition to the transport process.

It may be possible that all the dissolution patterns involving simultaneous change of phase to lower energy one are illustrated according to equation (4) and the dissolution curve of an anhydrate obtained by the dispersed amount method generally has a maximum point.

Dependence of Rate Constant of Transport Process on Rotating Velocity at Various Temperatures

When the dissolution of anhydrate was examined by the rotating disk method, a linear relationship, as shown in Fig. 6, was obtained according to equation (6), the slope being $k_t C_{SH}$. Fig. 7 and 8 show the results obtained for the anhydrates of *p*-hydroxybenzoic acid and

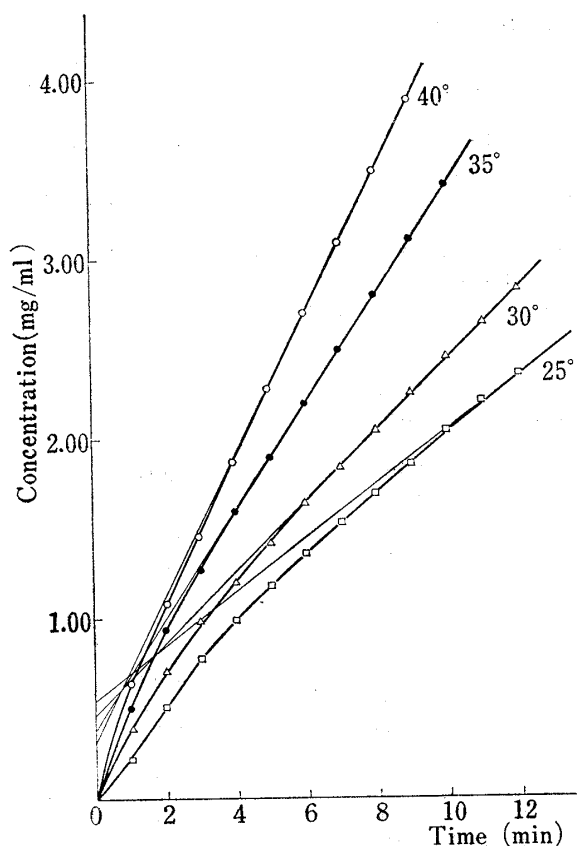


Fig. 7. Dissolution of *p*-Hydroxybenzoic Acid Anhydrate at Various Temperatures under 300 rpm

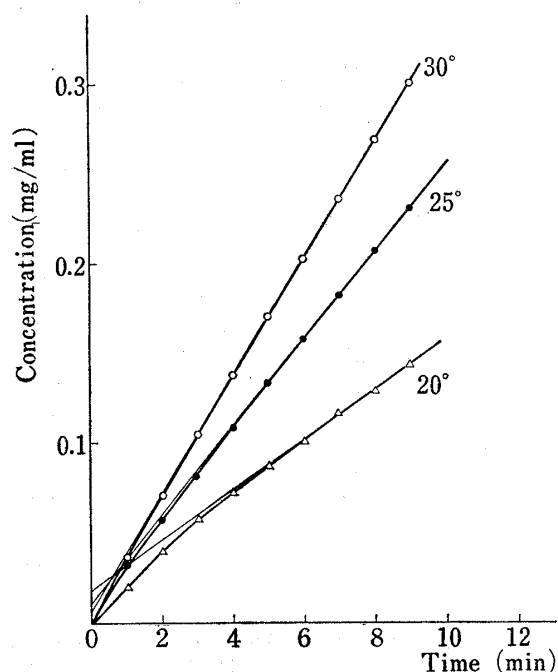


Fig. 8. Dissolution of Phenobarbital Anhydrate at Various Temperatures under 300 rpm

phenobarbital, respectively. The values of the slope, $k_t C_{SH}$, were in good agreement with those obtained for the respective hydrates. k_t was given by C_{SH} obtained preliminarily and its dependence on the rotating velocity of disk at various temperatures is shown in Tables II and III. Calculating from the values of k_t obtained above, the diffusion coefficient, D , and the diffusion layer thickness, δ , were obtained according to Levich equation,^{16,17)} as shown in Tables IV and V. The temperature dependence of k_t gave the activation energy E_a , as shown in Table VI. The values of E_a obtained seemed reasonable compared with data which had been reported as to other organic compounds.^{11,18)} Additionally, it is shown in Tables IV and V that δ was little affected by temperature, as was expected.

16) V.G. Levich, "Physicochemical Hydrodynamics," Prentice Hall, 1962.

17) V.G. Levich, *Acta Physicochim.*, U.R.S.S., 17, 257 (1942).

18) H. Nogami, T. Nagai, E. Fukuoka, and T. Yotsuyanagi, *Chem. Pharm. Bull.* (Tokyo), 17, 23 (1969).

TABLE II. Apparent Dissolution Constants, k_t , and Rate Constants, K_t , per Unit Area in Unit Volume of Transport Process of *p*-Hydroxybenzoic acid at Various Temperatures under Different Rotating Velocities of Disk in Water

Temperature (°C)	$k_t \times 10^2$ (min ⁻¹) Rotating velocity of disk (rpm)						
	600	500	300	200	120	100	60
40	4.79	4.40	3.34	2.73	—	2.26	—
35	4.33	3.97	3.07	2.52	—	2.14	—
30	3.93	3.59	2.75	2.28	1.87	1.73	1.58
25	3.55	3.22	2.51	2.07	—	—	—
	$K_t \times 10$ (cm/min)						
	600	500	300	200	120	100	60
40	3.39	3.11	2.36	1.93	—	1.60	—
35	3.06	2.81	2.17	1.78	—	1.51	—
30	2.78	2.54	1.94	1.61	1.32	1.22	1.12
25	2.51	2.28	1.78	1.47	—	—	—

TABLE III. Apparent Dissolution Rate Constants, k_t , and Rate Constants, K_t , per Unit Area in Unit Volume of Transport Process of Phenobarbital at Various Temperatures under Different Rotating Velocities of Disk in Water

Temperature (°C)	$k_t \times 10^2$ (min ⁻¹) Rotating velocity of disk (rpm)		
	600	300	200
30	3.35	2.34	1.91
25	3.01	2.10	1.72
20	2.73	1.91	1.57
	$K_t \times 10$ (cm/min)		
	600	300	200
30	2.37	1.66	1.35
25	2.13	1.49	1.22
20	1.93	1.35	1.11

TABLE IV. Diffusion Coefficients, D , and Diffusion Layer Thicknesses, δ , of *p*-Hydroxybenzoic Acid at Various Temperatures

Temperature (°C)	$D \times 10^6$ (cm ² /sec)	$\delta \times 10^3$ (cm) Rotating velocity of disk (rpm)			
		600	500	300	200
40	10.8	1.92	2.10	2.76	3.37
35	9.75	1.91	2.08	2.70	3.29
30	8.49	1.83	2.11	2.62	3.16
25	7.75	1.85	2.03	2.61	3.16

TABLE V. Diffusion Coefficients, D , and Diffusion Layer Thicknesses, δ , of Phenobarbital at Various Temperatures

Temperature (°C)	$D \times 10^6$ (cm ² /sec)	$\delta \times 10^3$ (cm) Rotating velocity of disk (rpm)		
		600	300	200
30	6.74	1.70	2.44	3.00
25	5.94	1.67	2.39	2.92
20	5.21	1.62	2.31	2.82

TABLE VI. Activation Energy, E_a of Crystallization Process and of Transport Process (cal/mole)

	Crystallization process	Transport process
<i>p</i> -Hydroxybenzoic acid	14100	3490
Phenobarbital	9990	3630

Saturated Concentrations of Anhydrate and Hydrate of the Respective Compounds at Various Temperatures

The saturated concentration of hydrate, C_{SH} , was obtained by the dispersed amount method. The saturated concentration of anhydrate, C_{SA} , was determined from the slope of the initial dissolution curve by rotating disk method, according to equation (8), as shown in Fig. 6. The values obtained are shown in Tables VII and VIII. Generally, it is hardly possible to determine by a usual equilibrium method the solubility of the metastable or unstable phase which changes during dissolution. However, the rotating disk method described in this paper may be useful to presume a solubility of such phase.

TABLE VII. Saturated Concentrations, C_{SA} and C_{SH} , and Values of $C_{SA}-C_{SH}$ of *p*-Hydroxybenzoic Acid at Various Temperatures

Temperature (°C)	Anhydrate C_{SA} ^{a)}	Hydrate C_{SH} (mg/ml)	$C_{SA}-C_{SH}$
40	16.62	12.90	3.72
35	13.51	10.01	3.50
30	10.76	7.65	3.11
25	8.62	5.97	2.65

^{a)} Values estimated from dissolution curves.

TABLE VIII. Saturated Concentrations, C_{SA} and C_{SH} and Values of $C_{SA}-C_{SH}$ of Phenobarbital at Various Temperatures

Temperature (°C)	Anhydrate C_{SA} ^{a)}	Hydrate C_{SH} (mg/ml)	$C_{SA}-C_{SH}$
30	1.51	1.41	0.10
25	1.32	1.16	0.16
20	1.13	0.73	0.21

^{a)} Values estimated from dissolution curves.

Temperature Dependence of Rate Constant of Crystallization Process

Putting the intercept b obtained from Fig. 7 or 8 and the values of k_i and $(C_{SA}-C_{SH})$ into equation (7), the rate constant of crystallization process, k_r , was calculated as shown in Tables IX and X. The values of b are listed in Tables XI and XII.

It is probable that the crystallization process is independent of the rotating velocity of disk, because this process takes place in the Volmer layer on the surface of solid.¹⁹⁾ Accordingly, it may be supported that the present experimental method, *i.e.*, the rotating disk method,

19) M. Volmer, *Physik. Z.*, 22, 646 (1921).

TABLE IX. Rate Constants, K_r , of Crystallization Process of *p*-Hydroxybenzoic Acid at Various Temperatures under Different Rotating Velocities of Disk in Water

Temperature (°C)	$k_r \times 10$ (min ⁻¹) Rotating velocity of disk (rpm)			
	600	500	300	200
40	4.00	3.89	3.88	3.75
35	2.77	2.70	2.72	2.65
30	1.88	1.89	1.83	1.81
25	1.23	1.18	1.20	1.17

TABLE X. Rate Constants, K_r of Crystallization Process of Phenobarbital at Various Temperatures under Different Rotating Velocities of Disk in Water

Temperature (°C)	$k_r \times 10$ (min ⁻¹) Rotating velocity of disk (rpm)		
	600	300	200
30	3.72	3.90	3.82
25	2.83	2.80	2.75
20	2.29	2.22	2.19

TABLE XI. Values of b of *p*-Hydroxybenzoic Acid Anhydrate at Various Temperatures under Different Rotating Velocities of Disk in Water

Temperature (°C)	$b \times 10$ (mg/ml) Rotating velocity of disk (rpm)			
	600	500	300	200
40	4.46	4.20	3.20	2.70
35	5.45	5.13	3.95	3.32
30	6.50	6.15	4.68	3.90
25	7.64	7.25	5.50	4.68

TABLE XII. Values of b of Phenobarbital Anhydrate at Various Temperatures under Different Rotating Velocities of Disk in Water

Temperature (°C)	$b \times 10$ (mg/ml) Rotating velocity of disk (rpm)		
	600	300	200
30	0.08	0.06	0.05
25	0.17	0.12	0.10
20	0.25	0.18	0.15

is useful to obtain the value of k_r . The activation energy of crystallization process, E_{ac} , was calculated from the temperature dependence of k_r , as shown in Table VI. The values of E_{ac} obtained above were similar to that of the interfacial release of barbital in its dissolution and thus seemed to be reasonable regarding the dissolution and crystallization process of organic medicinals.¹⁸⁾

Thermodynamic Relationship of the Transition from Anhydrate to Hydrate

From the temperature dependence of the saturated concentrations of anhydrate, C_{SA} , and of hydrate, C_{SH} , the thermodynamic functions of the transition from anhydrate to hydrate

TABLE XIII. Thermodynamic Functions of the Transition from Anhydrate to Hydrate of *p*-Hydroxybenzoic Acid and Phenobarbital

Substance	ΔH (cal/mole)		ΔS (e.u.)	T_t (°C)
	Anhydrate	Hydrate		
<i>p</i> -Hydroxybenzoic acid	8140	9690	-4.3	84
Phenobarbital	5260	7400	-6.9	37

were calculated as shown in Table XIII. The enthalpy change, ΔH , and the entropy change, ΔS , obtained were reasonable compared with the past data reported on organic medicinals.⁶⁾ The van't Hoff plots regarding anhydrate and hydrate showed linear relationships in the experimental temperature range and both the straight lines crossed each other at 84° in the case of *p*-hydroxybenzoic acid and at 37° in the case of phenobarbital. These intersections indicated the respective transition temperatures.

It was interesting that the value of $(C_{SA}-C_{SH})$ in the case of *p*-hydroxybenzoic acid increased with temperature as shown in Table VII. This fact informed that there might be a maximum point on the plot of $(C_{SA}-C_{SH})$ against temperature, because C_{SA} should be equal to C_{SH} at the transition temperature, *i.e.*, $(C_{SA}-C_{SH})=0$. Then, the discussion is attempted as follows. Since the van't Hoff plot is expected to give a linear relationship as described above, the following expressions may be possible.

$$\log C_{SA}=m_1/T+n_1 \quad (9)$$

$$\log C_{SH}=m_2/T+n_2 \quad (10)$$

where T is the temperature in °K, and m_1, m_2, n_1 and n_2 are constants. From equations (9) and (10),

$$C_{SA}-C_{SH}=\exp(m_1/T+n_1)-\exp(m_2/T+n_2) \quad (11)$$

Equation (11) is differentiated to yield

$$\frac{d(C_{SA}-C_{SH})}{dT}=1/T^2[m_2 \cdot \exp(m_2/T+n_2)-m_1 \cdot \exp(m_1/T+n_1)] \quad (12)$$

Since the solubility of organic compound generally increases with temperature, both m_1 and m_2 may be negative. Therefore, equation (12) shows mathematically that equation (11) has a extremum, and thus it is reasonably expected that $(C_{SA}-C_{SH})$ gets maximum as the temperature rises. However, such a maximum is not always observed in the experimental temperature range, as was not done in the case of phenobarbital as shown in Table VIII.

Finally, the model proposed in this paper was considered to be reasonable because of the good mutual relationships of k_t , k_r , C_{SA} , and C_{SH} obtained above, offering a useful method to analyze the various dissolution phenomena involving simultaneous phase changes.