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Dissolution Behavior and Gastrointestinal Absorption of Sulfamethoxazole from Sulfamethoxazole-Polyvinylpyrrolidone Coprecipitates[1]

Hitoshi Sekikawa,*,[a] Naomi Yagi,[a] Jun Sakuragi,[a] Kaede Tanaka,[a] Mieko Sakamoto,[a] Megumi Itoh,[a] Masahiko Takada,[a] and Takaichi Arita[b]

Faculty of Pharmaceutical Sciences, Higashi-Nippon-Gakuen University,[a] 1757 Banchi, Kanazawa, Ishikari-Tohbetsu, 061-02, Japan, and Department of Pharmacy, Hokkaido University Hospital, School of Medicine, Hokkaido University,[b] Kita 14-jo, Nishi 5-Chome, Kita-ku, Sapporo, 060, Japan

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Coprecipitates of sulfamethoxazole (SMZ)-polyvinylpyrrolidone (PVP) were prepared in various weight ratios. The X-ray diffraction spectra indicated that SMZ in the coprecipitates was not crystalline. Comparative studies were made on the *in vitro* dissolution and the *in vivo* absorption of the coprecipitate and SMZ alone. The dissolution rate of SMZ from the SMZ–PVP coprecipitates was markedly increased in distilled water and in J.P.IX disintegration media at pH 1.2 and 7.5. *In vivo* absorption studies of each preparation were carried out in five male subjects by measuring the urinary excretion rate of total SMZ. The excretion rate and the cumulative amount of total SMZ following oral administration of the coprecipitate were greater than those after administration of SMZ alone.

Keywords——sulfamethoxazole; bioavailability; polyvinylpyrrolidone; coprecipitate; urinary excretion; gastrointestinal absorption; dosage form; sulfonamide; dissolution

Several attempts[2–6] have been made to enhance the bioavailability of poorly water-soluble drugs that showed nonequivalent therapeutical effects or areas under the blood concentration curve (AUC) following the oral administration of different preparations.[7] The authors reported on the modification of the dissolution characteristics of some poorly water-soluble drugs by coprecipitating the drug with polyvinylpyrrolidone (PVP) and obtained better bioavailability following the administration of the coprecipitates than of the drugs alone.[8,9] Sulfamethoxazole (SMZ), a long-acting suflonamide, exhibits poor water-solubility. Watanabe *et al.*[10] pointed out that the AUC of the drug varied among several preparations. The authors investigated the modification of the dissolution characteristics of SMZ by coprecipitation with PVP. Gastrointestinal absorption was also evaluated in human subjects.

Experimental

Materials——SMZ (J.P.IX) was obtained from Shionogi Pharmaceutical Co. Ltd., Osaka (Sinomin, lot DRO3). The mean particle size of SMZ was 630±140 μm (Green diameter). PVP K-15 (average molecular weight of 10000) was obtained from Daiichi Pure Chemicals Co., Tokyo. All other chemicals were of reagent grade.

Preparation of the Coprecipitates and the Physical Mixture——The coprecipitates and the physical mixture were prepared in the same manner as reported in the previous papers.[8,9] The coprecipitates were passed through sieves to obtain particles in the size range of 500—840 μm.

Dissolution Rate Studies——Dissolution rates of SMZ from the preparations in 500 ml of J.P.IX disintegration media No. 1 (pH 1.2) and No. 2 (pH 7.5) and distilled water were measured at 37.0±0.1°C. A stainless steel three-bladed propeller (60 mm in diameter and about 3 cm^2 per blade) was rotated at 50 rpm. The amounts of the preparations were 105 mg and 9.45 g of SMZ equivalent, corresponding to one-third and thirty times the solubility of SMZ in distilled water, respectively, if the drug in the preparation was completely dissolved in the solution. The SMZ concentration in the solution was analyzed in 0.1 N NaOH at 256 nm

using a Hitachi 100-20 spectrophotometer, after filtration through a membrane filter (Millipore Co., Massachusetts, pore size 0.2 μm).

X-Ray Diffraction Patterns——The X-ray diffraction patterns were obtained with a Rigaku Denki D-9C diffractometer.

Subjects——The subjects were five male volunteers whose ages ranged from 23 to 33 (average of 25 yeras) and whose weights ranged from 57 to 80 kg (average of 62 kg).

Urinary Excretion of Total SMZ——SMZ (1000 mg) or the coprecipitate (weight ratio of SMZ: PVP= 1: 3, 4000 mg) was orally administered to the subjects, who had fasted after the evening meal prior to the morning during which the sample was to be administered. No food or beverage was given to the subjects for 4 h postadministration, except for water (60 ml/h) to maintain the normal volume of urine. At least 2 weeks were allowed between experiments. The total amount of SMZ, comprising free SMZ, N^4-acetylsulfamethoxazole, the main metabolite in human urine,[11] and other minor metabolites[12] in urine, was assayed by the colorimetric method[13] after acid hydrolysis.

Results and Discussion

1. The Properties of the Coprecipitates

Figure 1 shows the X-ray powder diffraction spectra of SMZ powder, physical mixture, the samples prepared by the coprecipitating method at different SMZ-to-PVP weight ratios, and PVP powder. On coprecipitation with PVP, the sharp diffraction peaks attributed to SMZ crystals disappeared, and only the halo was observed in 1: 1 and 1: 3 SMZ-to-PVP weight ratio preparations. In the case of the preparation of 3: 1 SMZ-to-PVP ratio, however, diffraction peaks were observed. As mentioned in the previous paper,[14] an appropriate drug-to-PVP ratio may be necessary to inhibit the recrystallization of the drug during the solvent-removing process in the preparation of the coprecipitates. The complexing tendency between SMZ and PVP was sufficient to yield coprecipitates in ethanolic solution. The apparent stability constant of the presume complex was 1.47 M^{-1} at 37°C (vinylpyrrolidone equivalent).

In the measurements with the differential scanning calorimeter, the endothermic peak that accompanied the melting of SMZ crystals (171°C) was no longer seen in the coprecipitates. These results indicate that SMZ in the coprecipitates might be present in an amorphous state

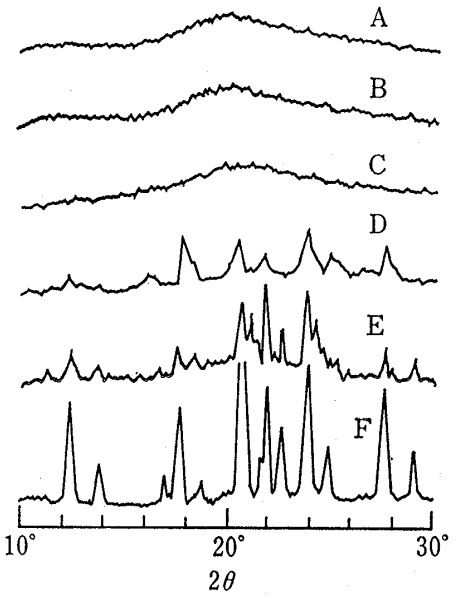

Fig. 1. Comparison of X-Ray Diffraction Spectra of Preparations of Different Sulfamethoxazole–PVP Ratios

Key: A, PVP alone; B, 1: 3; C, 1: 1; D, 3: 1; E, physical mixture, 1 : 3; F, sulfamethoxazole alone.

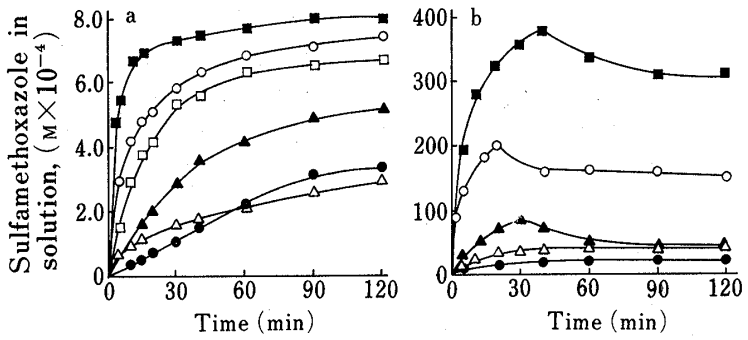

Fig. 2a. Dissolution Profiles of Sulfamethoxazole from Test Preparations containing 105 mg Sulfamethoxazole Equivalent in Distilled Water

Key: ■, sulfamethoxazole: PVP K-15=1: 5 coprecipitate; ○, 1: 3 coprecipitate; □, 1: 2 coprecipitate; ▲, 1: 1 coprecipitate; △, 1: 3 physical mixture; ●, sulfamethoxazole alone.
Each point represents the mean of three determinations.

Fig. 2b. Dissolution Profiles of Sulfamethoxazole from Test Preparations containing 9.45 g Sulfamethoxazole Equivalent in Distilled Water

Key: Symbols are the same as in Fig. 2a.
Each point represents the mean of three determinations.

in the PVP matrix or might have very fine structure below the limit of detection by these instrumental analyses.

2. Dissolution Studies

The dissolution behavior of preparations is shown in Fig. 2. The coprecipitates exhibited faster dissolution rates than SMZ alone or as a physical miuture. The dissolution rate of SMZ in the coprecipitate was greater when the ratio of SMZ-to-PVP was smaller (Fig. 2a). The final pH of the solution was 3.8. When the amount of the preparation was 9.45 g SMZ equivalent, the concentration of SMZ following the dissolution of the coprecipitates exceeded the solubility (2.49×10^{-3} M) and reached a peak, then decreased gradually. The supersaturation, however, continued for a long period because PVP in the solution prevented the recrystallization of the drug.[15] SMZ in the physical mixture dissolved more rapidly than SMZ alone in the first few minutes, then more slowly than the drug alone. In the earlier period, PVP in the medium from the physical mixture might lower the surface tension of the medium, and result in wetting of the SMZ crystal surface. Then, PVP might increase the viscosity of the solution, resulting in slower dissolution of the drug.

Figure 3 shows the dissolution patterns of SMZ from the preparations in J.P.IX disintegration media No. 1 and No. 2. The dissolution profiles were similar to that in distilled water. Since the pK_a values are 1.76 and 5.81,[13] only a little SMZ is considered to be ionized in each medium, so that the dissolution characteristics of the SMZ molecule alone were improved. The coprecipitates exhibited faster dissolution of SMZ than SMZ alone, irrespective of the pH of the solution.

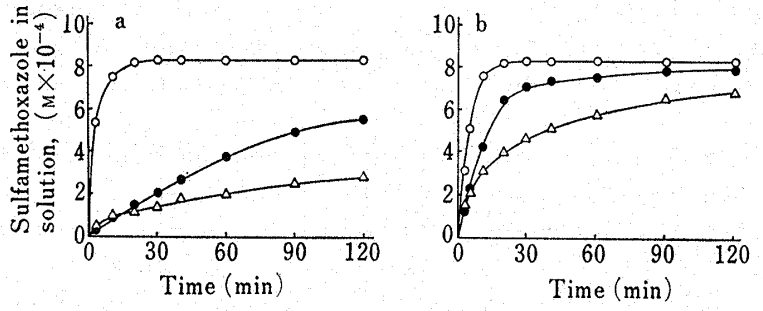

Fig. 3a. Dissolution Profiles of Sulfamethoxazole from Test Preparations containing 105 mg Sulfamethoxazole Equivalent in J.P.IX Disintegration Medium No. 1

Key: ○, sulfamethoxazole: PVP K-15=1:3 coprecipitate; △, 1:3 physical mixture; ●, sulfamethoxazole alone.
Each point represents the mean of three determinations.

Fig. 3b. Dissolution Profiles of Sulfamethoxazole from Test Preparations containing 105 mg Sulfamethoxazole Equivalent in J.P.IX Disintegration Medium No. 2

Key: Symbols are the same as in Fig. 3a.
Each point represents the mean of three determinations.

3. Urinary Excretion of Total SMZ

The mean urinary excretion rates of total SMZ in five human subjects are shown in Fig. 4. Excretion rates during the first 5.5 h differed significantly between preparations. Following the administration of SMZ alone, the maximum value of mean urinary excretion rate of total SMZ appeared in the 7—8 h period (among individuals, 6—12 h). In the case of the coprecipitate, the maximum value appeared in the 6—7 h period (among individuals, 4—7 h). Excretion rate at this maximum corresponded to almost 1.32 times the rate following the administration of SMZ alone in this period, and was 1.16 times as great as the maximum of SMZ alone. No significant difference was found between them after 7.5 h postadministration.

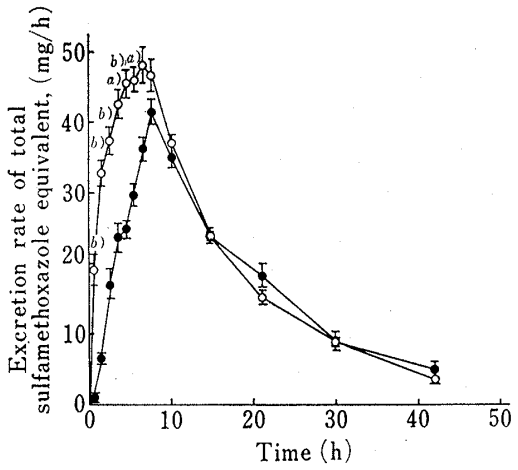

Fig. 4. Urinary Excretion Rate of Total Sulfamethoxazole following the Oral Administration of 1000 mg Sulfamethoxazole (●) and 4000 mg Coprecipitate (○)

Each point represents the mean ± S.E. of five subjects. Significant differences: *a*) $p < 0.05$; *b*) $p < 0.01$.

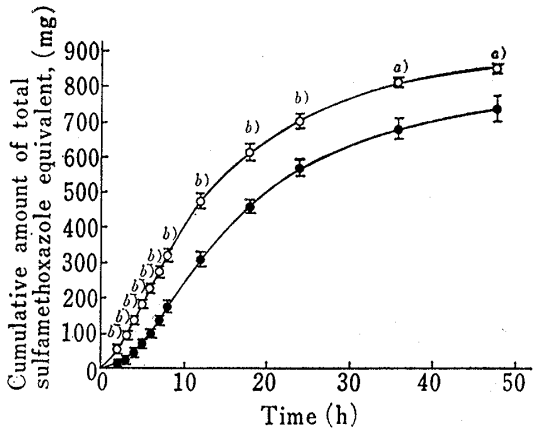

Fig. 5. Cumulative Urinary Excretion of Total Sulfamethoxazole following the Oral Administration of 1000 mg Sulfamethoxazole (●) and 4000 mg Coprecipitate (○)

Each point represents the mean ± S.E. of five subjects. Significant differences: *a*) $p < 0.05$; *b*) $p < 0.01$.

Figure 5 shows the mean cumulative amount of total SMZ excreted during 48 h following the administration of the two preparations. The mean recoveries of total SMZ in urine in 48 h following the administration of SMZ alone and the coprecipitate were 74.1% (range 57.7—83.5%) and 85.0% (range 82.7—88.8%) as SMZ equivalent, respectively. The difference was significant between them at all times. The intersubject variations of the cumulative amounts were considerably smaller when the coprecipitate was administered. The bioavailability of SMZ in the coprecipitate was considered to be 1.15 times greater than that of SMZ alone, up to 48 h.

The authours have already reported on the modification of the dissolution characteristics of sulfisoxazole (SI) by coprecipitation with PVP.[8] When SI–PVP coprecipitate was administered to subjects, the total SI excreted in urine was 1.06 times greater than that of SI alone. The difference was not statistically significant. The solubilituy of SI in distilled water, however, was lower (8.75×10^{-5} M) than that of SMZ. Thus, sulfonamides that have two pK_a values might show variable dissolution behavior in the gastrointestinal tract. Coprecipitation of the drug resulted in improvement of the dissolution behavior and gastrointestinal absorption of the drug irrespective of the pH of the dissolution media.

The present study showed that the improvement of the dissolution rate of SMZ brought about by coprecipitation with PVP resulted in increases in both rate and extent of bioavailability of SMZ and reduced the extent of variation in these parameters.

References and Notes

1) This study was presented at the 101st Annual Meeting of the Pharmaceutical Society of Japan, Kumamoto, April 1981.
2) *a*) W.L. Chiou and S. Riegelman, *J. Pharm. Sci.*, **60**, 1281 (1971); *b*) R. Kaur, D.J.W. Grant, and T. Eaves, *ibid.*, **69**, 1317 (1980).
3) K. Yamamoto, S. Matsuda, M. Nakano, T. Arita, and Y. Nakai, *Yakugaku Zasshi*, **97**, 367 (1977).
4) *a*) M. Mayersohn and M. Gibaldi, *J. Pharm. Sci.*, **55**, 1323 (1966); *b*) A.P. Simonelli, S.C. Mehta, and W.I. Higuchi, *ibid.*, **58**, 538 (1969); *c*) E.I. Stupak, H.A. Rosenberg, and T.R. Bates, *J. Pharmacokin. Biopharm.*, **2**, 511 (1974).
5) *a*) R.G. Stoll, T.R. Bates, K.A. Nieforth, J. Swarbrick, J. Ueda, and T. Nagai, *ibid.*, **26**, 2952 (1978).
7) J. Doluisio, D. Fedder, G. Manley, T. Mattei, C.H. Nightingale, and W. Barr, *J. Am. Pharm. Assoc.*, **NS13**, 278 (1973).
8) H. Sekikawa, M. Nakano, and T. Arita, *Yakugaku Zasshi*, **98**, 62 (1978).

9) *a*) H. Sekikawa, J. Fujiwara, T. Naganuma, M. Nakano, and T. Arita, *Chem. Pharm. Bull.*, **26**, 3033 (1978); *b*) H. Sekikawa, T. Naganuma, J. Fujiwara, M. Nakano, and T. Arita, *ibid.*, **27**, 31 (1979).
10) Y. Watanabe, M. Sano, K. Motohashi, Y. Takagi, and Y. Doi, *Yakugaku Zasshi*, **98**, 676 (1978).
11) H. Nishimura, K. Nakajima, S. Okamoto, N. Shimaoka, and K. Sasaki, *Shionogi Kenkyusho Nenpo*, **8**, 779 (1958).
12) M. Ueda and K. Kuribayashi, *Yakugaku Zasshi*, **84**, 1104 (1964).
13) T. Koizumi, T. Arita, and K. Kakemi, *Chem. Pharm. Bull.*, **12**, 413 (1964).
14) H. Sekikawa, M. Nakano, and T. Arita, *Chem. Pharm. Bull.*, **26**, 118 (1978).
15) H. Sekikawa, M. Nakano, and T. Arita, *Chem. Pharm. Bull.*, **27**, 1223 (1979).