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Dissolution Kinetics of Complexes of Sulfamethoxazole and Sulfamonomethoxine with 18-Crown-6[1]

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The dissolution profiles of the complexes of sulfamethoxazole (SMO) and sulfamonomethoxine (SMM) with 18-crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane, 18-C-6) involving simultaneous decomplexation were investigated kinetically in detail by a dispersed amount method and a stationary disk method in comparison with those of intact SMO and SMM. The dissolution rates of the complex before and after the phase change, R_c and R_o, respectively, the saturated concentrations of complex and intact drug, C_{Sc} and C_{So}, respectively, the rate constant of crystallization process, k_r, and the dissolution rate constant, k_t, were calculated by the stationary disk method.

Analyzing the values of k_r and k_t obtained at various temperatures, the activation energies of crystallization and dissolution process were determined. The activation energy of crystallization process seemed small compared with the past data reported on organic medicinals.

Keywords——complex; dissolution kinetics; 18-crown-6; sulfamethoxazole; sulfamonomethoxine; decomplexation; crystallization process; stationary disk method; dispersed amount method

Regarding the enhancement of solubility and dissolution rate due to crystalline modifications, kinetical investigations have been done for the dissolution of polymorphs,[3] and solvates.[4] However, there is found only a few report for the dissolution kinetics of complexes.[5]

In a previous paper,[6] the authors investigated the interaction of 18-crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane, 18-C-6), one of the most familiar crown ethers,[7] with sulfonamides as the guest molecules, and it was observed that the solid complexes of sulfamethoxazole (SMO) and sulfamonomethoxine (SMM) with 18-C-6 were obtained from benzene solution under the stoichiometry of 1:1, and a preliminary dissolution study in aqueous solution was also done for SMM/18-C-6 complex.[8]

The present study was attempted to investigate their dissolution profiles kinetically in detail by a dispersed amount method[4b] and a stationary disk method[9] in comparison with those of intact SMO and SMM.

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[1] This paper forms Part X of "Pharmaceutical Interactions in Dosage Forms and Processing." The preceding paper, Part IX: N. Nambu, M. Shimoda, Y. Takahashi, H. Ueda, and T. Nagai, *Chem. Pharm. Bull.* (Tokyo), **26**, 2952 (1978).

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[5] *a*) K. Sekiguchi and K. Ito, *Chem. Pharm. Bull.* (Tokyo), **13**, 405 (1965); *b*) T. Higuchi and I.H. Pitman, *J. Pharm. Sci.*, **62**, 55 (1973).

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Experimental

Materials——18-C-6 used was of the reagent grade. SMO supplied by Shionogi Pharmaceutical Co., Ltd., was used after recrystallization from 30 v/v % acetone–water system. SMM supplied by Dai-ichi Pharmaceutical Co., Ltd., was used after recrystallization from 30 v/v % acetone–water system. The monohydrate of SMM was formed by this recrystallization.[8] The anhydrate of SMM was prepared in the same way as described in the previous paper.[8]

Preparation of SMO/18-C-6 Complex——Following the previous paper,[6] 5 g of SMO and 5.2 g of 18-C-6 in 100 ml of benzene were sealed in a flask and stirred well for 10 days at 10°. After equilibration the complex formed was filtered out, washed with benzene and dried under vacuum for 24 hr to remove the solvent completely.

Preparation of SMM/18-C-6 Complex——Four grams of SMM anhydrate and 6 g of 18-C-6 in 100 ml of benzene were sealed in a flask and stirred well for 10 days at 10°. Then, the procedure was carried out in the same way as described in the previous paper.[8]

Identification of the Respective Compounds——Powder X-ray diffractometry, infrared absorption spectrophotometry, and differential scanning calorimetry were employed in the same way as described in the previous papers.[6,8]

Procedure for Dissolution Study——a) Dispersed Amount Method:[4b,8] Following the previous paper,[8] a certain excess of sample powder (about three or six times as much as the saturated concentration) was subjected to the experiment in 50 ml of 0.2 N HCl. The sampling was done by an one ml G-4 glass filter attached pipette. The concentrations of SMO and SMM were determined according to ultraviolet (UV) absorption method after diluting with 0.2 N HCl. The others were exactly the same as described in the previous paper.[8]

b) Stationary Disk Method: Following the previous paper,[8] the experimental conditions were as follows: 300 ml of 0.2 N HCl[10] at 30°, 35°, and 40°; the rotating velocities of stirrer at 100, 300, and 600 rpm; the disk of 1.3 cm diameter compressed under 150 kg/cm^2. When the samples were compressed to make the disks, the phase change transition by the pressure was not observed. At an appropriate time interval, 2 ml of the solution was sampled out, the resultant want of volume was compensated by adding the dissolution medium of the same temperature. The concentration was determined according to UV absorption method.

Results and Discussion

As shown in Fig. 1, the dissolution curves of SMO/18-C-6 and SMM/18-C-6 complexes in 0.2 N HCl by the dispersed amount method were almost similar to that of SMM/18-C-6

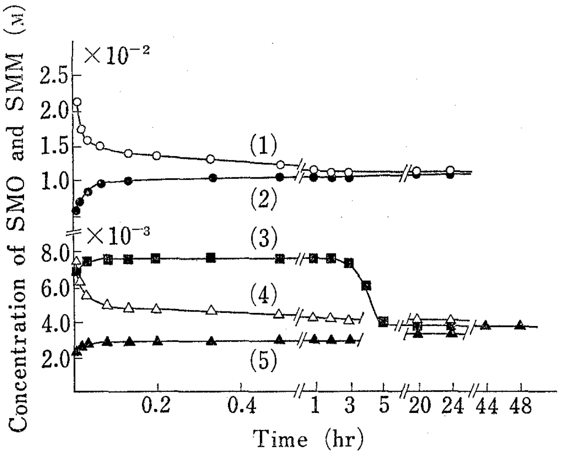

Fig. 1. Dissolution Behaviors of SMO/18-C-6 Complex (1), SMO (2), SMM Anhydrate (3), SMM/18-C-6 Complex (4), and SMM Hydrate (5) in 50 ml of 0.2 N HCl at 30° by Dispersed Amount Method

Sample amount: SMO/18-C-6 complex, 800 mg; SMO, 480 mg; SMM/18-C-6 complex, 500 mg;SMM hydrate, 334 mg; SMM anhydrate, 314 mg.

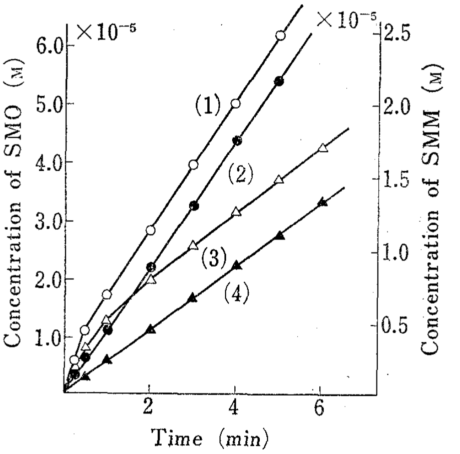

Fig. 2. Initial Dissolution Curves of SMO/18-C-6 Complex (1), SMO (2), SMM/18-C-6 Complex (3), and SMM Hydrate (4) in 300 ml of 0.2 N HCl by Stationary Disk Method (30°, 300 rpm)

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[10] Considering the solubilities of SMO and SMM, 0.2 N HCl was good enough to determine the dissolution rate in this study.

complex in water described in the previous paper.[8] However, the curves fell to the respective solubility levels of SMO and SMM in 24—48 hr, as was fast compared with the case in water.[8] Therefore, it may be considered that the decomplexation accompanying the crystallization finished fast and a special interaction of SMO or SMM with 18-C-6 was hardly observed in 0.2 N HCl. Practically, the stability constants of SMO/18-C-6 and SMM/18-C-6 systems were 2.72 and 1.65 M^{-1}, respectively, in 0.2 N HCl at 30°, which were negligibly small compared with those in benzene.[6] This result might indicate that HCl inhibits the interaction of 18-C-6 with sulfonamides,[6] though further investigations should be made in detail. Anyhow, the above fact might be favorable for determining the dissolution parameters of these complexes quantitatively by stationary disk method.

Dissolution Behavior observed by Stationary Disk Method

As shown in Fig. 2, the dissolution rates of the complexes in 0.2 N HCl were not represented by the Noyes-Nernst equation. This result might be due to the decomplexation accompanying the crystallization and the change to the stable forms in the initial dissolution stage, *i.e.*, to SMO and SMM hydrate, respectively. Here, the slopes of the dissolution curves of the complexes after the decomplexation accompanying the crystallization were almost the same as those of the intact SMO and SMM hydrate. Moreover, the change of the surface area releasing sulfonamides seemed negligible in the initial dissolution stage.[8]

Considering that the diffusion constant of complex is almost the same as that of the intact SMO or SMM,[5b,11] the following equations for the dissolution in the initial stage are given in the same way as described in the previous paper.[4b]

$$\frac{dC}{dt} = k_t\{C_{Sc}\cdot\exp(-k_r t) + C_{So}[1-\exp(-k_r t)]\} \qquad (1)$$

$$C = k_t(C_{Sc} - C_{So})[1-\exp(-k_r t)]/k_r + k_t C_{So} t \qquad (2)$$

where C_{Sc} is the saturated concentration of the complex, C_{S_0} the concentration at the time t which corresponded to the concentration of SMO and SMM in the bulk liquid at equilibrium,

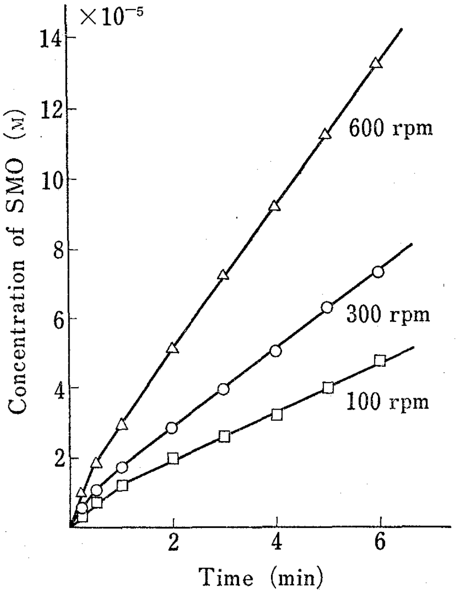

Fig. 3. Initial Dissolution Curves of SMO/18-C-6 Complex in 300 ml of 0.2 N HCl under Various Stirring Conditions at 30° by Stationary Disk Method

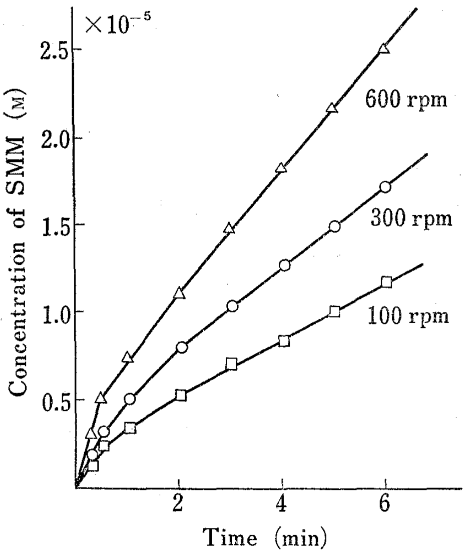

Fig. 4. Initial Dissolution Curves of SMM/18-C-6 Complex in 300 ml of 0.2 N HCl under Various Stirring Conditions at 30° by Stationary Disk Method

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11) T. Higuchi, S. Dayal, and I.H. Pitman, *J. Pharm. Sci.*, 61, 695 (1972).

k_t the dissolution rate constant, and k_r the rate constant of the crystallization process. Then the apparent dissolution parameters[12] of these complexes were obtainable by the analysis of the dissolution curves in the initial dissolution stage as follows.

a) Effect of Stirring Conditions on Dissolution Behavior for Complexes

Figures 3 and 4 show the results obtained for the dissolution of SMO/18-C-6 and SMM/18-C-6 complexes in 0.2 N HCl, respectively. The dissolution rate before and after the phase change, R_c and R_o, respectively, and the other parameters described in equations (1) and (2) for the complexes were calculated under the various stirring conditions, and summarized in Table I. The values of R_c and C_{Sc} of these complexes were two or three times greater than that of R_o and C_{Sc}, indicating that the complexation with 18-C-6 was very effective in an enhancement of dissolution rate and solubility of these sulfonamides. From the other point of view, k_r values were extremely large as compared with the data reported as to the crystallization process involving a phase change from anhydrate to hydrate.[4b] These large k_r values indicate that the decomplexation accompanying the crystallization from the complex to the original component took place in the exactly initial dissolution stage. In this connection, it seemed hardly possible to determine the solubility of these complexes by an usual equiliblium method. Therefore, the stationary disk method employed in this study may be useful to presume a solubility of complex. Additionary, k_r values were almost constant in spite of the change of stirring conditions. Therefore, it may be considered that the crystallization process took place in the Volmer layer on the surface of solid.[4b,13]

TABLE I. Dissolution Rates before and after Decomplexation, R_c and R_o, Saturated Concentrations, C_{Sc} and C_{So}, and Rate Constants of Crystallization and Dissolution Process, k_r and k_t under Various Stirring Conditions at 30°

Complex	Stirring condition (rpm)	$R_c \times 10^5$ (M/min)	$R_o \times 10^5$ (M/min)	$C_{Sc} \times 10^2$ (M)	$C_{So} \times 10^2$ (M)	k_r (min^{-1})	$k_t \times 10^3$ (min^{-1})
SMO/18-C-6	600	4.00	2.03	2.19	1.11	1.65	1.83
	300	2.30	1.14	2.23	1.11	1.54	1.03
	100	1.35	0.690	2.17	1.11	1.65	0.622
SMM/18-C-6	600	1.03	0.345	1.16	0.390	1.55	0.885
	300	0.710	0.225	1.18	0.390	1.54	0.577
	100	0.443	0.155	1.12	0.390	1.53	0.397

b) Effect of Temperature on Dissolution Behavior for Complexes

Figures 5 and 6 show the results obtained for SMO/18-C-6 and SMM/18-C-6 complexes in 0.2 N HCl, respectively. The values of dissolution rate after the phase change were in good agreement with those obtained for intact SMO and SMM hydrate at all the temperature region. The dissolution parameters obtained are shown in Table II. These values increased more or less with an increase of the bulk liquid temperature. The temperature dependence of k_r and k_t gave the apparent activation energy, E_a, of crystallization and dissolution process, as summarized in Table III. The values of E_a of crystallization process of SMM/18-C-6 complex was somewhat larger than that of SMO/18-C-6 complex, suggesting that the crystallization of SMM/18-C-6 complex involved that of SMM anhydrate to hydrate. From the other point of view, the value of E_a of crystallization process seemed small compared with the data

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12) The words "apparent dissolution parameters" were used here because both the decomplexation and the phase change processes might take place simultaneously and thus the intrinsic dissolution parameters could not be determined.

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

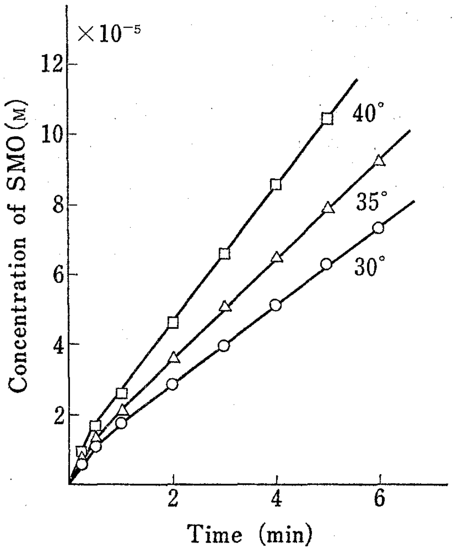

Fig. 5. Initial Dissolution Curves of SMO/18-C-6 Complex in 300 ml of 0.2 N HCl at Various Temperatures under Stirring Condition of 300 rpm by Stationary Disk Method

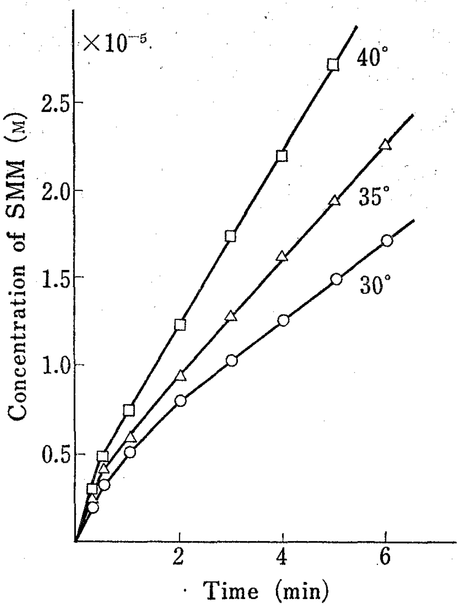

Fig. 6. Initial Dissolution Curves of SMM/18-C-6 Complex in 300 ml of 0.2 N HCl at Various Temperatures under Stirring Condition of 300 rpm by Stationary Disk Method

Table II. Dissolution Rates before and after Decomplexation, R_c and R_o, Saturated Concentrations, C_{Sc} and C_{So}, and Rate Constants of Crystallization and Dissolution Process, k_r and k_t at Various Temperatures under Stirring Conditions of 300 rpm

Complex	Temperature (C°)	$R_c\times10^5$ (M/min)	$R_o\times10^5$ (M/min)	$C_{Sc}\times10^2$ (M)	$C_{So}\times10^2$ (M)	k_r (min^{-1})	$k_t\times10^3$ (min^{-1})
SMO/18-C-6	40	3.20	1.98	2.64	1.64	2.09	1.21
	35	2.70	1.45	2.43	1.31	1.78	1.11
	30	2.30	1.14	2.23	1.11	1.54	1.03
SMM/18-C-6	40	1.23	0.483	1.45	0.571	2.48	0.846
	35	0.900	0.323	1.32	0.473	1.93	0.683
	30	0.710	0.225	1.23	0.390	1.54	0.577

Table III. Activation Energy, E_a, of Crystallization Process and of Dissolution Process in 0.2 N HCl (kcal/mol)

Complex	Crystallization process	Dissolution process
SMO/18-C-6	5.49	2.91
SMM/18-C-6	8.23	6.86

reported as to the crystallization process involving a phase change from anhydrates to hydrates.[4b] This result may indicate that the decomplexation and the crystallization of these complexes took place easily in the exactly initial dissolution stage.

The values of E_a of the dissolution process obtained seemed reasonable compared with the past data reported on organic medicinals.14)

The above results proved that dissolution kinetics of these complexes could be analyzed by the same way as described for the anhydrate changing to hydrate in the previous paper.4b)

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