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Dissolution Profile and Bioavailability of Sulfamonomethoxine/18-Crown-6 Complex in Comparison with Sulfamonomethoxine Anhydrate and Hydrate[1)]

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Dissolution profiles of sulfamonomethoxine (SMM)/18-crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane) complex, SMM anhydrate and SMM hydrate were investigated by dispersed amount method and stationary disk method, and also *in vivo* absorption study of these compounds in dogs was carried out in comparison with the data of the dissolution behaviors.

According to the dispersed amount method, the concentration of SMM rose quickly and then decreased gradually when the complex was dispersed. On the other hand, a characteristic convex dissolution curve was observed in the case of the anhydrate. This result indicated that the dissolution rate of complex was extremely large, but its decomplexation accompanying the change to the hydrate form in water was also rapid compared with that of the anhydrate. The rate constant of phase change for the complex to the hydrate form, which was calculated by stationary disk method, was extremely large compared with that for the anhydrate.

It was observed that the plasma levels of SMM increased extremely by the administration of the anhydrate form. An increase of plasma levels was also observed in the case of the complex.

Keywords——complex; 18-crown-6; sulfamonomethoxine; dissolution profile; stationary disk method; dispersed amount method; bioavailability; beagle dogs

It is well known that the bioavailability of drugs may vary according to crystalline modifications,[3)] such as polymorphs, solvates and complexes.

In a previous paper,[1)] the authors investigated the interaction of 18-crown-6 (1,4,7,10,13,16-hexaoxacyclooctadecane), one of the most familiar crown ethers,[4)] with sulfonamides as the guest molecules, and it was observed that the solid complex of sulfamonomethoxine (SMM) with 18-crown-6 was obtained in benzene solution under the stoichiometry 1:1.

In order to have an understanding of the bioavailability of this complex, the present study was attempted to investigate its dissolution profile and *in vivo* absorption in comparison with those of SMM anhydrate and hydrate. The dissolution study was done by a dispersed amount method[5)] and a stationary disk method,[6)] and the *in vivo* absorption study by an oral administration in dogs.

Experimental

Materials——18-Crown-6 used was of the reagent grade. SMM used was supplied by Dai-ichi Pharmaceutical Co., Ltd.

1) This paper forms Part VII of "Pharmaceutical Interactions in Dosage Forms and Processing." The preceding paper, Part VI: K. Takayama, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.* (Tokyo), **25**, 2608 (1977).
2) Location: *Ebara-2-4-41, Shinagawa-ku, Tokyo 142, Japan.*
3) *e.g.*, J.K. Haleblian, *J. Pharm. Sci.*, **64**, 1269 (1975).
4) C.J. Pederson, *J. Am. Chem. Soc.*, **89**, 7017 (1967).
5) *a*) H. Nogami, T. Nagai, and T. Yotsuyanagi, *Chem. Pharm. Bull.* (Tokyo), **17**, 499 (1969); *b*) K. Sekiguchi, E. Owada, and K. Ito, *Chem. Pharm. Bull.* (Tokyo), **15**, 873 (1967).
6) Y. Hamada, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.* (Tokyo), **23**, 1205 (1975).

Preparation of Anhydrate and Hydrate of SMM——The hydrate of SMM, which dehydrated at 118—126° and melted at 205°, was obtained by recrystallization from 30 v/v % acetone–water system. The anhydrate, which melted at 205°, was prepared by heating the hydrate at 105° for 4 hr according to the description in J.P. IX.[7]

Preparation of SMM/18-Crown-6 Complex——On referring to the solubility diagram described in the previous paper,[1] 4 g of SMM anhydrate and 6 g of 18-crown-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. This procedure was suitable for preparing a large amount of the complex, but the fully purified one was not obtained, containing a trace of the starting components. However, this grade of sample seemed to cause no trouble for the present study, and thus this product was used without further purifications.

Identification of the Respective Compounds——This was done by powder X-ray diffractometry, infra-red absorption spectrophotometry, and differential scanning calorimetry. In the case of the complex, the additional methods were applied to confirm the formation in the same way as reported in the previous paper.[1]

Procedure for Dissolution Study——a) Dispersed Amount Method[5]: Using a dissolution cell similer to that described by Sekiguchi, *et al.*,[5b] a certain excess of sample powder as shown in Fig. 1, which corresponded to 60 mg of the anhydrate, was weighed accurately and put in the dissolution cell, which was kept at 30° by circulating the constant temperature water in the outer vessel. To this was added 50 ml of distilled water, which was previously kept at 30°. Immediately after the addition, a vigorous agitation was applied by a magnetic stirrer. The solution was sampled out at an appropriate interval by a 1 ml cotton-filter attached pipette. The concentration of SMM was determined according to ultraviolet (UV) absorption method after diluting with water.

b) Stationary Disk Method[6]: The procedure employed was the same as described in the previous paper.[6] Every experiment was carried out under the following conditions; 300 ml of 1/15 M phosphate buffer solution at pH 7.0 at 30°; the rotating velocity of stirrer at 300 rpm; the disk of 1 cm diameter compressed under 150 kg/cm^2. When the samples were compressed to make the disks, the phase transition by the pressure was not observed. At an appropriate interval, 3 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.

***In Vivo* Absorption Study**——Six healthy male beagle dogs weighing about 10 kg were used in every experiment after fasting for 24 hr. They were randomly divided into three groups, *i.e.*, two each group, to make the cross-over experiment at intervals of one week over three weeks according to a Latin square design. In every experiment, they were administered orally with a dosage form of powders of the respective samples wrapped in two pieces of oblate so that the dose corresponded to 300 mg of the anhydrate. Three milliliters of blood sample heparinized was collected from cephalic vein at 1, 2, 4, 6, 8, and 24 hr after the administration, and centrifuged to obtain the plasma sample, being stored in a refrigerator at −10°. The unchanged and total SMM in plasma samples were estimated according to the modified Bratton-Marshall procedure described by Ohshima, *et al.*[8]

Results and Discussion

Dissolution Behavior Observed by Dispersed Amount Method

When the complex was dispersed, the concentration of SMM rose very quickly and then decreased gradually as shown in Fig. 1. In the case of the hydrate, a normal dissolution curve was observed. On the other hand, in the case of the anhydrate, a characteristic convex dissolution curve was obtained. These results indicate that the dissolution rate of the complex was extremely large, and also its decomplexation accompanying the change to the hydrate form in water was rapid compared with that of the anhydrate. Therefore, the dissolution curve of the complex decreased gradually while the solubility of the anhydrate was maintained in a higher value than that of the hydrate in the relatively long period due to its gradual change to the hydrate form. As shown on the dissolution curve of the physical mixture of anhydrate with 18-crown-6, the phase change of the anhydrate to the hydrate was accelerated in the existence of 18-crown-6 in water. This result might give an explanation for the fact that the decrease of the curve for the complex was rapid compared with that for the anhydrate only.

7) It was ascertained that this condition was good enough to obtain the pure material.
8) Y. Ohshima, A. Kasahara, and M. Shibata, *Nippon Yakurigaku Zasshi*, **58**, 59 (1962).

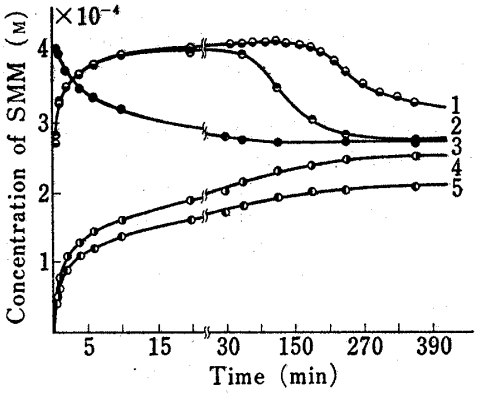

Fig. 1. Dissolution Behaviors of SMM Anhydrate (1), SMM Anhydrate/18-Crown-6 Physical Mixture (2), SMM/18-Crown-6 Complex (3), SMM Hydrate/18-Crown-6 Physical Mixture (4) and SMM Hydrate (5) in 50 ml Water at 30° by Dispersed Amount Method

1. anhydrate 60 mg,
2. anhydrate/18-crown-6 physical mixture (anhydrate 60 mg, 18-crown-6 39.8 mg),
3. complex 99.8 mg.
4. hydrate/18-crown-6 physical mixture (hydrate 64 mg, 18-crown-6 39.8 mg),
5. hydrate 64 mg.

The dissolution curve of the physical mixture of hydrate with 18-crown-6 was slightly higher than that of the hydrate. Namely, 18-crown-6 seemed to have a solubilizing effect on the intact hydrate in water.

Dissolution Behavior Observed by Stationary Disk Method

As shown in Fig. 2, the dissolution of the anhydrate was faster than those of the complex and the hydrate. This fact coincided with the result observed by the dispersed amount method. The dissolution curve of the complex was higher than that of the hydrate in the initial stage, but these were reversed after about 40 min. This result may be explained as follows. The dissolution rate of the complex was highest in the very initial stage as shown in Fig. 3, but the decomplexation accompanying the change to the hydrate form also seemed to be remarkable in the initial stage. Theoretically, the slope of the dissolution curve of the complex after the decomplexation accompanying the change to the hydrate should be coincided with that of the intact hydrate.[5a] Actually, however, the slope of the dissolution curve of the complex in this stage was rather small compared with that of the intact hydrate.

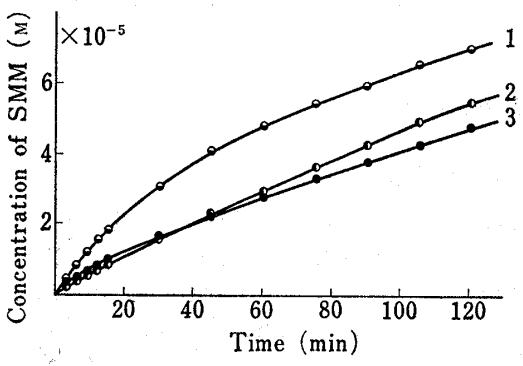

Fig. 2. Dissolution Curves of SMM Anhydrate (1), SMM Hydrate (2), and SMM/18-Crown-6 Complex (3) in 1/15 M Phosphate Buffer Solution at pH 7.0 at 30° by Stationary Disk Method

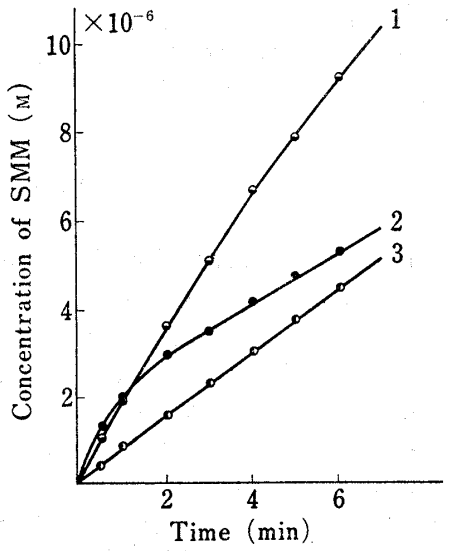

Fig. 3. Initial Dissolution Curves of SMM Anhydrate (1), SMM/18-Crown-6 Complex (2) and SMM Hydrate (3) in 1/15 M Phosphate Buffer Solution at pH 7.0 at 30° by Stationary Disk Method

Here, a decrease of the surface area releasing SMM in bulk liquid through the decomplexation accompanying the phase change, which might be pointed out as a reason for this result, seemed unimportant as follows. First, 18-crown-6 is so soluble that its crystal might not

come out on the surface releasing SMM upon the decomplexation. On the other hand, the crystal of SMM hydrate is considered to come out on the surface due to the dissolution of complex accompanying the formation of SMM hydrate of low solubility, and then the surface might be almost covered with the hydrate. Moreover, in a dissolution experiment of SMM hydrate in 1/15 M phosphate buffer solution at pH 7.0, 18-crown-6 gave no remarkable effect on the solubility and the dissolution rate. Therefore, in the initial stage of the dissolution of SMM/18-crown-6 complex, a change of the surface area releasing SMM seemed negligible.

Based on the above consideration, it might be assumed that the releasing area of SMM was almost kept constant during the initial dissolution stage of SMM/18-crown-6 complex. In other words, the dissolution parameters were obtainable by the analysis of dissolution curves in the same way as described in a previous paper.[5] Then, the dissolution rate before the phase change (R_b), the saturated concentration (C_s) and the rate constant of the phase change to the hydrate form (rate constant of crystallization process, k_r) for the anhydrate and the complex were calculated,[5a] and summarized in Table I. It was observed that the

Table I. Dissolution Rate before Phase Change (R_b), Saturated Concentration (C_s) and Rate Constant of Crystallization Process (k_r) in 1/15 M Phosphate Buffer Solution at pH 7.0 at 30° calculated by Stationary Disk Method

Materials	$R_b \times 10^6$ (M/min)	$C_s \times 10^3$ (M)	k_r (min^{-1})
SMM/18-crown-6 complex	2.52	5.97	1.39
SMM anhydrate	1.83	3.47	0.0582

k_r value for the complex was extremely large compared with that for the anhydrate. In other words, the decomplexation of this complex accompanying the phase change to the hydrate form may occur rapidly in aqueous solution. Although the data should be confirmed also for the physical mixture of anhydrate with 18-crown-6, there was a difficulty in making the disk used for the dissolution study by stationary disk method.

In Vivo Absorption Study

It is well known that the bioavailability of sulfonamides is enhanced by applications of crystalline modifications such as polymorphs and solvates.[3]

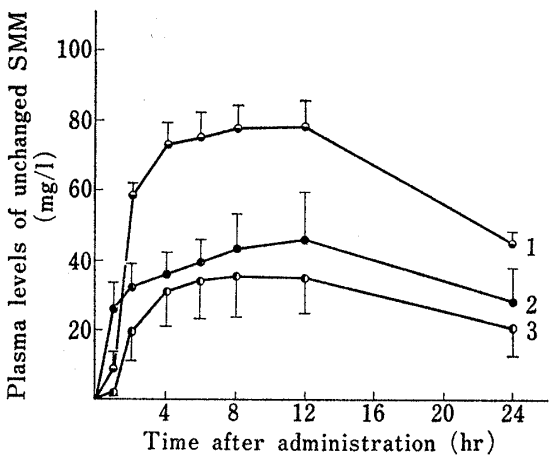

Fig. 4. Plasma Levels of Unchanged SMM after Oral Administration of 300 mg of SMM Anhydrate (1), 499.2 mg of SMM/18-Crown-6 Complex (2) and 319.3 mg of SMM Hydrate (3) to Six Beagle Dogs (mean ± S.E.)

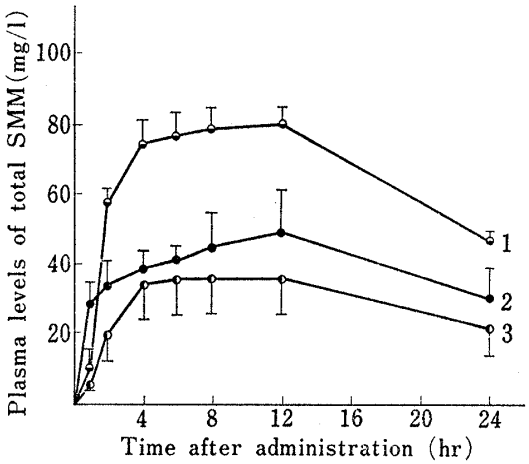

Fig. 5. Plasma Levels of Total SMM after Oral Administration of 300 mg SMM Anhydrate (1), 499.2 mg of SMM/18-Crown-6 Complex (2) and 319.3 mg of SMM Hydrate (3) to Six Beagle Dogs (mean ± S.E.)

In the present study, it was observed that the plasma levels of SMM increased remarkably by the administration of anhydrate form as shown in Fig. 4 and 5. In the case of the complex also, an increase of plasma levels of SMM was observed. Especially, at 1 hr after the administration of the complex, the level of SMM was higher than any other. At the same point, there was no increase of plasma levels of SMM in the case of the physical mixture of the hydrate with 18-crown-6. Therefore, the data of plasma levels of these samples seemed to be related to the dissolution profile.

These above results indicated that the bioavailability of SMM may increase by administration of the anhydrate form or the complex with 18-crown-6. However, also the toxicity, which will be reported separately,[9] should be taken into consideration.

Acknowledgement The authors are very grateful to Dai-ichi Pharmaceutical Co., Ltd. for supplying the materials.

9) K. Takayama, S. Hasegawa, S. Sasagawa, N. Nambu, and T. Nagai, *Chem. Pharm. Bull.* (Tokyo), **25**, 3125 (1977).