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Dissolution Mechanisms of Drug-Polyvinylpyrrolidone Coprecipitates in Aqueous Solution

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Coprecipitates of sulfamethizole-polyvinylpyrrolidone (PVP) and sulfisoxazole-PVP were prepared at various ratios. The dissolution rates of the drugs in the coprecipitates were greater when the ratio of drug to PVP was smaller. The dissolution rate of sulfamethizole in the coprecipitate was greater when PVP of smaller molecular weight was used. Dissolution patterns were different for sulfamethizole-PVP coprecipitate and sulfisoxazole-PVP coprecipitate; recrystallization of the drug was observed following the dissolution of sulfisoxazole-PVP coprecipitate, whereas no recrystallization was found in the dissolution of sulfamethizole-PVP coprecipitate. A new dissolution model for coprecipitate is proposed.

Keywords——coprecipitates; polyvinylpyrrolidone; dissolution mechanism; sulfisoxazole; sulfamethizole; coacervation; recrystallization; dosage forms; crystallization inhibition; supersaturation

When a poorly water-soluble drug is administered orally, the rate of absorption is controlled by its dissolution rate in the gastrointestinal tract.[2] In recent years, many methods to modify the dissolution characteristics of poorly water-soluble drugs have been investigated to obtain better bioavailability.[3–6] Among them, coprecipitation of the drug with a water-soluble material such as polyvinylpyrrolidone (PVP)[7,8] or a bile acid[9] has been studied. The authors were successful in improving the dissolution characteristics of some poorly water-soluble drugs by coprecipitation with PVP,[8] and obtained better bioavailability of some drugs following administration of coprecipitates.

These reports demonstrated an increase in the dissolution rate of the drugs as a result of coprecipitation. However, no data are available to clarify the dissolution mechanism of the coprecipitates in detail. The authors therefore investigated the dissolution characteristics of some drug-PVP coprecipitates, and examined the dissolution mechanisms of the coprecipi-

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2) *a*) S.A. Kaplan, in "Dosage Form Design and Bioavailability," J. Swarbrick, Ed., Lea and Febiger, Philadelphia, Pa, 1973, p. 20; *b*) J. Doluisio, D. Fedder, G. Manley, T. Mattei, C.H. Nightingale, and W. Barr, *J. Am. Pharm. Assoc.*, **NS13**, 278 (1973).

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6) *a*) W.L. Chiou and S. Riegelman, *J. Pharm. Sci.*, **58**, 1505 (1969); *b*) W.L. Chiou, *ibid.*, **66**, 989 (1977).

7) *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*) *Idem*, *ibid.*, **65**, 355 (1976); *d*) O.I. Corrigan and R.F. Timoney, *J. Pharm. Pharmacol.*, **27**, 759 (1975).

8) *a*) H. Sekikawa, M. Nakano, and T. Arita, *Yakugaku Zasshi*, **98**, 62 (1978); *b*) H. Sekikawa, J. Fujiwara, T. Naganuma, M. Nakano, and T. Arita, *Chem. Pharm. Bull.* (Tokyo), **26**, 3033 (1978); *c*) H. Sekikawa, T. Naganuma, J. Fujiwara, M. Nakano, and T. Arita, *ibid.*, **27**, 31 (1979).

9) *a*) R.G. Stoll, T.R. Bates, K.A. Nieforth, and J. Swarbrick, *J. Pharm. Sci.*, **58**, 1457 (1969); *b*) R.G. Stoll, T.R. Bates, and J. Swarbrick, *ibid.*, **62**, 65 (1973); *c*) R.K. Reddy, S.A. Khalil, and M.W. Gouda, *ibid.*, **65**, 1753 (1976).

tates in water. The authors earlier reported the mechanisms of drug coprecipitation with PVP in ethanol.[10] As PVP in the solution inhibits the crystallization of the drug during the process of removing the solvent from the drug-PVP mixture solution, the drug may be present in a non-crystalline form in the PVP matrix. The inhibitory effect of PVP on the crystallization of the drug was correlated with the intensity of the interaction between the drug and PVP. Crystallization of sulfamethizole was inhibited by PVP more strongly than that of sulfisoxazole in ethanolic solution. Dissolution characteristics of these sulfamethizole-PVP coprecipitates and sulfisoxazole-PVP coprecipitates were investigated and compared in the present study.

Experimental

Materials——Sulfisoxazole and sulfamethizole (both of J.P.IX grade) were obtained from Yamanouchi Pharmaceutical Co., Tokyo (Thiasin, lot FLF7) and Eisai Co., Tokyo (Urocydal, lot XC14GG), respectively. The mean particle sizes of sulfisoxazole and sulfamethizole, as measured by optical microscopy, were 81.8 μm and 111.9 μm (Green's diameter), respectively. PVP K-15, K-30 and K-90 (respective average molecular weights of 10000, 40000 and 360000) were obtained from Daiichi Pure Chemicals Co., Tokyo. All other chemicals were of reagent grade.

Preparation of the Drug-PVP Coprecipitates——Drug-PVP coprecipitates were prepared by the method reported in the previous papers.[8]

Dissolution Studies——Dissolution profiles of the drugs from the preparations in 300 ml of distilled water were measured at 37.0±0.1° in a constant-temperature water bath (Thermounit type HM, Taiyo Kagaku Kogyo Co.). The beaker had 500 ml capacity and 85 mm diameter. A stainless steel three-bladed propeller (40 mm in diameter and about 2 cm^2 area for each blade) was placed in the beaker at a depth of 30 mm from the bottom, and was rotated using a stirrer (MS-Stirrer, Tokyo Rikakikai Co.) at 60 rpm. The rate of rotation was checked occasionally using a hand tachometer (Teclock Co.). Each preparation was added directly to the dissolution medium. Suitable aliquots were removed at the specified times with a syringe, then filtered quickly through a membrane filter (TM-4, pore size 0.2 μm, Toyo Scientific Co.). The same volume of distilled water was added to the beaker. Sample solutions were diluted with 0.1 N NaOH prior to assay for sulfisoxazole at 255 nm, and with 0.1 N HCl prior to assay for sulfamethizole at 268 nm using a Hitachi 200-20 spectrophotometer. No significant absorbance was found for PVP over the wavelength range used for the drug analysis.

Crystallization Studies——Studies of the effect of PVP on the crystallization of the drugs were carried out using the apparatus reported in the previous paper.[10] After saturation of the drug in distilled water at 50°, the temperature was lowered at the rate of 12°/hr. About 0.1 gram of the drug was seeded into the saturated solution to induce immediate crystallization when PVP did not affect the crystallization of the drug. The volume of the solution was about 100 ml. A Teflon magnetic stirring bar (13 mm long) was used for agitation of the solution (240 rpm). At appropriate times, samples of about 2 ml were removed from the suspension with a syringe, then filtered through the membrane filter and assayed for the drugs by the procedures described above.

Observation of the Dissolution Process of the Coprecipitates by Optical Microscopy——An Olympus type BH optical microscope was used for observation of the dissolution process of the coprecipitates or physical mixtures.

Results and Discussion

Dissolution Rates of the Drug from the Coprecipitates at Various Drug-to-PVP Weight Ratios

Figure 1 shows the dissolution profiles of the sulfamethizole-PVP coprecipitates at various drug-to-PVP weight ratios, as a physical mixture and that of sulfamethizole alone.

The amount of the preparation used was 81.5 mg of sulfamethizole equivalent. This amount corresponded to about 1/3 of the solubility (3.02×10^{-3} M). The coprecipitates exhibited faster drug dissolution rates than sulfamethizole alone or the physical mixture. The dissolution rate of sulfamethizole in the coprecipitate was greater when the ratio of drug to PVP was smaller. The initial dissolution rate of sulfamethizole in the physical mixture was larger than that of sulfamethizole alone. This may be explained in terms of the dispersion

10) H. Sekikawa, M. Nakano, and T. Arita, *Chem. Pharm. Bull.* (Tokyo), **26**, 118 (1978).

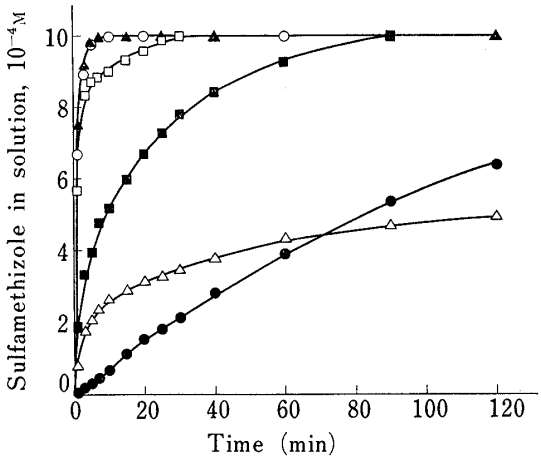


Fig. 1. Dissolution Profiles of Sulfamethizole from Six Test Preparations containing 81.5 mg of the Drug

Key: Sulfamethizole: PVP K-15 in the coprecipitates, ▲, 1:5; ○, 1:4; □, 1:3; ■, 1:2; △, 1:5 physical mixture; ●, drug alone.
Each point represents the mean of three determinations.

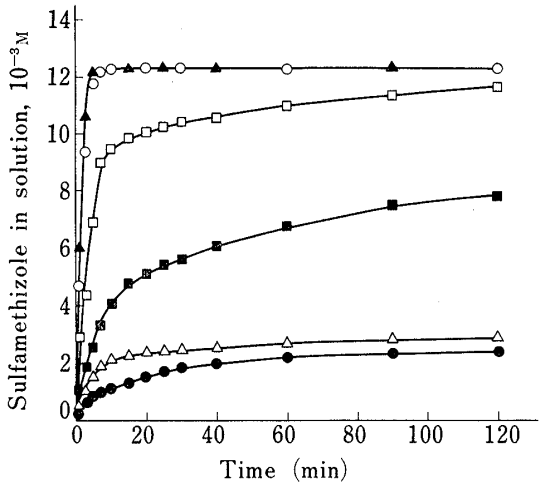


Fig. 2. Dissolution Profiles of Sulfamethizole from Six Test Preparations at 37° using Larger Amounts of the Preparations (1 g of the drug)

The symbols are the same as in Fig. 1.
Each point represents the mean of three determinations.

effect of additives[11] and by a possible lowering of the surface tension of the medium by PVP, resulting in better wetting of the sulfamethizole crystal surface. The lower dissolution rate in the physical mixture observed in the later stages may be due to the greater viscosity of the solution around the crystals.

The dissolution patterns of the drug from the coprecipitates at various drug-to-PVP weight ratios were similar to those of sulfisoxazole-PVP coprecipitates[8a] or other drug-PVP coprecipitates.[8b,c]

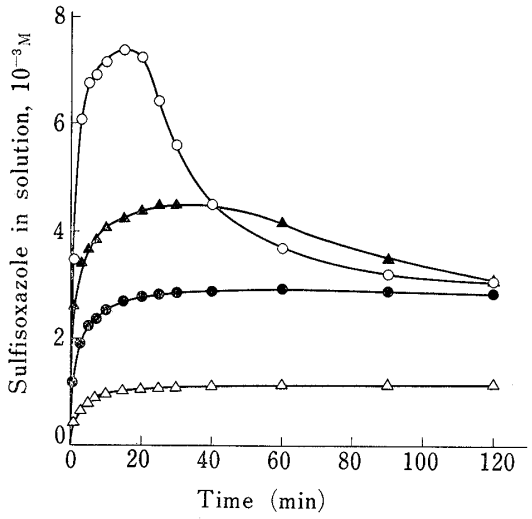


Fig. 3. Dissolution Profiles of Sulfisoxazole from 1:4 Sulfisoxazole-PVP K-15 Coprecipitates with 3.5 g (○), 1.75 g (▲), 1.05 g (●) and 0.35 g (△) of the Coprecipitates

These amounts correspond to about 10, 5, 3 and 1 times the normal sulfisoxazole solubility, respectively.
Each point represents the mean of three determinations.

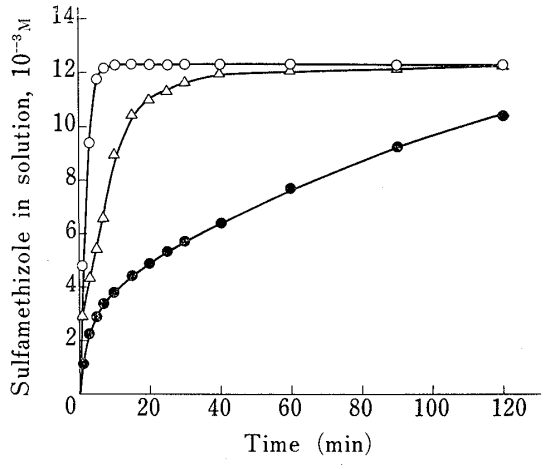


Fig. 4. Dissolution Profiles of Sulfamethizole from 1:4 Sulfamethizole-PVP Coprecipitates prepared with PVP of Different Molecular Weights

Key: ○, K-15 (mol.wt. 10000); △, K-30 (mol.wt. 40000); ●, K-90 (mol.wt. 360000)
Each point represents the mean of three determinations.

11) N. Shah, R. Pytelwski, H. Eisen, and I. Jarowski, *J. Pharm. Sci.*, **63**, 339 (1974).

Figure 2 shows the dissolution characteristics of sulfamethizole-PVP coprecipitates at various drug-to-PVP weight ratios when larger amounts of the preparations (1 gram of sulfamethizole equivalent) were subjected to dissolution.

The amount of the drug corresponded to almost 4 times the solubility. The coprecipitates again exhibited faster drug dissolution rates than sulfamethizole alone or the physical mixture. Furthermore, the dissolution rate of the drug in the coprecipitate was greater when the ratio of drug to PVP was smaller. Coprecipitates of 1: 4 and 1: 5 weight ratios dissolved completely within 10 min. The concentration following the dissolution of these coprecipitates exceeded the solubility of sulfamethizole in this medium, indicating supersaturation. This supersaturated solution was stable, and recrystallization did not occur under the experimental conditions used.

Sulfisoxazole-PVP coprecipitates, however, showed dissolution patterns (Fig. 3) different from those of sulfamethizole-PVP coprecipitates.

Figure 3 shows plots following the dissolution of 1: 4 sulfisoxazole-PVP coprecipitates containing about 1, 3, 5 and 10 times the solubility limit of sulfisoxazole. During the dissolution of the preparations containing 3, 5 and 10 times the solubility of the drug, the concentration of the drug exceeded its normal solubility within a few minutes, peaked, and then decreased gradually. This indicates recrystallization of the drug. Even so, the supersaturated condition was maintained for a long period.

Dissolution Rates of the Drug from Coprecipitates with PVP of Various Molecular Weights

Figure 4 shows the dissolution profiles of sulfamethizole in coprecipitates with PVP of various molecular weights at a 1: 4 weight ratio of sulfamethizole-PVP.

The dissolution rate of the drug from the coprecipitate in PVP of lower molecular weight was greater, *i.e.*, K-15>K-30>K-90. This tendency was similar to those of sulfisoxazole-PVP coprecipitates[8a] or phenytoin-PVP coprecipitates.[8b]

Crystallization Studies

To investigate the supersaturation of the solution following the dissolution of drug-PVP coprecipitates, the effect of PVP on the crystallization of sulfisoxazole and sulfamethizole in aqueous solutions was investigated.

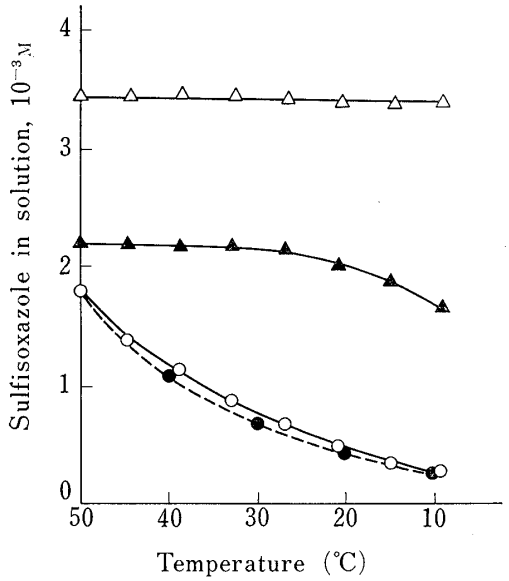


Fig. 5. Effect of PVP K-15 Concentration on the Crystallization of Sulfisoxazole in Aqueous Solution

Key: —△—, 3%; —▲—, 1%; —○—, none; ···●···, solubility.

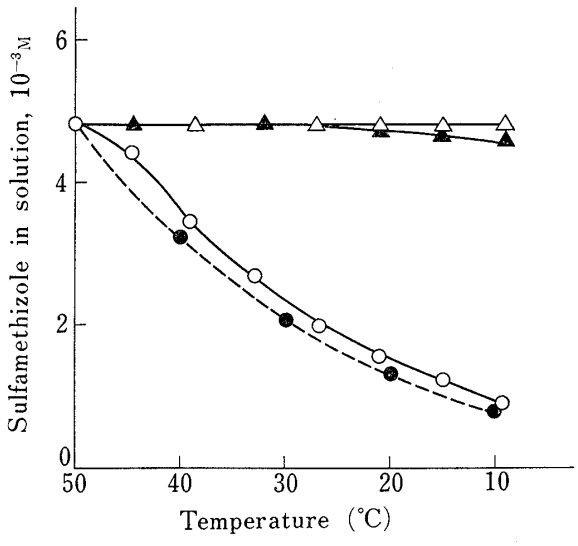


Fig. 6. Effect of PVP K-15 Concentration on the Crystallization of Sulfamethizole in Aqueous Solution

Key: —△—, 0.05%; —▲—, 0.005%; —○—, none; ···●···, solubility.

PVP has been shown to inhibit or retard the crystallization of some drugs in ethanolic solution.[10]

Figure 5 shows the effect of PVP on the crystallization of sulfisoxazole. After saturation with the drug at 50°, the temperature of the solution was lowered. If additives do not affect the crystallization of the drug, the concentration of the drug should decrease on lowering the temperature of the solution. Crystallization of sulfisoxazole was not inhibited by 1% PVP, though it was retarded, whereas it was inhibited by 3% PVP under the experimental conditions used.

Figure 6 shows that PVP inhibited the crystallization of sulfamethizole at a very low concentration (0.05%). The effect of PVP on crystallization was thus greater in sulfamethizole than in sulfisoxazole. This tendency was similar to that in ethanolic solution.[10]

Observation of the Dissolution Process of the Drug from the Coprecipitates by Optical Microscopy

Figure 7 shows photomicrographs following the dissolution of the 1: 4 sulfisoxazole-PVP coprecipitate in distilled water.

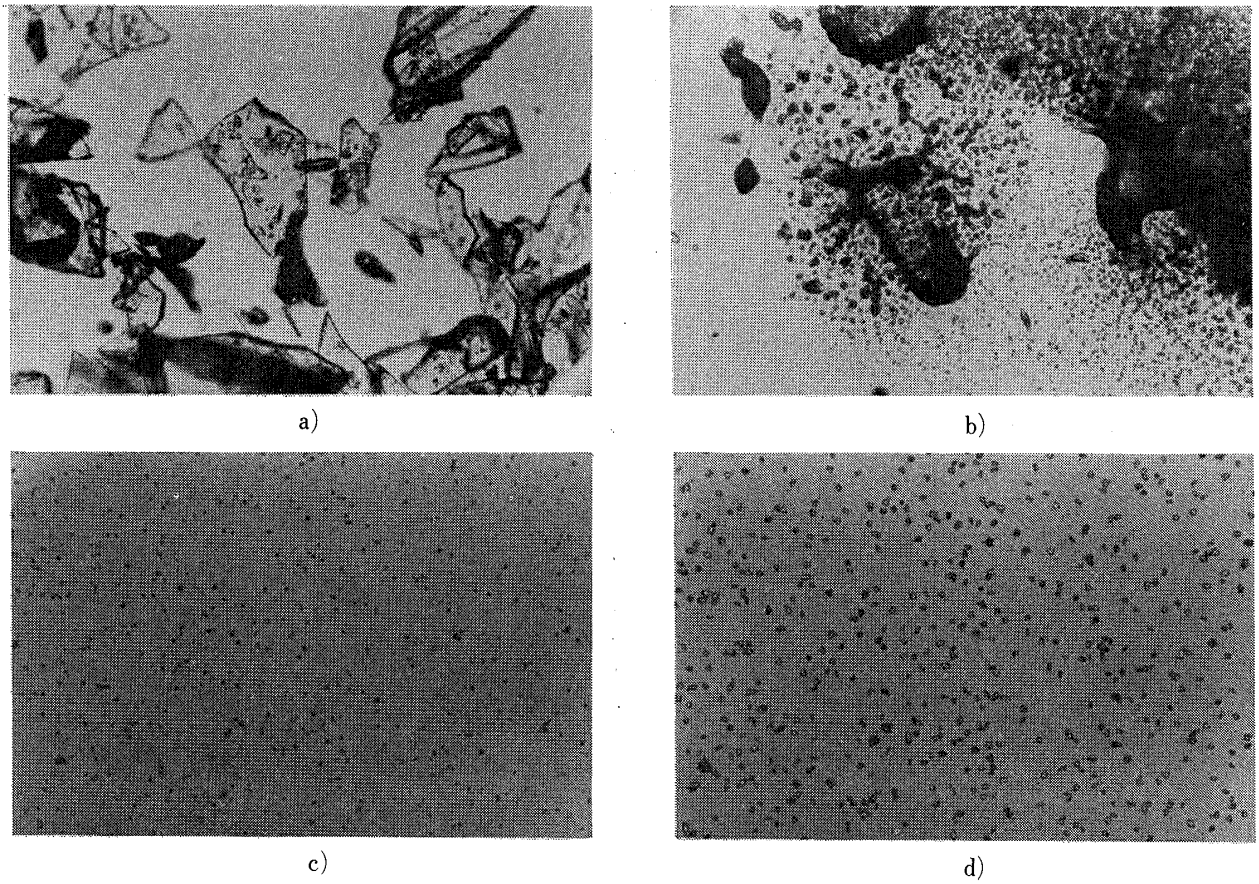
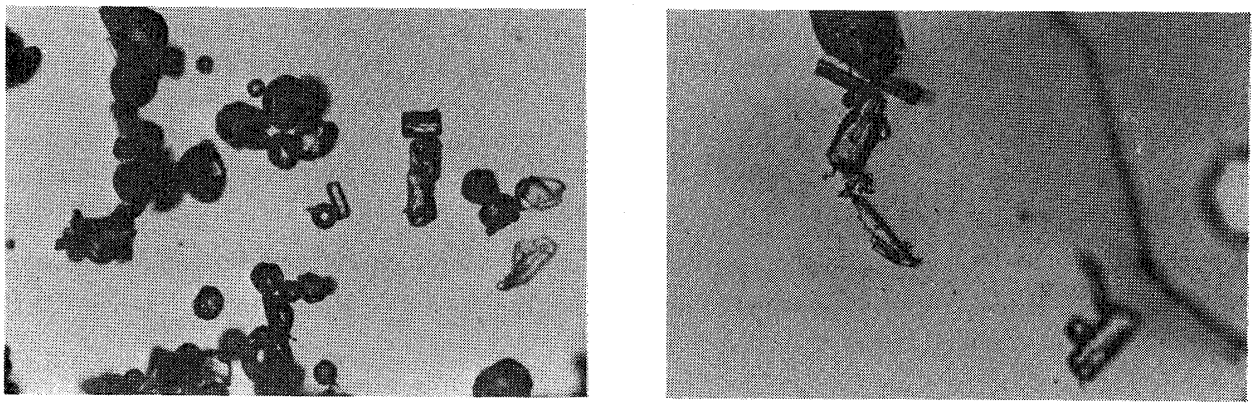


Fig. 7. Photomicrographs of the Dissolution Process of 1:4 Sulfisoxazole-PVP K-15 Coprecipitate

Key: a) the coprecipitate prior to dissolution,
b) at 2 min after the addition of water, micro-coacervate droplets are observed in the vicinity of the coprecipitate,
c) at 10 min, crystalline sulfisoxazole starts to appear,
d) at 30 min, the size of the crystals has increased.

In photomicrographs, micro-coacervate droplets were observed. These micro-coacervate droplets disappeared upon addition of a further amount of water. No crystalline sulfisoxazole was seen in the pictures. At 10 min, fine sulfisoxazole crystals were found in the solution. Subsequently, crystal growth was observed.

Figure 8 shows photomicrographs following the dissolution of 1:4 sulfisoxazole-PVP physical mixture in distilled water. After PVP in the physical mixture had dissolved, crystalline sulfisoxazole still remained in the system.

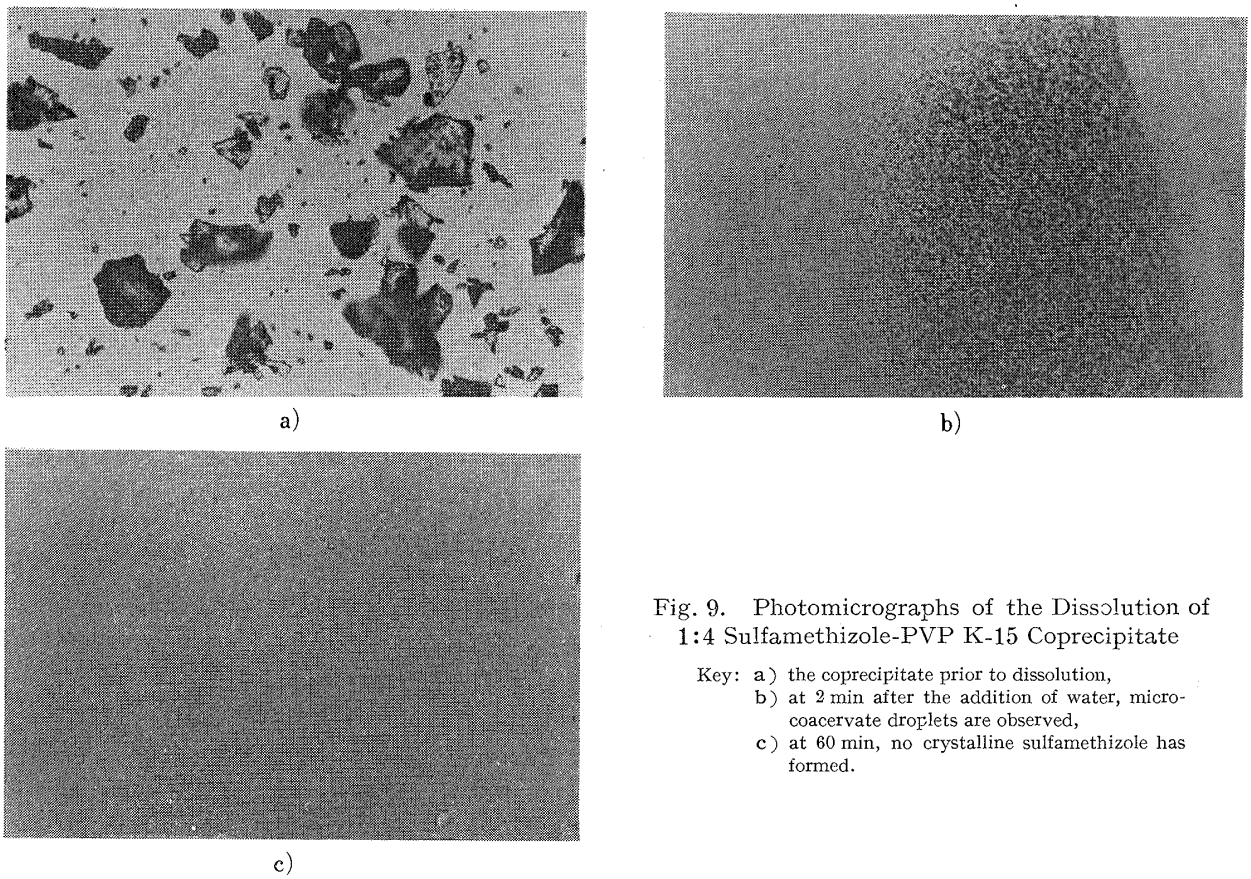


a) b)

Fig. 8. Photomicrographs of the Dissolution Process of 1:4 Sulfisoxazole-PVP K-15 Physical Mixture

Key: a) the physical mixture prior to dissolution
b) at 5 min after the addition of water, crystalline sulfisoxazole still remains.

Figure 9 shows photomicrographs following the dissolution of the 1:4 sulfamethizole-PVP coprecipitate. Micro-coacervate droplets were observed, but no crystalline sulfamethizole appeared even after 60 min.



a) b)

c)

Fig. 9. Photomicrographs of the Dissolution of 1:4 Sulfamethizole-PVP K-15 Coprecipitate

Key: a) the coprecipitate prior to dissolution,
b) at 2 min after the addition of water, micro-coacervate droplets are observed,
c) at 60 min, no crystalline sulfamethizole has formed.

General Consideration of the Dissolution Mechanisms of Drug-PVP Coprecipitates

The dissolution mechanism of drug-PVP coprecipitates has been postulated to involve the release of finely dispersed drug in the PVP matrix into the aqueous medium with highly water-soluble PVP molecules.[7b] The theory does not, however, explain the dissolution patterns of the drug from coprecipitates of different drug-to-PVP weight ratios, or the supersaturation of the solution. The authors now propose a new dissolution model for the dissolution of drug-PVP coprecipitates. The proposed process is illustrated in Fig. 10.

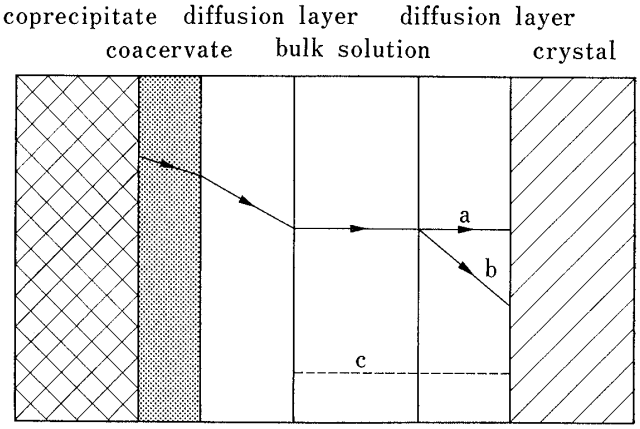


Fig. 10. A Model for the Dissolution and Recrystallization of the Drug from the Coprecipitate

Key: a, no recrystallization; b, slow recrystallization c, solubility.

It may be considered that the drug in the coprecipitate is not crystalline, since PVP inhibits the crystallization of the drug during evaporation of the solvent from a drug-PVP solution.[10] When the coprecipitate is added to an aqueous medium, both non-crystalline drug and water-soluble PVP dissolve in the medium. Since PVP is coacervated by the addition of some electrolytes or aromatic compounds,[12] in the vicinity of the coprecipitate, high concentrations of both drug and PVP result in coacervated PVP droplets. The formation of coacervated droplets of PVP is reversible, *i.e.*, coacervated droplets disappear when the drug concentration or PVP concentration decreases. If the ratio of drug to PVP is larger, coacervated droplets do not disappear immediately, but remain until the drug concentration is sufficiently lowered. Consequently, the dissolution rate of the drug in the coprecipitate is smaller when the ratio of drug to PVP is greater (Fig. 1 and 2).

When coprecipitates prepared from PVP of different molecular weights are compared, the coprecipitate prepared from PVP of smaller molecular weight dissolved faster (Fig. 4). Viscosity effects of the dissolved polymer may be one of the factors that influence the dissolution rate of the drug, but coacervation may still be the major factor. PVP of larger molecular weight has been shown to be coacervated by the addition of smaller amounts of electrolytes[12] or aromatic compounds.[12,13] When coprecipitates containing the same drug-to-PVP ratio are added to aqueous media, coacervated droplets of PVP in the neighborhood of the coprecipitate tend to disappear if PVP of smaller molecular weight is used. Dissolution studies using PVP K-15, K-30 and K-90 for the preparation of coprecipitates provided support for this view.

Drug and PVP released from the coacervated droplets diffuse towards the bulk solution through the diffusion layer. The drug concentration in the bulk solution is thus gradually increased, then exceeds the solubility, *i.e.*, it supersaturates. Recrystallization of the drug from the supersaturated solution then begins to take place. This recrystallization process differs among different drugs.

In sulfisoxazole-PVP coprecipitates, PVP in the solution inhibits or retards the crystallization of the drug. When the rate of recrystallization is only retarded, the appearance of a peak in the dissolution curve results following the dissolution of the preparation, that is,

12) H. Sekikawa, R. Hori, T. Arita, K. Ito, and M. Nakano, *Chem. Pharm. Bull.* (Tokyo), **26**, 2489 (1978).
13) H. Sekikawa, K. Hanada, R. Hori, and T. Arita, 92nd Annual Meeting of the Pharmaceutical Society of Japan, Osaka, April 1972.

the apparent dissolution curve represents the difference of the rate of dissolution and the rate of recrystallization. When the rate of dissolution is greater than the rate of recrystallization, an upward curve is obtained. At the peak, the rates of dissolution and recrystallization are considered to be equal. After the peak, the rate of recrystallization exceeds the rate of dissolution. PVP in the solution, however, retains the supersaturated condition for a long period (Fig. 3).

In sulfamethizole-PVP coprecipitates, PVP in the solution strongly inhibits the recrystallization of sulfamethizole. The supersaturated solution is stable and no peak was observed in the dissolution curve (Fig. 2).

The preparation of a water-soluble salt of a poorly water-soluble drug is one of the methods used to increase the dissolution rate. Some drugs, however, are considered to be recrystallized in the gastrointestinal tract following oral administration of the salts. Coprecipitates of poorly water-soluble drugs with PVP are expected to provide a better bioavailability because they exhibit greater dissolution rates of the drugs and dissolved drugs are often kept in a supersaturated state in the presence of PVP for a long period.

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