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Inhibitory Effect of Polyvinylpyrrolidone on the Crystallization of Drugs[1]

Hitoshi Sekikawa, Masahiro Nakano, and Takaichi Arita

Faculty of Pharmaceutical Sciences, Hokkaido University[2]

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In order to clarify the mechanism of coprecipitation of the drug with polyvinylpyrrolidone (PVP), the temperature of absolute ethanol solution saturated with various drugs, was lowered at a constant rate from 50° to 10°, and the inhibitory effect of PVP on the crystallization of drugs was examined. The interaction of these drugs with PVP in absolute ethanol was also investigated and compared with the effect of PVP on the crystallization of drugs. The crystallization of sulfamethizole and sulfisoxazole which interacted strongly with PVP were strongly inhibited and/or retarded over the temperature range studied. PVP retarded, but did not inhibit the crystallization of sulfamerazine. Crystallization of caffeine and nalidixic acid, which interacted poorly with PVP, was not affected by PVP. N-Vinyl-2-pyrrolidone, the monomer unit of PVP molecule, did not affect the crystallization of sulfisoxazole. PVP K-30 showed the strongest effect among K-15, K-30 and K-90. Polyethylene glycol and polysorbate 80 did not affect the crystallization of sulfisoxazole. Sulfamethizole and sulfisoxazole formed coprecipitates with PVP, whereas caffeine and nalidixic acid did not form coprecipitates with PVP. Sulfamerazine on the other hand did not form well-defined coprecipitate with equal weight ratio of PVP. The mechanism of coprecipitation of drug with PVP may be the inhibition of crystallization of drug by PVP, when the solution containing both drug and PVP is evaporated. The drug loses its crystal structure in PVP matrix. Coprecipitation does not occur when PVP does not inhibit the crystallization of drug.

Keywords——polyvinylpyrrolidone; crystallization inhibition; sulfonamides; caffeine; nalidixic acid; coprecipitate; interaction

In recent years, numerous methods to modify the dissolution characteristics of poorly water-soluble drugs were investigated to obtain better bioavailability.[3–6] Among them, coprecipitation of drugs with a water-soluble polymer such as polyvinylpyrrolidone (PVP) has been examined.[7–11] Coprecipitates may be defined as follows. Following the dissolution of a drug and PVP in an organic solvent such as ethanol or chloroform, the solvent is evaporated *in vacuo*. Among the products left after evaporation of the solvent *in vacuo* from the solution of a drug and PVP, the drug-PVP mixture where crystal structure of the drug is lost in PVP matrix may be called the coprecipitate. No report is available as to which drugs form coprecipitates with PVP and what ratio of drugs to PVP is required to form well-defined coprecipitates.

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3) A.H. Goldberg, M. Gibaldi, and J.L. Kaning, *J. Pharm. Sci.*, **54**, 1145 (1965).
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It has been suggested that PVP may influence the crystallization of drug from the solution.[12,13] The inhibitory effect of PVP on the crystallization of several drugs has been studied to clarify the mechanism of coprecipitation of drug with PVP.

The solution saturated with drug at constant temperature becomes supersaturated by lowering temperature. As the drug in solution reaches the surface of the crystal of the drug through the diffusion layer, crystal growth proceeds, and the concentration of the drug in the solution falls. The extent of crystallization of the drug can be known by the determination of the concentration of the drug in solution. The interaction between these drugs and PVP was studied, and compared with the inhibitory effect of PVP on the crystallization of drugs.

Experimental

Materials——PVP K-15, K-30 and K-90 were obtained from Daiichi Pure Chemicals Co., Tokyo. N-Vinyl-2-pyrrolidone (Wako Pure Chemical Ind.) was used as the monomer unit of PVP molecule. Polyethylene glycol 400 (Koso Chemical Co.), 6000 (Nakarai Chemicals Co.) and 20000 and polysorbate 80 (both from Wako Pure Chemical Ind.) were also used. Sulfisoxazole (Yamanouchi Pharmaceutical Co.), sulfamethizole (Eisai Co.), nalidixic acid (Daiichi Seiyaku Co.) and caffeine (Sanko Seiyaku Kogyo Co.) were of J.P. IX. grade. Sulfamerazine was obtained from sodium sulfamerazine (Tanabe Seiyaku Co.) by addition of hydrochloric acid solution, and recrystallized from ethanol. (mp 235°). Absolute ethanol was obtained by dehydration and distillation of ethanol following the conventional procedures.

Apparatus for Crystallization Studies——The crystallization studies were carried out in 100 ml water-jacketted beaker (50 mm in diameter) controlled by water from the thermobath (Haake Model KT 33) connected to the programmer (Haake Model TP 32 and Model PG 11) to lower temperature of the bath at a constant rate. After saturation of absolute ethanol with the drug at 50°, the temperature was lowered. The lowering speed of the temperature was 12°/hr. About 0.1 g of the drug was seeded into the saturated solution to induce an immediate crystallization, when PVP did not affect the crystallization. The volume of the solution was about 100 ml. To study the effect of stirring speed on the crystallization, a stainless steel three-braded propeller (40 mm in diameter) was employed at a depth of 20 mm from the bottom. A Teflon magnetic stirring bar (13 mm long) was also used. At appropriate time intervals, 2 ml samples were removed from the suspension with a pipette equipped with cotton filter. Samples were diluted with ethanol prior to assay for sulfisoxazole at 269 nm, sulfamethizole at 284 nm, sulfamerazine at 270 nm, nalidixic acid at 258 nm and caffeine at 273 nm using a Hitachi Type 200-20 spectrophotometer. No significant absorbance was found for PVP over the wavelength range used for the drug analysis.

Solubility Determinations——To study the interaction between drugs and PVP, equilibrium solubility of drugs in absolute ethanol and 5.0% (w/v) PVP K-15 solution in absolute ethanol, were determined at 10.0°, 20.0°, 30.0°, 40.0° and 50.0°. After equilibrium, sample solutions were removed by a syringe, and filtered through the membrane filter (Sartorius Membrane Filter SM 11607, pore size 0.2 μ) quickly. The samples were assayed as described above.

X-Ray Diffraction Patterns——X-Ray powder diffraction patterns were obtained with a Rigaku Denki D-9C X-Ray Diffractometer.

Results and Discussion

Formation of Coprecipitates

Coprecipitates of drugs with PVP were attempted to be prepared by conventional method. As shown in Fig. 1, X-ray diffraction patterns of the products revealed that coprecipitates were not necessarily formed in all cases. Sulfisoxazole formed coprecipitate with 3 times as much PVP, and lost its crystal structure in it. However, when the weight ratio of sulfisoxazole to PVP was 10: 1, sulfisoxazole crystal peak still remained in the X-ray diffraction pattern. In this case, well-defined coprecipitate was not formed. In the case of the product of nalidixic acid with 5 times as much PVP, its crystal peak still remained. Nalidixic acid did not form coprecipitate with PVP under the present experimental conditions.

12) M.A. Moustafa, A.R. Ebian, S.A. Khalil, and M.M. Motawi, *J. Pharm. Sci.*, **64**, 1485 (1975).
13) A.P. Simonelli, S.C. Mehta, and W.I. Higuchi, *J. Pharm. Sci.*, **59**, 633 (1970).

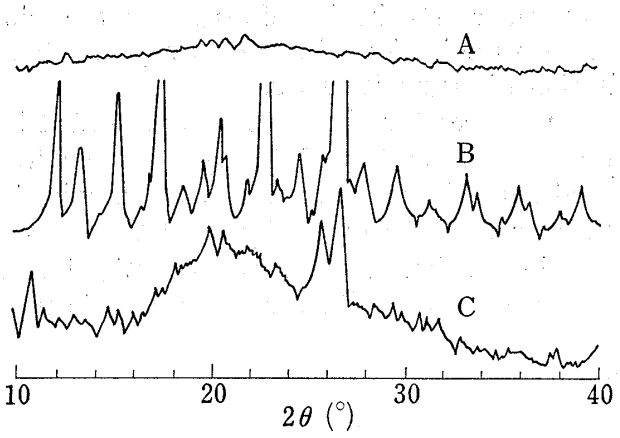

Fig. 1. Comparison of X-Ray Diffraction Spectra for Preparations Obtained from Ethanol Solutions of Drugs and PVP

A, sulfisoxazole: PVP=1:3.
B, sulfisoxazole: PVP=10:1.
C, nalidixic acid: PVP=1:5.

As the coprecipitates were not always formed, other drugs were examined. With equal weight ratio of drug to PVP, sulfamethizole and sulfisoxazole formed coprecipitates with PVP. Sulfamerazine, nalidixic acid and caffeine, however, did not form well-defined coprecipitates with PVP.

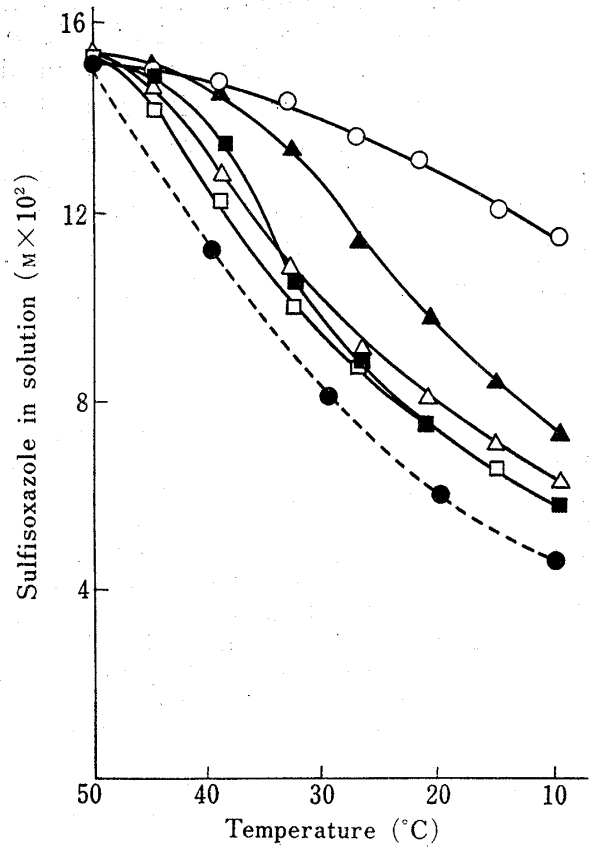

Fig. 2. Effect of Stirring Speed on the Crystallization of Sulfisoxazole in Ethanol

—○—, no stirring; —▲—, 60 rpm, propeller; —△—, 120 rpm, propeller; —□—, 240 rpm, propeller —■—, 240 rpm, stirring bar; ---●---, solubility.

Crystallization of Drugs

1. Effect of Stirring Speed on the Crystallization of the Drugs——The solution saturated with a drug at a certain temperature precipitates the crystal of drug, when the temperature of the solution is lowered. In this process, drug molecule in the supersaturated solution moves through the diffusion layer to the crystal surface, and crystal growth occurs. As this process is opposite of the dissolution process, crystallization may be accelerated by stirring the solution to make the diffusion layer thin.[12,14] Different stirring conditions were studied to know the effect of stirring on the crystallization of the drug.

Fig. 2 shows the effect of stirring speed on the crystallization of sulfisoxazole. The dotted line in the Fig. 2 indicates the solubility of sulfisoxazole in absolute ethanol at each temperature. As the temperature of the solution saturated with sulfisoxazole at 50° was lowered, the concentration of sulfisoxazole in the solution decreased, indicating that the crystallization had taken place. Without stirring, the rate of decrease in concentration was small, indicating that crystallization does not proceed in parallel with the lowering temperature. In the case of using a propeller, rate of crystallization of sulfisoxazole increased with rate of revolutions, and amount in solution approached the equilibrium solubility curve. The difference in rate of crystallization became smaller above 120 rpm. Use of a stirring bar at 240 rpm proved that there was little difference between the stirring bar and the propeller. Owing to the use of absolute ethanol, it was not suitable to use the propeller, because absolute ethanol absorbs water in the air, and/or vaporized and thereby change in the solubility of the drug may be caused. Though rates of crystallization were different among drugs used, stirring bar was used in these studies at 240 rpm. In addition, vinyl membrane (Saran

14) S.C. Mehta, P.D. Bernardo, W.I. Higuchi, and A.P. Simonelli, *J. Pharm. Sci.*, **59**, 638 (1970).

Wrap, Asahi-Dow Co.) covered the water-jacketted beaker to prevent absorption of water in the air, vaporization, and variation of the temperature at the surface of the solution.

2. **Effects of PVP Concentration on the Crystallization of Drugs**——Effects of PVP on the crystallization of five drugs were studied in absolute ethanol solution.

a. Sulfisoxazole: Fig. 3 shows the effect of PVP K-15 on the crystallization of sulfisoxazole. In the absence of PVP, the crystallization proceeded with lowering temperature. However, the crystallization was inhibited and/or retarded when PVP was present. The higher the PVP concentration was, the stronger the effect was. In spite of the seeding of the crystal of sulfisoxazole, crystallization did not proceed in the presence of PVP. The lower concentration, 0.001% (w/v) PVP inhibited the crystallization from 50° to 39°, 0.01% (w/v), to 34°, and crystallization speeds were not so fast as without PVP. 0.1% (w/v) PVP inhibited the crystallization of sulfisoxazole completely within this experimental temperature range. Supersaturated sulfisoxazole was apparently stable.

b. Sulfamethizole: PVP K-15 inhibited and/or retarded the crystallization of sulfamethizole in the same way as in sulfisoxazole (Fig. 4). The effect of PVP became stronger with PVP concentration, that is, higher concentration of PVP kept larger supersaturation ratio. The crystallization of sulfamethizole was completely inhibited by 0.01% (w/v) PVP within this experimental temperature range. This effect of PVP on sulfamethizole was stronger than that on sulfisoxazole. In the case of sulfisoxazole and sulfamethizole, the crystallization began sharply at 0.001% PVP. The solutions were clouded with very small crystals. The drug in the supersaturated solution, therefore, is not likely to deposit on the crystals seeded previously.

c. Sulfamerazine: The effect of PVP K-15 on the crystallization of sulfamerazine was

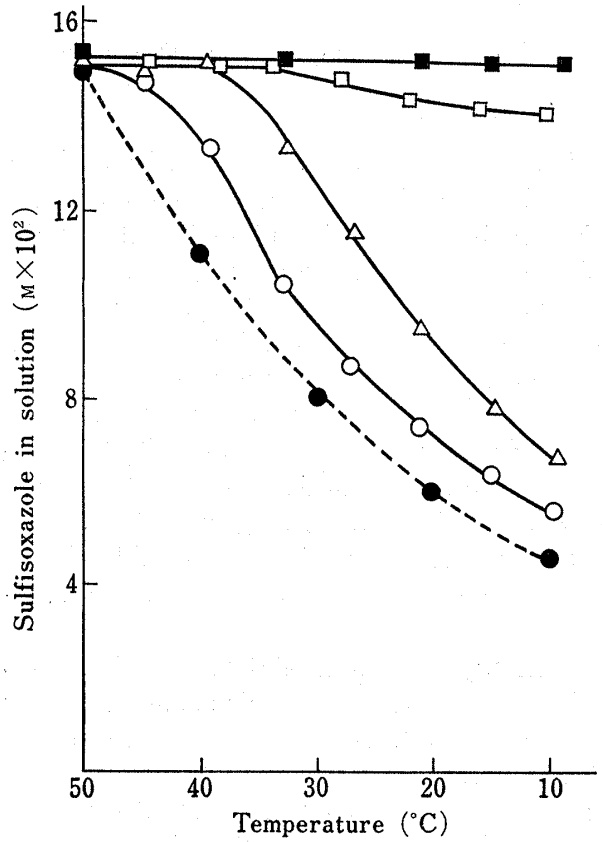

Fig. 3. Effect of PVP K-15 Concentrations on the Crystallization of Sulfisoxazole

—■—, 0.1%; —□—, 0.01%; —△—, 0.001%; —○—, none; ---●---, solubility.

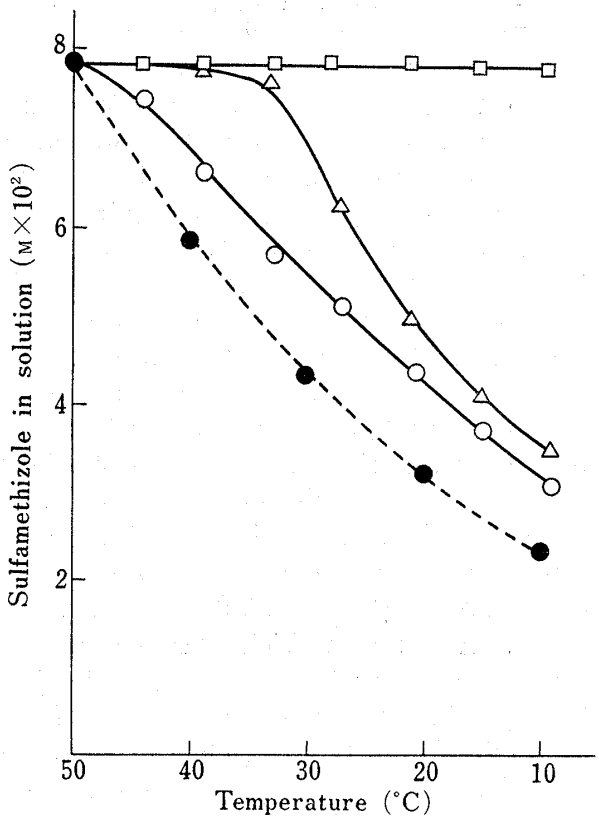

Fig. 4. Effect of PVP K-15 Concentrations on the Crystallization of Sulfamethizole

—□—, 0.01%; —△—, 0.001%; —○—, none· ---●---, solubility.

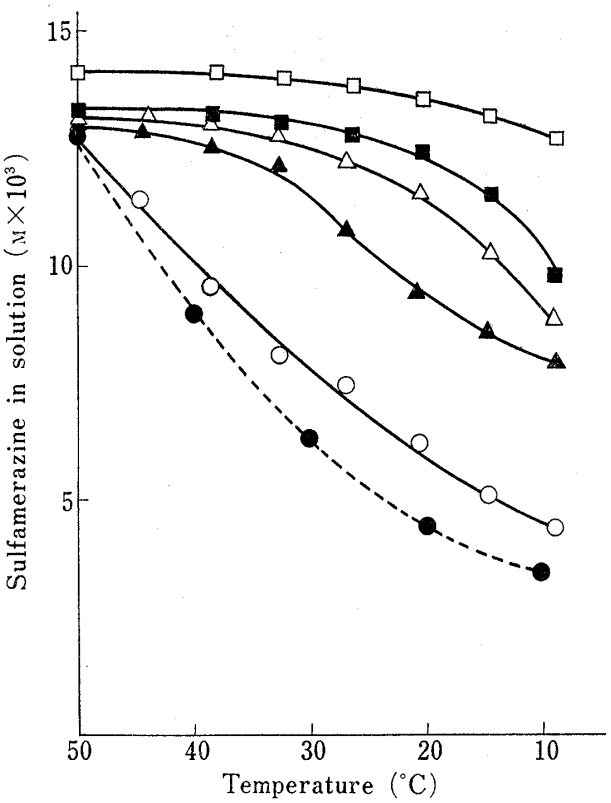

Fig. 5. Effect of PVP K-15 Concentrations on the Crystallization of Sulfamerazine

—□—, 1.0%; —■—, 0.5%; —△—, 0.3%; —▲—, 0.1%; —○—, none; ---●---, solubility.

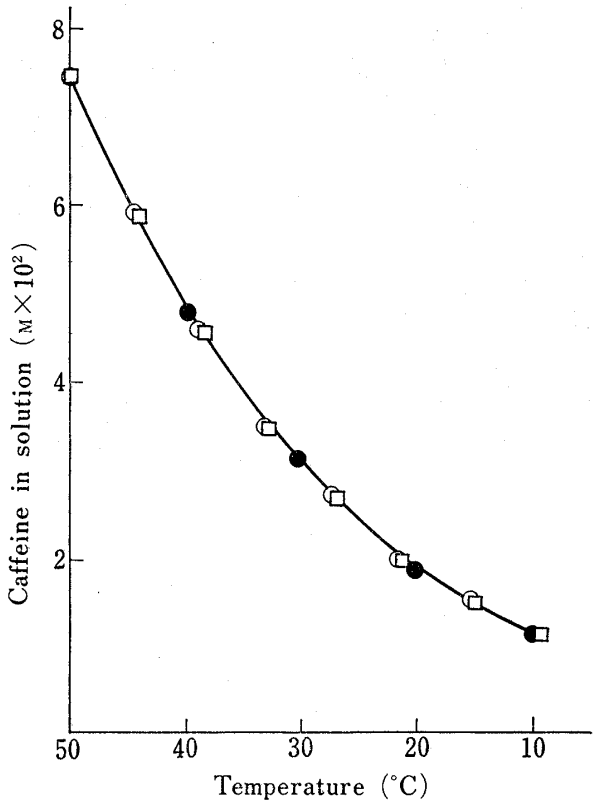

Fig. 6. Effect of PVP K-15 on the Crystallization of Caffeine

—□—, 1.0% PVP; —○—, without PVP —●—, solubility.

not so strong as that on sulfisoxazole or sulfamethizole (Fig. 5).

Higher concentration of PVP was used in this case than sulfisoxazole or sulfamethizole. Crystallization of sulfamerazine in the presence of PVP set in very slowly as soon as the temperature was lowered. Crystallization of sulfamerazine was not inhibited by 3.0% (w/v) PVP. In the presence of PVP, however, crystallization of sulfamerazine was slow, indicating the retardatory effect of PVP. The solution was not clouded with small crystals as in the case of sulfisoxazole or sulfamethizole. It may be considered that small amount of sulfamerazine molecule in the supersaturated solution deposits on the seeded crystals.

d. Caffeine: Caffeine as well as urea has been found not to interact with PVP.[15] As shown in Fig. 6, there was no effect of PVP on the crystallization of caffeine. By lowering temperature of the saturated solution of caffeine, it crystallized readily to approach its equilibrium solubility, with or without PVP. Caffeine is a easily crystallizing drug itself.

e. Nalidixic Acid: PVP K-15 did not affect the crystallization of nalidixic acid (Fig. 7). Nalidixic acid interacts only weakly with PVP in aqueous solution. Nalidixic acid was not affected by 1.0% (w/v) PVP as caffeine.

3. **Effect of the Molecular Weight of PVP on the Crystallization of Drug**——PVP K-15 inhibited and/or retarded the crystallization of sulfisoxazole and sulfamethizole, and retarded the crystallization of sulfamerazine. The effect of PVP of different molecular weight on the crystallization of sulfisoxazole was studied (Fig. 8 and Fig. 9).

Fig. 8 shows the effect of N-vinyl-2-pyrrolidone, the monomer unit of PVP molecule, on the crystallization of sulfisoxazole. The concentration as high as 0.1% (w/v) and 1.0% (w/v) of N-vinyl-2-pyrrolidone did not inhibit the crystallization of sulfisoxazole. The

15) H. Sekikawa, T. Arita, R. Hori, and K. Ito, to be published.

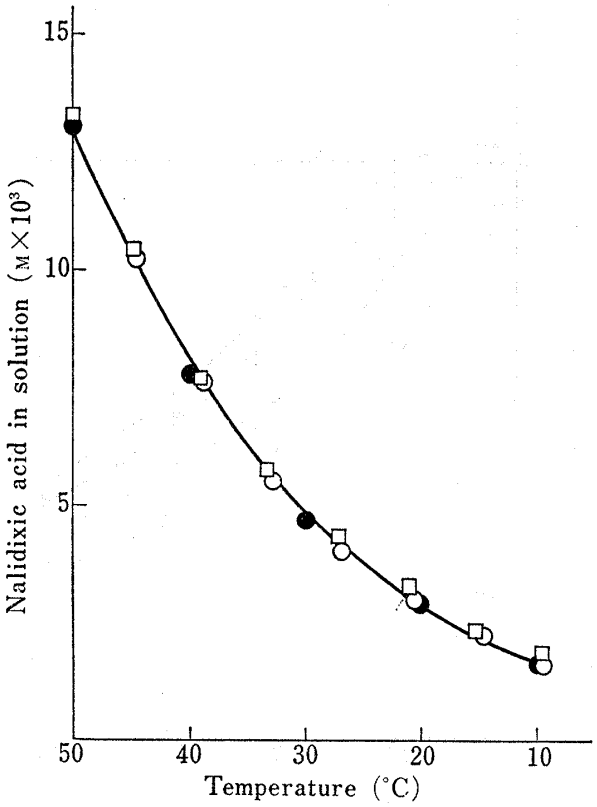

Fig. 7. Effect of PVP K-15 on the Crystallization of Nalidixic Acid

—□—, 1.0% PVP; —○—, without PVP; ---●---, solubility.

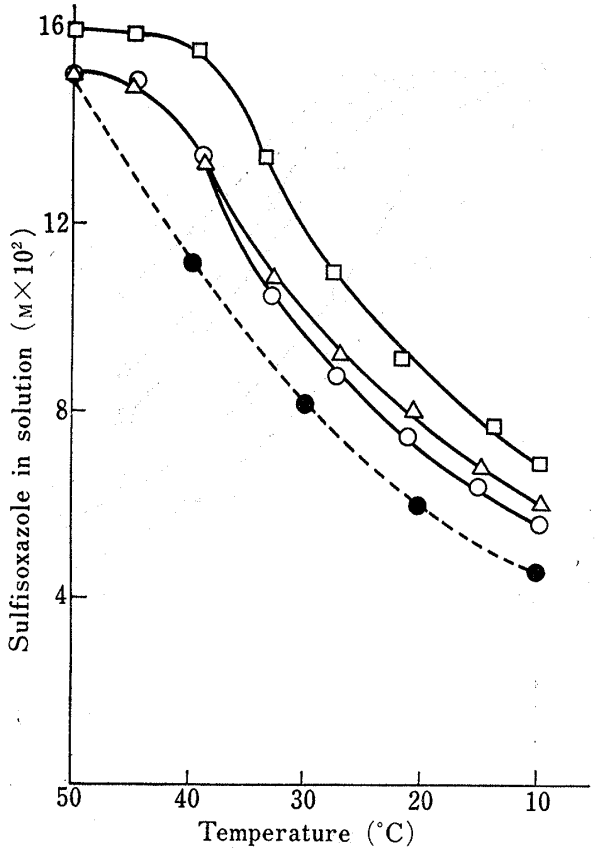

Fig. 8. Effect of N-Vinyl-2-pyrrolidone Concentration on the Crystallization of Sulfisoxazole

—□—, 1.0%; —△—, 0.1%; —○—, none, ---●---, solubility.

monomer unit of PVP molecule did not have the inhibitory and/or retardatory effect on the crystallization of sulfisoxazole. It is thus expected that an inhibitory effect is associated with polymer.

Fig. 9 shows the comparison of three types of PVP; K-15, K-30 and K-90 (average molecular weight of each PVP is approximately 10000, 40000 and 360000 respectively). The inhibitory and/or retardatory effect decreased in the following order; K-30>K-90> K-15. This indicates that the effect reaches maximum at a certain molecular weight, and decreases with further increase in molecular weight.

4. The Effect of Polyethylene Glycol and Polysorbate 80 on the Crystallization of the Drug

Polyethylene glycol 400, 6000 and 20000, the synthetic water-soluble polymer, and polysorbate 80, non-ionic surfactant, were studied on their effects on the crystallization of sulfisoxazole. The results are shown in Fig. 10.

Polyethylene glycol 400 and polysorbate 80 increased the solubility of sulfisoxazole. In spite of their high concentration, they did not have the inhibitory or retardatory effect on the crystallization of sulfisoxazole. Polyethylene glycol 6000 and 20000 were used in this study, but these polyethylene glycols began to precipitate itself at about 37° and 40°, respectively, because of their low solubility in ethanol. Polyethylene glycols or polysorbate 80 are not thus suitable for the coprecipitation of drugs from ethanol.

The Relation of PVP-Drug Interaction to Inhibitory Effect of PVP on the Crystallization of Drugs

Studies on the inhibitory effect of PVP on the crystallization of drugs, revealed that there were three types of drug. First, the drugs crystallization of which are inhibited and/or

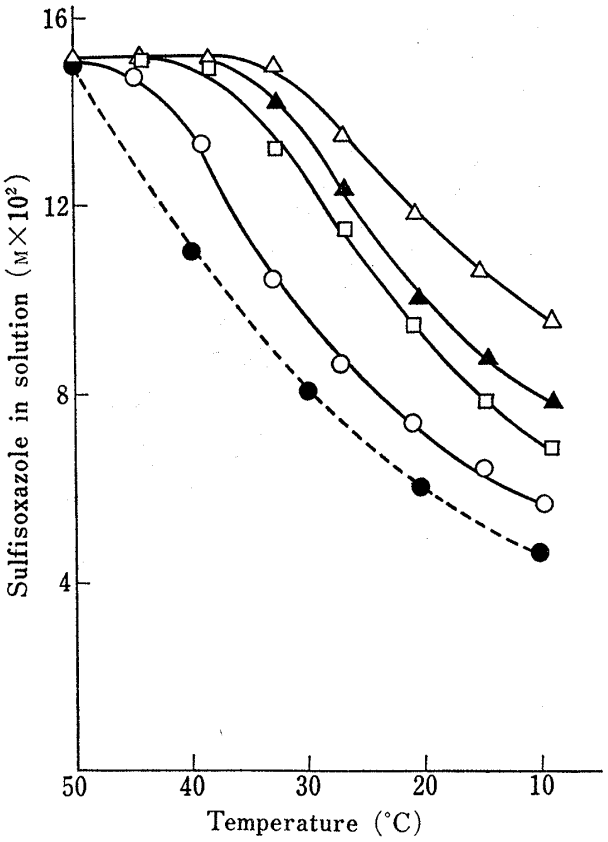

Fig. 9. Effect of Molecular Weight on PVP of the Crystallization of Sulfisoxazole

—△—, K-30; ▲——, K-90; —□—, K-15; —○—, none; ---●---, solubility.
Concentration of each PVP was 0.001%

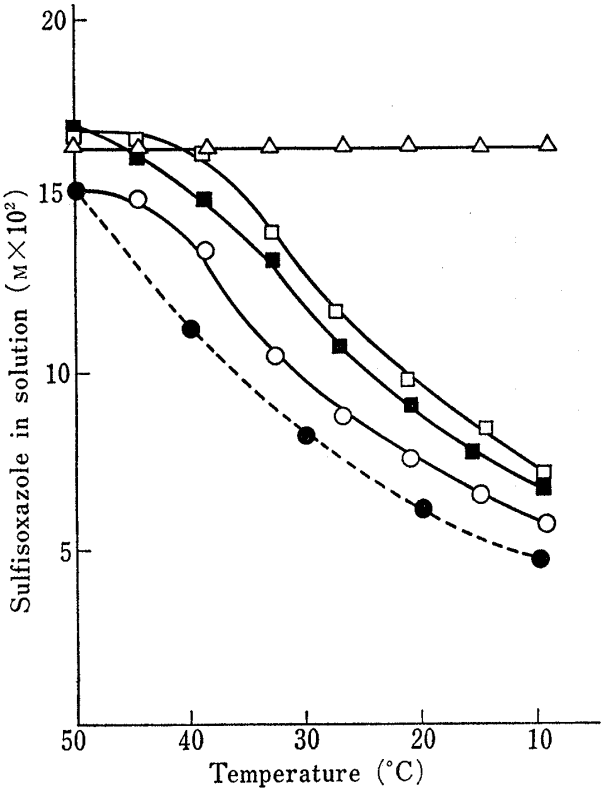

Fig. 10. Effect of PVP K-15 (△), Polyethylene Glycol 400 (□) and Polysorbate 80 (■) on the Crystallization of Sulfisoxazole

—○—, without polymer; ---●---, solubility.
Concentration of each polymer was 1.0%.

retarded by PVP; sulfisoxazole and sulfamethizole, secondly, the drug crystallization of which is retarded but not inhibited; sulfamerazine, and lastly, the drugs crystallization of which are not inhibited nor retarded; caffeine and nalidixic acid.

Viscosity of PVP may not be the major inhibitory factor, because lower concentration of PVP inhibited the crystallization of sulfisoxazole and sulfamethizole, and effects were different among the drugs at the same PVP concentration. Rather, the interaction between PVP and drugs may be the inhibitory and/or retardatory factor in the crystallization.

Solubilities of five drugs were determined in ethanol and 5.0% (w/v) PVP K-15 solution in ethanol at 10.0, 20.0, 30.0, 40.0 and 50.0°. Apparent stability constants, K, of possible complex between these drugs and PVP were evaluated according to the equation reported by Higuchi and Zuck,[16] and listed in Table I. Also, mole of drugs solubilized by PVP are listed in Table II. Data are converted to molarity of drug solubilized by 1M vinylpyrrolidone equivalent.

The apparent stability constants of drugs with PVP are generally small, but the difference is evident among them. The values of K at 50° are in order of the inhibitory effect of PVP on the crystallization. The apparent stability constants of nalidixic acid and caffeine are much smaller than those of sulfamethizole, sulfisoxazole and sulfamerazine. They belong to the group of compounds crystallization of which were not inhibited nor retarded by PVP. The value of K of sulfamethizole is larger than that of sulfisoxazole. Sulfamethizole is a drug crystallization of which was strongly inhibited and/or retarded by PVP. For sulfamerazine,

16) T. Higuchi and D.A. Zuck, *J. Am. Pharm. Assoc., Sci. Ed.*, 42, 137 (1953).

Table I. Apparent Stability Constants of Possible Complexes between Drugs and Polyvinylpyrrolidone K-15

Drug	K, M^{-1}				
Temp. (°C)	10.0	20.0	30.0	40.0	50.0
Sulfamethizole	2.62	2.39	1.99	1.85	1.74
Sulfisoxazole	1.76	1.60	1.44	1.31	1.13
Sulfamerazine	1.97	1.76	1.55	1.32	1.11
Nalidixic acid	0.403	0.291	0.222	0.163	0.128
Caffeine	0.126	0.0944	0.0768	0.0584	0.0440

Table II. Solubilizing Effect of Polyvinylpyrrolidone K-15 on the Drugs

Drug	Solubilized by 1M vinylpyrrolidone equivalent (M$\times 10^2$)				
Temp. (°C)	10.0	20.0	30.0	40.0	50.0
Sulfamethizole	5.51	6.58	7.85	9.75	12.1
Sulfisoxazole	7.52	8.89	10.4	12.5	14.5
Sulfamerazine	0.631	0.770	0.950	1.16	1.39
Nalidixic acid	0.0646	0.0814	0.102	0.127	0.167
Caffeine	0.118	0.166	0.215	0.264	0.315

the values of K are larger than that of sulfisoxazole up to 40°. The value of K at 50° is smaller than those of sulfisoxazole and sulfamethizole.

Drugs solubilized by PVP in ethanol are compared in Table II. The amount solubilized by PVP is larger in sulfisoxazole and sulfamethizole. In spite of the value of K in Table I, sulfamerazine solubilized by PVP is small because of its low solubility in ethanol. In the same manner, nalidixic acid solubilized by PVP is small because of its low solubility in ethanol. Among five drugs, sulfisoxazole is solubilized most by PVP.

On the basis of these results, sulfamethizole and sulfisoxazole, having large K values and solubilized much by PVP, were strongly inhibited and/or retarded by PVP in the crystallization. The process of the crystallization of the drug from supersaturated solution consists of two processes; generation of the crystal nucleus and growth of the crystal. In these processes, PVP might inhibit the association of the drug molecule to form the crystal nucleus and inhibit the crystal growth. The effect is increased by the increase in PVP concentration.

Sulfamerazine, having larger K value, but solubilized less by PVP because of its low solubility in ethanol, may not have a strong interacting force with PVP as sulfamethizole or sulfisoxazole. So, PVP may not interfere with the association of the drug molecule to form the crystal nucleus strongly. Crystallization of sulfamerazine occurs slowly even in the presence of PVP.

PVP does not affect the crystallization of caffeine and nalidixic acid, because it interacts only weakly with these drugs.

N-Vinyl-2-pyrrolidone, the monomer unit of PVP molecule, did not inhibit the crystallization of sulfisoxazole, though it increased the solubility of sulfisoxazole. A suitable molecular length may be required to form the polymer net upon the crystal surface or among the drug molecules as proposed by Simonelli, *et al.*[13]

A Consideration of the Mechanism of Coprecipitation of the Drug with PVP

From these results, the mechanism of coprecipitation of the drug with PVP is now considered. The drug-PVP preparations were prepared by removing the solvent under reduced pressure from the solution containing both drug and PVP. As the evaporation proceeds, the concentration of drug reaches solubility, and then, exceed solubility. PVP

in the solution, however, inhibits the crystallization of the drug, and supersaturation is maintained. The degree of supersaturation is increased, and the concentration is increased also. PVP loses its solvent with the drug, if the concentration of PVP is high enough to inhibit the crystallization of the drug. The solid drug appears from the solution without crystallization, that is, without exhibiting its crystal structure in PVP matrix. Coprecipitates thus formed do not give the X-ray diffraction peak.

In the case of sulfamethizole and sulfisoxazole, coprecipitates are easily prepared by the suitable weight ratio of PVP to the drugs; 1:1 or 2:1, *etc.*[7] However, if ratio of PVP to drug is not large enough to inhibit the crystallization of the drug, well-defined coprecipitate is not formed. The preparation B in Fig. 1 shows the characteristic sulfisoxazole crystal peak.

Sulfamerazine did not form well-defined coprecipitate with equal weight ratio of PVP. Caffeine and nalidixic acid, not inhibited nor retarded by PVP in the crystallization, did not form coprecipitates with any ratio of PVP. This agreed with the result of the crystallization experiment.

Thus, coprecipitation of the drug with PVP is due to the inhibitory effect of PVP on the crystallization of the drug. It may be predicted if coprecipitate is formed from the drug with PVP from the knowledge of the interaction between them beforehand.

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