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Solubilization of Water-Insoluble Organic Powders by Ball-Milling in the Presence of Polyvinylpyrrolidone*

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Phenothiazine, acridine, chloranil and vitamin K_3 were ball-milled in the presence of polyvinylpyrrolidone (PVP) and the variation of the solubility and the dissolution rate of them in distilled water was investigated.

Solubility of these substances in distilled water increased remarkably by ball-milling in the presence of PVP. An increase of the solubility of phenothiazine and acridine was mainly contributed to a decrease of molecular weight of PVP by ball-milling. But an increase of the solubility of chloranil and vitamin K_3 was contributed to the interaction of them with PVP caused by ball-milling.

The dissolution rate of these four substances in distilled water from the mixture with PVP increased remarkably by ball-milling.

The signals of phenothiazine and acridine in the X-ray diffraction diagrams of the mixture with PVP disappeared by ball-milling, and the similar tendency was also observed in case of vitamin K_3. On the contrary, new signals were observed in the diagrams of the mixture of PVP and chloranil by ball-milling.

It was considered that the four substances dispersed in the solid particles of PVP in fine particles by ball-milling, which caused an increase of the solubility and the dissolution rate of them in distilled water and the change in the crystalline structure of them.

An interesting phenomenon was observed in the course of studying the influence of the addition of organic powders on degradation of polyvinylpyrrolidone (PVP). The supernatant obtained by the centrifugal separation of the aqueous suspension of the ball-milled mixture of PVP and organic powders slightly soluble in distilled water was colorless at the first stage of ball-milling, but the supernatant was colored gradually with the lapse of the ball-milling time. This fact seems to suggest the possibility of an increase of solubility of slightly soluble organic powders in distilled water by ball-milling in the presence of PVP.

In this paper, influence of ball-milling organic powders in the presence of PVP on their solubility in distilled water was investigated.

Experimental

The materials used were PVP K90 and PVP K30 of Wako Pure Chemicals Industries LTD., PVP K15 Daiichi Pure Chemicals Co. LTD., α-pyrrolidone, phenothiazine and acridine of guaranteed grade of Tokyo Kasei Industries LTD., chloranil of guaranteed grade of Wako Pure Chemicals Industries LTD., and vitamin K_3 of guaranteed grade of Daichi Pure Chemicals Co. LTD.. Mean molecular weight of PVP K90, PVP K30 and PVP K15 by viscometry were 9.6×10^5, 4.0×10^4 and 7.5×10^3, respectively.[2] Chroloform and carbon tetrachloride were of guaranteed grade.

Stainless steel balls of true density of 8.2 g/cm³ and in diameter of 1.9 cm and 2.5 cm were used. The ratio of the number of balls in diameter of 1.9 cm to the number of balls in diameter of 2.5 cm was kept to be 3.0 in all the experiments in this paper. Various amounts of balls and materials were inserted in a stainless steel mill in the inside diameter of 10 cm and in capacity of 870 ml. The mill was revolved at the velocity of 110 rpm, which was 0.74 times of the critical velocity at which the gravitational force of balls was equal to the centrifugal force given to the balls by the revolution of a mill.[3] In case of ball-milling in nitrogen,

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* Dedicated to the memory of Prof. Eiji Ochiai.

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[2] N. Kaneniwa and A. Ikekawa, *Yakuzaigaku*, **31**, 201 (1971).

[3] N. Kaneniwa, A. Ikekawa, and K. Hashimoto, *Chem. Pharm. Bull.* (Tokyo), **21**, 676 (1973).

the lid of a mill refered to the previous paper was used.[2)] Various kinds of the samples obtained by ball-milling under various conditions were tabullated in Table I, where mean molecular weight of PVP by viscometry was obtained by the method in the previous paper.[4)]

Table I. The Ball-Milled Samples

Sample number	Ball-milled material	Addition	Weight content of addition (w/w%)	W_s(g)[a)]	J_b[b)]	Ball-milling atmosphere	Ball-milling time (hr)	M[c)]
1	PVP K90	phenothiazine	10	20	0.22	nitrogen	211	5.0×10^4
2	PVP K90	acridine	10	10	0.22	nitrogen	31	6.0×10^5
3	PVP K90	acridine	10	10	0.43	nitrogen	8	6.8×10^5
4	PVP K90	acridine	10	20	0.22	nitrogen	251	7.5×10^4
5	PVP K90	acridine	10	20	0.22	air	207	2.6×10^4
6	PVP K90	chloranil	10	20	0.22	air	200	1.1×10^6
7	PVP K90	chloranil	5	10	0.43	nitrogen	134	8.6×10^5
8	PVP K90	chloranil	5	10	0.43	air	98	3.2×10^4
9	PVP K90	chloranil	10	10	0.43	air	201	6.3×10^5
10	PVP K90	chloranil	10	10	0.43	air	261	2.8×10^4
11	PVP K90	chloranil	20	10	0.43	air	252	4.3×10^5
12	PVP K90	chloranil	40	10	0.43	air	251	3.2×10^5
13	PVP K90	chloranil	70	10	0.43	air	257	1.4×10^5
14	PVP K15	chloranil	5	10	0.43	air	54	7.8×10^3
15	PVP K90	vitamin K_3	10	20	0.22	nitrogen	251	1.1×10^5
16	PVP K90			20	0.22	nitrogen	420	2.1×10^4
17	phenothiazine			5	0.43	air	31	
18	acridine			5	0.43	air	31	
19	chloranil			10	0.43	air	62	
20	vitamin K_3			5	0.43	air	31	

a) W_s: The total weight of the sample inserted in a mill.
b) J_b: the ratio of the total volume of balls to the capacity of a mill[3)]
c) M: molecular weight of PVP by viscometry

The equilibrium aqueous solutions of the substances slightly soluble in distilled water were prepared as follows from various samples. The weighed amount of the sample was suspended in 3 ml of distilled water in a test tube in diameter of 1.5 cm, and the suspension was kept at 30° for six days, occasionally shaken intensely. Both original and individually ball-milled powders of phenothiazine and chloranil continued to dissolve in distilled water even after six days from the time of the preparation. But dissolution of slightly soluble powders in distilled water from the other samples was equilibrated within six days. Then, the suspension was centrifuged and the supernatant was filtered through the milipore filter of 0.45 μm (HAWPO 1300) and the filtrate was used for the spectroscopic measurements.

The absorption spectra of the equilibrium aqueous solutions and the chloroform solutions of the samples were measured with a Hitachi recording spectrophotometer (Model EPS-2), the fluorescence spectra of the equilibrium solutions were measured with a Hitachi fluorescence spectrometer (Model MPF-2A), infrared (IR) spectra of the chloroform solutions and KBr tablets of the samples were measured with a Hitachi IR spectrometer (Model EPI-2) and absorbance of the absorption maximum of the slightly soluble powders in the solution was measured with a Hitachi Perkin Elmer spectrophotometer (Model 139). Electron spin resonance (ESR) spectra of the samples were measured with an ESR spectrometer (Model JES-PE). X-ray diffraction diagramms of the samples were measured with a JEOL X-ray diffractometer (Model JDX-7E).

The dissolution rate of the slightly soluble powders in distilled water from various samples was measured as follows. Immediately after the weighed amount of the sample was suspended in 100 ml of distilled water of 30° in a flask in capacity of 200 ml, the flask was shaken twice per second in amplitude of 10 cm in a thermobath of 30°. Approximately 1.5 ml of the suspension was pipetted at intervals and filtered through a milipore filter of 0.45 μm (HAWPO 1300) and absorbance of the absorption maximum of the slightly soluble powders in the filtrate was measured.

Results and Discussion

1) Interaction between PVP and Slightly Soluble Organic Substances in the Aqueous Solutions

Influence of the addition of PVP on the absorption spectra and the fluorescence spectra of the equilibrium aqueous solutions of the slightly soluble substances was investigated, in

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4) N. Kaneniwa and A. Ikekawa, *Chem. Pharm. Bull.* (Tokyo), **20**, 1536 (1972).

order to clarify whether the substances interacted with PVP or not. In the absorption spectra of the equilibrium solution of phenothiazine, the peak at 353 nm disappeared and a new peak appeared at 304 nm by the addition of PVP (Fig. 1). In the fluorescence spectra of the equilibrium solutions of phenothiazine, intensity of fluorescence at the peak of 436 nm decreased remarkably and a new peak was observed at 377 nm by the addition of PVP (Fig. 2). But remarkable change was not observed in the absorption spectra and the fluorescence spectra of the equilibrium solutions of the other insoluble substances by the addition of PVP.

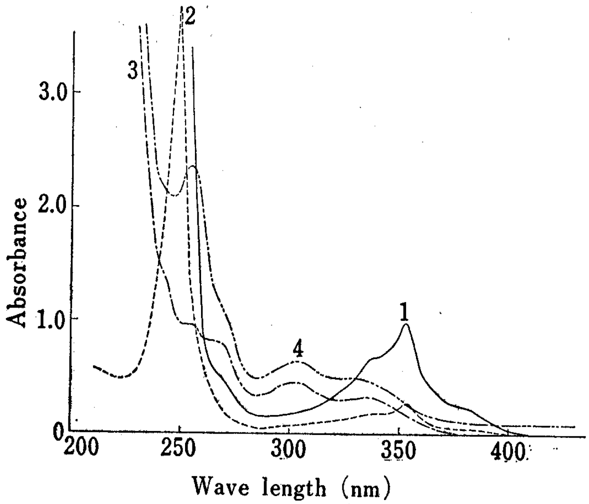

Fig. 1. Absorption Spectra of the Equilibrium Aqueous Solutions of Phenothiazine prepared from Various Samples

sample
1 ————: 41 mg of phenothiazine
2 ------------: The solution of "1" was diluted with distilled water to 1/4
3 —·—·—·—: 50 mg of the mixture of PVP K15 and ball-milled phenothiazine in the ratio of 9:1 by weight
4 ------------: 52 mg of the mixture of PVP K90 and phenothiazine in the ratio of 9:1 by weight ball-milled in nitrogen for 211 hours (The sample No. 1 in Table I) The equilibrium solution was diluted with distilled water to 1/10.

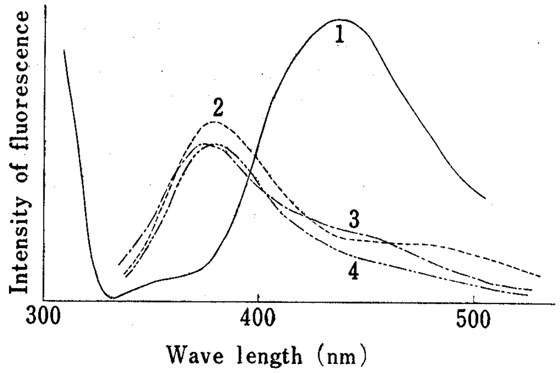

Fig. 2. Fluorescence Spectra of the Equilibrium Aqueous Solutions of Phenothiazine prepared from Various Samples

exciting wave length 304 nm
sample
1 ————: 41 mg of phenothiazine
2 ------------: 50 mg of the mixture of PVP K15 and ball-milled phenothiazine in the ratio of 9:1 by weight
3 —·—·—·—: 25 mg of the mixture of PVP K90 and phenothiazine in the ratio of 9:1 by weight
4 ------------: 52 mg of the mixture of PVP K90 and phenothiazine in the ratio of 9:1 by weight ball-milled in nitrogen for 211 hours (the sample No. I in Table I)

The equilibrium solutions of slightly soluble substances in the aqueous solutions of various concentration of PVP were prepared and influence of the concentration of PVP on solubility of the slightly soluble substances in the solution of PVP was investigated. As shown in Fig. 3, solubility of acridine increased with an increase of the concentration of PVP. Solubility of acridine was higher in the solution of PVP K15 than in the solution of PVP K90, PVP K30 or α-pyrrolidone. Solubility of phenothiazine and chloranil in the aqueous solution of PVP or α-pyrrolidone was too small to be obtained. But the same tendecy was also observed in case of phenothiazine (Fig. 4). In contrast with this finding, solubility of vitamin K_3 in the solution of PVP was influenced little by the concentration and molecular weight of PVP, and this tendency was also observed in case of chloranil (Fig. 5 and 6).

It was verified from the above findings that phenothiazine and acridine interacted with PVP in the aqueous solutions and that interaction between PVP and chloranil or vitamin K_3 in the solution could be ignored.

2) Influence of Ball-milling Organic Powders in the Presence of PVP on Solubility of them in Distilled Water

As shown in Fig. 7 and 8, solubility of acridine and vitamin K_3 in the aqueous solution of PVP increased by ball-milling in the presence of PVP. Absorbance of the absorption

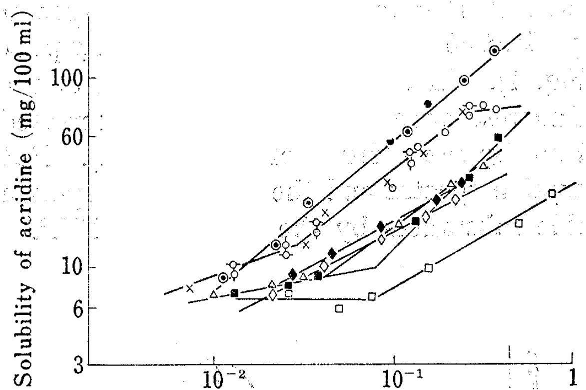

Fig. 3. Influence of the Concentration of PVP or α-Pyrrolidone on Solubility of Acridine in Their Aqueous Solution

sample	the type of PVP or α-pyrrolidone in the solution
□: 10 mg of original acridine[a]	α-pyrrolidone
⊙: 10 mg of original acridine	PVP K15
■: 10 mg of original acridine	PVP K30
△: 10 mg of original acripine	PVP K90
×: various amounts of the sample No. 4 inTable I[b]	
●: 20 mg of the sample No. 4 in Table I	PVP K15
○: 20 mg of the sample No. 4 in Table I	the sample No. 16 in Table I
ϕ: 10 mg of original acridine	the sample No. 16 in Table I
-○-: 10 mg of ball-milled acridine	the sampe No. 16 in Table I
◆: various amounts of the sample No. 2 in Table I	
◇: various amounts of the sample No. 3 in Table I	

a) For example, an equilibrium soution was obtained by suspending 10 mg of original acridine in 3 ml of the aqueous solution of various concentration of α-pyrrolidone.

b) For example, an equilibrium solution was obtained by suspending various amounts of the sample No. 4 in Table I in 3 ml of distilled water.

The above explanatory notes fora) and b) are also applied to Fig. 4, 5 and 6.

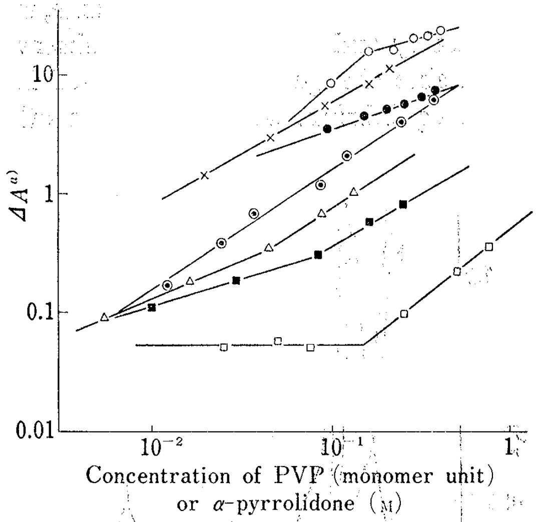

Fig. 4. Influence of the Concentration of PVP or α-Pyrrolidone on Solubility of Phenothiazine in Their Aqueous Solution

sample	the type of PVP or α-pyrrolidone in the solution
□: 10 mg of original phenothiazine	α-pyrrolidone
⊙: 10 mg of original phenothiazine	PVP K15
■: 10 mg of original phenothiazine	PVP K30
△: 10 mg of original phenothiazine	PVP K90
×: various amounts of the sample No. 1 in Table I	
●: 20 mg of the sample No. 1 in Table I	PVP K15
○: 20 mg of the sample No. 1 in Table I	the sample No. 16 in Table I

a) The difference of absorbance of the equilibrium aqueous solution of phenothiazine at 304 nm from that of the aqueous solution of the same concentration of PVP

maximum of phenothiazine and chloranil in the equilibrium solutions also increased by ball-milling in the presence of PVP (Fig. 9 and 10). A large amount of the precipitated particles was observed in the suspension of 10 mg of the physical mixture of PVP and chloranil in the ratio of 95: 5 by weight in 3 ml of distilled water, even after keeping the suspension at 30° for more than a week from the time of the preparation, occasionally shaking intensely. But by adding 10 mg of the ball-milled mixture (the sample No. 8 in Table I) in 3 ml of distilled water, almost all the part of the solid particles dissolved rapidly and extremely small amount of the suspended particles was observed, even after five minutes from the time of the preparation. It was considered from this finding that the results in Fig. 9 and 10 were due to an increase of solubility of phenothiazine and chloranil by ball-milling in the presence of PVP. Nakai, *et al.* also reported that solubility of diphenylhydantoin was doubled by vibro-milling in the presence of crystalline cellulose, though the mechanism was not clarified.[5] But, as mentioned in the preceeding paragraph, solubility of phenothiazine, original chloranil and

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[5] K. Yamamoto, Y. Takayama, S. Nakano, K. Arita, and Y. Nakai, The 95 th Annual Meeting of Pharmaceutical Society of Japan, Nishinomiya, Apr. 1965, p. 4Q3-3.

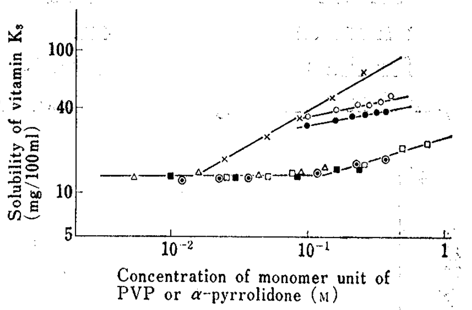

Fig. 5. Influence of the Concentration of PVP or α-Pyrrolidone on Solubility of Vitamin K_3 in Their Aqueous Solution

sample	the type of PVP or α-pyrrolidone in the solution
□: 10 mg of vitamin K_3	α-pyrrolidone
⊙: 10 mg of vitamin K_3	PVP K15
■: 10 mg of vitamin K_3	PVP K30
△: 10 mg of vitamin K_3	PVP K90
×: Various amounts of the sample No. 15 in Table I	
●: 20 mg of the sample No.15 in Table I	PVP K15
○: 20 mg of the sample No. 15 in Table I	the sample No. 16 inTable I

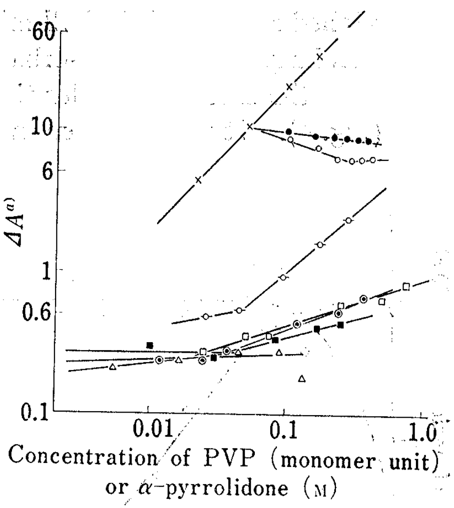

Fig. 6. Influence of the Concentration of PVP or α-Pyrrolidone on Solubility of Chloranil in Their Aqueous Solutions

a) the difference of absorbance of the equilibrium aqueous solution of chloranil at 295 nm from that of the aqueous solution of the same concentration of PVP

sample	the type of PVP or α-pyrrolidone in the solution
□: 10 mg of chloranil	α-pyrrolidone
⊙: 10 mg of chloranil	PVP K15
■: 10 mg of chloranil	PVP K30
△: 10 mg of chloranil	PVP K90
×: various amounts of the sample No. 8 in Table I	
-○-: various amounts of the sample No. 7 in Table I	
●: 20 mg of the sample No. 8 in Table I	PVP K15
○: 20 mg of the sample No. 8 in Table I	the sample No. 16 in Table I

chloranil ball-milled in the absence of PVP in the aqueous solution of PVP or α-pyrrolidone was so small that the concentration of them in the solution could not be obtained by the spectroscopic method. The samples No. 8 and No. 10 in Table I were almost completely soluble in a little volume of distilled water and a straight line passing through an origin and with a slope of 1.0/(3.1 mg/100 ml) was obtained by the plot of ΔA *versus* the concentration of chloranil in the solution, where ΔA was the difference of absorbance of chloranil in the solution at 295 nm from the absorbance of the aqueous solution of the same concentration of PVP. But solubility of chloranil from all the samples used in this paper could not be obtained by the value of the slope, for it was suggested that ΔA for the solution of chloranil from the mixture with PVP at 295 nm decreased by ball-milling the mixture after the lapse of the induction period, as mentioned later in this paper.

In case of ball-milling PVP in the presence of phenothiazine, acridine or vitamin K_3 in nitrogen or in the presence of chloranil, induction period of more than 50 hours, after the lapse of which molecular weight of PVP began to decrease, was observed. Absorbance of the absorption maximum of the equilibrium solution of phenothiazine from the ball-milled mixture with PVP at 304 nm increased remarkably with a decrease of molecular weight of PVP by ball-milling after the induction period (Fig. 9). Absorbance of the equilibrium aqueous solution of phenothiazine from the ball-milled mixture with PVP K90 at 304 nm was larger than the absorbance of the solution from the physical mixture of PVP K15 and phenothiazine, though molecular weight of PVP ball-milled in the presence of phenothiazine was higher than that of PVP K15. Absorbance at 304 nm for the equilibrium solution obtained by suspending the weighed amount of the ball-milled mixture in the solution of various concentration of PVP ball-milled in nitrogen was larger than the absorbance for the solution from the ball-milled mixture. Absorbance at 304 nm for the equilibrium solution obtained by suspending the weighed amount of the ball-milled mixture in the solution of various concentration of PVP K15 was larger than the absorbance for the solution from the physical mixture of PVP K15 and phenothiazine and smaller than the absorbance for the solution from the ball-milled mixture (Fig. 4). It was reported in the previous paper that a new signals was observed at 2400

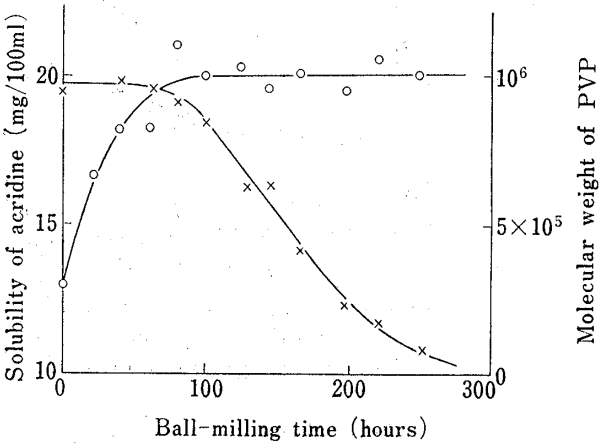

Fig. 7. An Increase of Solubility of Acridine in Distilled Water and a Decrease of Molecular Weight of PVP by Ball-Milling the Mixture of PVP K90 and Acridine in the Ratio of 9: 1 by Weight in Nitrogen

Thirty mg of the ball-milled sample was used for the preparation of the equilibrium solution.
○: solubility of acridine
x : molecular weight of PVP

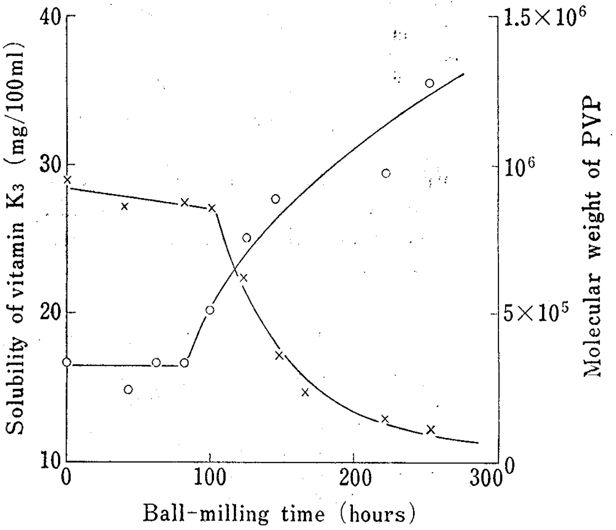

Fig. 8. An Increase of Solubility of Vitamin K_3 in Distilled Water and a Decrease of Molecular Weight of PVP by Ball-Milling the Mixture of PVP K90 and Vitamin K_3 in the Ratio of 9: 1 by Weight in Nitrogen

Thirty mg of the sample was used for the preparation of the equilibrium solution.
○: solubility of vitamin K_3
x : molecular weight of PVP

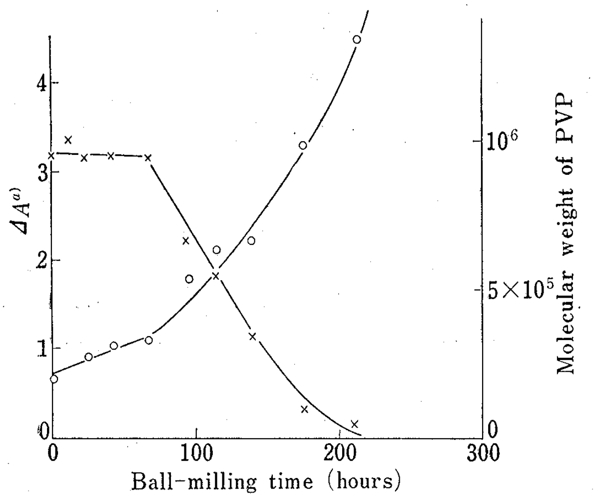

Fig. 9. An Increase of Absorbance of the Equilibrium Aqueous Solutions of Phenothiazine at 304 nm and a Decrease of Molecular Weight of PVP by Ball-Milling the mixture of PVP K90 and Phenothiazine in the Ratio of 9: 1 by Weight in Nitrogen

Thirty mg of the ball-milled sample was used for the preparation of the equilibrium solution.
○: $\Delta A^{a)}$
x : molecular weight of PVP
a) the difference of absorbance of the equilibrium solution of phenothiazine at 304 nm from that of the aqueous solution of the same concentration of PVP

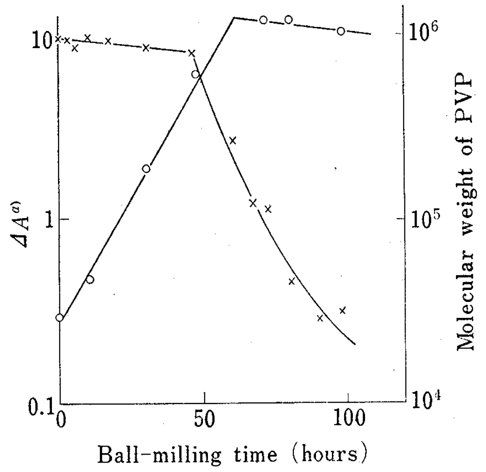

Fig. 10. An Increase of Solubility of Chloranil in Distilled Water and a Decrease of Molecular Weight of PVP by Ball-Milling the Mixture of PVP K90 and Chloranil in the Ratio of 95: 5 by Weight in Air

Twenty mg of the sample was used for the preparation of the equilibrium solution.
○: $\Delta A^{a)}$ x : molecular weight of PVP
a) the difference of absorbance of the equilibrium solution of chloranil at 295 nm from that of the aqueous solution of the same concentration of PVP

cm^{-1} region in the IR spectra of the chloroform solutions of PVP by ball-milling in nitrogen and that the signal was considered to be due to formation of N^+ by ball-milling.[6] The absorption spectra and the fluorescence spectra of the equilibrium aqueous solutions and the chloroform solutions of the mixture of PVP and phenothiazine were not influenced by ball-milling. The ball-milled mixture was suspended in distilled water, the suspension was centrifuged and the supernatant was removed. The IR spectra of the KBr tablets of the powders of the precipitates obtained by repeating the above procedure several times were identical with those of original phenothiazine. It is considered from the above findings that an increase of absorbance of phenothiazine in an aqueous solution of PVP at 304 nm is not only due to a decrease of molecular weight of PVP but also due to the chemical structure of PVP partially changed by ball-milling.

As shown in Fig. 3, solubility of acridine in an aqueous solution of PVP increased with a decrease of molecular weight of PVP. Solubility of acridine obtained by suspending a certain amount of original acridine, ball-milled acridine or acridine ball-milled with PVP in the solution of various concentration of PVP ball-milled in nitrogen was nearly identical with the solubility in the equilibrium aqueous solutions from the ball-milled mixture of PVP and acridine. But solubility of acridine increased by ball-milling in the presence of PVP K90, even when the ball-milling time was below the induction period and molecular weight of PVP decreased little by ball-milling (Fig. 7). The IR spectra of the chloroform solutions of the mixture of PVP and acridine were not influenced by ball-milling. The IR spectra of the KBr tablets of acridine purified from the ball-milled mixture with PVP by the procedure referred to purification of phenothiazine was nearly identical with those of original acridine. It is shown from the above facts that an increase of solubility of acridine in the equilibrium aqueous solution by ball-milling in the presence of PVP is due to a decrease of molecular weight of PVP by ball-milling. In addition, it is considered that interaction of acridine with PVP caused by ball-milling also contributes to an increase of the solubility.

Equilibrium aqueous solutions of chloranil were prepared by suspending various amounts of the ball-milled mixture with PVP K90 in distilled water. Absorbance of chloranil in the equilibrium solution at 295 nm increased with an increase of the amount of the mixture suspended in distilled water, that is, with an increase of the concentration of PVP, whether molecular weight of PVP decreased by ball-milling or not. Absorbance of chloranil in the equilibrium solution from the ball-milled mixture at 295 nm was much larger than the absorbance from the physical mixture with PVP. Absorbance of chloranil at 295 nm in the equilibrium solutions obtained by suspending a certain amount of the ball-milled mixture with PVP in an aqueous solution of various concentration of PVP K90 ball-milled in nitrogen or original PVP K15 decreased slightly with an increase of the concentration of PVP (Fig. 6). The similar tendency was also observed concerning solubility of vitamin K_3, as shown in Fig. 5. It is probable that interaction between PVP and chloranil or vitamin K_3 is caused in the solid state by ball-milling and that the interaction contributes to an increase of solubility of chloranil and vitamin K_3 in distilled water. As shown in Fig. 10, absorbance of chloranil in the equilibrium solution at 295 nm increased gradually and reached maximum at the induction period, but after the lapse of the induction period, the absorbance decreased slightly by ball-milling, which was considered to be due to the interaction between PVP and chloranil caused by ball-milling as mentioned later in this paper. Solubility of vitamin K_3 in the equilibrium solution from the mixture with PVP began to increase remarkably with a decrease of molecular weight of PVP by ball-milling after the lapse of the induction period (Fig. 8).

In Fig. 11 are shown the IR spectra of the KBr tablets of the physical mixture and the ball-milled mixture of chloranil and PVP. Transmittance of the physical mixture at 1580 cm^{-1} region decreased and the transmittance at 1100 cm^{-1} seemed to decrease by ball-milling.

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6) N. Kaneniwa and A. Ikekawa, *Chem. Pharm. Bull.* (Tokyo), **22**, 2990 (1974).

Prichard assighened the band around 1580 cm^{-1} region to be a ν (C=C) mode and the band around 1100 cm^{-1} region to be ν (C–Cl) coupled with the ν(C–C) mode.[7]

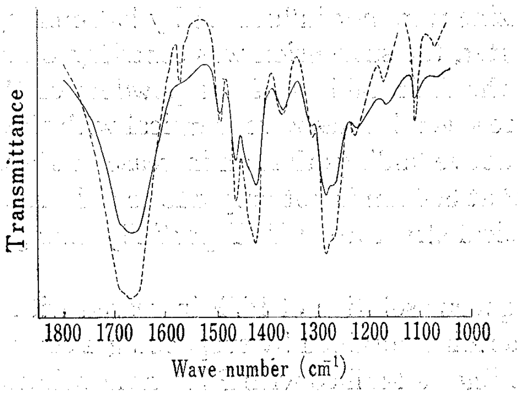

Fig. 11. IR Spectra of the KBr Tablets of the Mixtures of PVP and Chloranil

----------: the physical mixture of PVP K15 and chloranil in the ratio of 95: 5 by weight
———: the mixture of PVP K90 and chloranil in the ratio of 95: 5 by weight ball-milled in air for 98 hours (sample No. 8 in Table I).

The absorption spectra of some aliphatic amine-chloranil mixtures have recently been studied.[8,9] It was reported that the band around 285 nm, characteristic of chloranil in solvents such as ethanol or *n*-heptane was absent, but that an absorption was observed in the region of 320—380 nm. It was argued that this band was the perturbed 285 nm band of chloranil and that formation of an *n*-π intermolecular charge-transfer "outer complex" with the amine increased the electronic charge on the chloranil component of the complex so that the electronic transition at 285 nm more closely approached the transition of the semiquinone anion derived from chloranil.[8,10] Foster observed two absorption maximums in the region of 303—314 nm and around 356 nm in the absorption spectra of the aqueous ethanol solutions of chloranil and ethylamine, diethylamine or triethylamine. The solution of ethylamine and chloranil showed two maximums in the range of 300—400 nm, a band at 303 nm which decreased with the lapse of the time and a band at 356 nm which increased with the lapse of the time. He obtained dark green precipitates by shaking the suspension of chloranil in triethylamine at room temperature. A signal was observed at 314 nm in the absorption spectrum of the solution of this green solid in triethylamine and this solid showed a strong ESR single line absorption. From the parallelism with the sodium salt of the chloranil semiquinone ion concenrning optical absorption, ESR and IR spectra, he suggested that the green adduct was formed by a single electron transfer from triethylamine to chloranil. Acidification of the green adduct with dilute aqueous hydrochloric acid precipitated pure chloranil. This fact indicated that no replacement of chlorine in the chloranil moiety occurred. He also assumed from the spectroscopic investigation that the absorption maximum around 356 nm was due to 2,5-dichloro-3,6-bis-(ethylamino or diethylamino)-*p*-benzoquinone or 2,3,5-trichloro-6-(2′-diethylaminovinyl)-*p*-benzoquinone formed by decomposition of the adduct of chloranil and ethylamine, diethylamine or triethylamine respectively.[11]

The similar phenomena were also observed for the ball-milled mixture of PVP and chloranil. The color of the physical mixture of PVP and chloranil gradually turned from yellow into green by ball-milling for the time below the induction period. After the lapse of the induction period, the green mixture turned into violet by ball-milling. A peak was observed around 290 nm in the absorption spectra of the equilibrium aqueous solutions of chloranil. In the absorption spectra of the equilibrium solutions of the ball-milled mixture of PVP and chloranil, absorbance around 290 nm was large and a small shoulder was observed around 310 nm. This tendency was remarkable in case of the violet powders. A new peak was also observed around 363 nm in the absorption spectra of the equilibrium solution of the violet mixture (Fig. 12). As shown in Fig. 13, absorbance of the chloroform solutions of the physical

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[7] F. Elizabeth Prichard, *Spectrochimica Acta*, **20**, 127 (1964).
[8] M.A. Slifkin, *Nature*, **195**, 635 (1962).
[9] J.B. Birks and M.A. Slifkin, *Nature*, **197**, 42 (1962).
[10] M.A. Slifkin, *Nature*, **198**, 130 (1963).
[11] R. Foster, *Recueil*, **83**, 711 (1964).

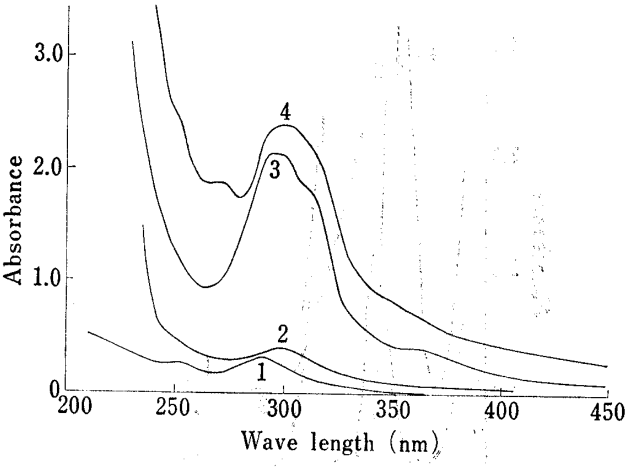

Fig. 12. Absorption Spectra of the Equilibrium Aqueous Solutions of Chloranil prepared from Various Samples

sample
1 36 mg of chloranil
2 20 mg of the mixture of PVP K90 and chloranil in the ratio of 9: 1 by weight
3 80 mg of the sampe No. 8 in Table I
The equilibrium solution was diluted with distilled water to 1/20.
4 42 mg of the sample No. 6 in Table I

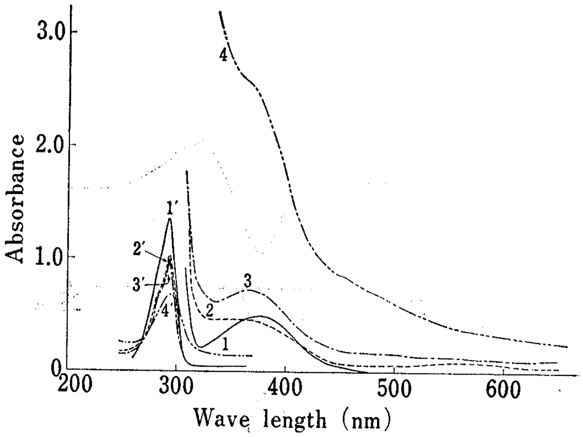

Fig. 13. Absorption Spectra of the Chloroform Solutions of Chloranil prepared from Various Samples

The folowing samples were dissolved in 3 ml of chloroform, respectively.
1 ———: 1.5 mg of chloranil
2 -------: 30 mg of the mixture of PVP K15 and ball-milled chloranil in the ratio of 95: 5 by weight
3 —·—·—: 33 mg of the sample No. 7 in Table I
4 -·-·-·-: 32 mg of the sample No. 8
i' (i=1, 2, 3 or 4)
the diluent of 1/45 of the solution of i

mixture of PVP and chloranil at 295 nm decreased gradually by ball-milling. A new peak appeared at 380 nm and absorbance of the new peak increased with the lapse of the ball-milling time.

ESR spectra of the ball-milled mixtures of PVP and chloranil were measured by inserting in a sample tube of quartz glass in diameter of 4 mm a pyrex tube in diameter of approximately 1 mm containing the powders of the sample. Approximately 210 hours of the induction period was observed by ball-milling the mixture under the condition for the samples No. 9 and No. 10 in Table I. As shown in Fig. 14, a signal was observed in the ESR spectra of the mixture ball-milled for the time around the induction period, but no signal was observed in the spectra of the sample No. 10 in Table I. But, by the measurement of the powders directly inserted in the sample tube, a broad signal was also observed in the spectra of the sample No. 10. It was considered from this finding that density of the radical formed by ball-milling the mixture of PVP and chloranil was large around the induction period and that the density decreased gradually by ball-milling after the induction period.

Foster found that the chloranil semiquinone anion was generated by the addition of strong alkali to the solution of chloranil.[11] In the absorption spectra of chloranil in the aqueous solution of 1N of sodium hydroxide, absorption maximums were observed at 330 nm and 535 nm. Four peaks were observed at 293 nm, 315 nm, 360 nm and 530 nm in the absorption spectra of the equilibrium solution of the violet powders of the ball-milled mixture of PVP and chloranil. The peaks at 360 nm and 530 nm disappeared by acidification of the equilibrium solution with hydrochloric acid (Fig. 15). It is probable that the peaks at 360 nm and 530 nm for the ball-milled mixture are due to the radical like the chloranil semiquinone anion generated by the interaction of chloranil with PVP. But little amount of the precipitates was observed by acidification of the equilibrium solution of the violet powders of the ball-milled mixture. On the contrary, precipitates were observed by acidification of the solution of the green powders. It is suggested from the above findings that the peak around 310 nm in the absorption spectra of the equilibrium aqueous solutions of the ball-milled mixtures of PVP and chloranil is due to the adduct of PVP and chloranil formed by an electron transfer from PVP to chloranil without replacement of chlorine in the chlorianil moiety. It may be

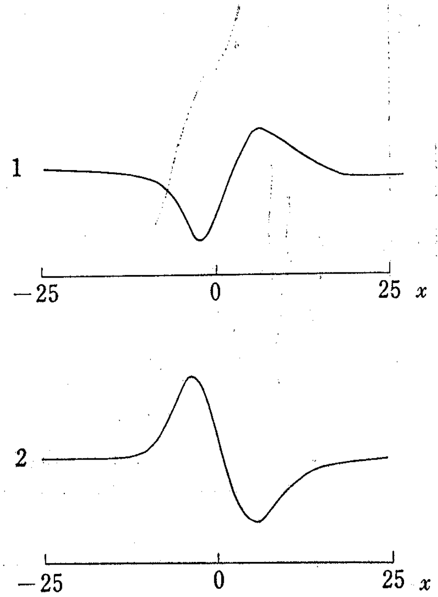

Fig. 14. Electron Spin Resonance Spectra of the Powders of the Ball-Milled Mixtures of PVP K90 and Chloranil

1 the sample; ball-milling time: 215 hours
ball-milling condition: the same as the condition for the sample No. 10 in Table I
field: $3360 \pm x$ gauss
Measurement was made by inserting in a sample tube of quartz in diameter of 4 mm a pyrex tube in diameter of 1 mm containing the powders of the ball-milled mixture.

2 the sample; No. 10 in Table I
field: $3356 \pm x$ gauss
Measurement was made by inserting the ball-milled powders directly into a sample tube of quartz in diameter of 4 mm.

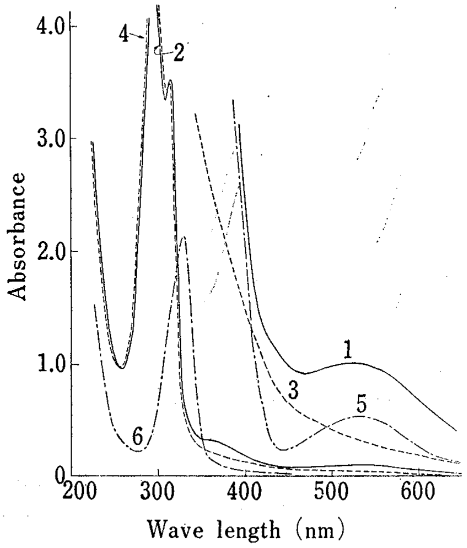

Fig. 15. Comparison of the Absorption Spectra of the Aqueous Solution of the Mixture of PVP K90 and Chloranil Ball-Milled in Air with those of the Alkaline Solution of Chloranil

1 3 ml of the aqueous solution of 11.8 mg of the sample No. 10 in Table I
2 the diluent of "1" with distilled water to 1/5
3 the solution of the mixture of 2 ml of distilled water and 1 ml of the diluted hydrogen chloride of JP grade containing 11.8 mg of the sample No. 10 in Table I
4 the diluent of "3" with the mixture of 3 ml of distilled water and 1 ml of diluted hydrogen chloride of JP grade to 1/5
5 10 ml of the aqueous solution of 1N of sodium hydroxide containing 9.3 mg of chloranil immediately after the preparation (Reddish needle-shaped solids were precipitated gradually with the lapse of the time.)
6 the diluent of "5" with the aqueous solution of 1N of sodium hydroxide to 1/45

also suggested that the peak around 360 nm is due to the product of a structure similar to the chloranil semiquinone ion radical which is derived from the adduct of PVP and chloranil possibly by replacement of chlorine in the chloranil moiety with PVP.

The yellow mixture of PVP and vitamin K_3 turned into reddish orange by ball-milling. Absorbance of the chloroform solutions on the mixture of PVP and vitamin K_3 at the wave length longer than 400 nm increased by ball-milling, as shown in Fig. 16. The IR spectra of the KBr tablets of vitamin K_3 purified from the ball-milled mixture with PVP by the procedure referred to purification of phenothiazine were identical with those of original vitamin K_3. Vitamin K_3 is soluble and PVP is insoluble in carbon tetrachloride. A reddish orange solution was obtained by the extraction of the aqueous suspension of the ball-milled mixture of PVP and vitamin K_3 with carbon tetrachloride. The IR spectra of the chloroform solutions of the powders obtained by drying the reddish orange carbon tetrachloride solution were similar to those of the physical mixture of them (Fig.17). It is suggested that interaction is caused between PVP and vitamin K_3 by ball-milling the mixture.

Fig. 18 shows the variation of absorbance of chloranil in the equilibrium aqueous solutions from the ball-milled mixture with PVP at 295 nm with the content of chloranil in the mixture.

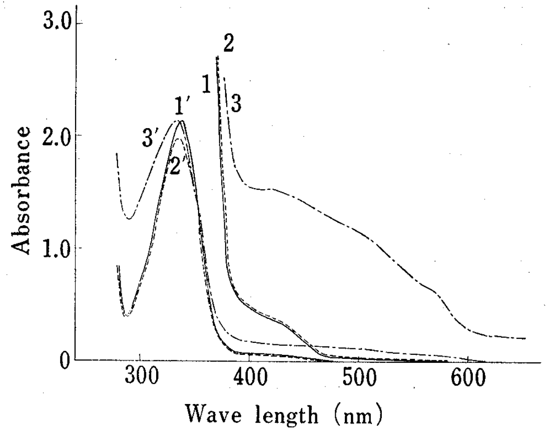

Fig. 16. Absorption Spectra of the Chloroform Solutions of Vitamin K_3 prepared from Various Samples

sample
1 ————: 3 ml of the solution of 3 mg of vitamin K_3
2 -----------: 3 ml of the solution of 33 mg of the mixture of PVP K15 and vitamin K_3 in the ratio of 9: 1 by weight
3 —·—·—: 3 ml of the solution of 32 mg of the sample No. 15 in Table I
i' (i=1, 2 or 3)
the diluent of 1/9 of the solution "i"

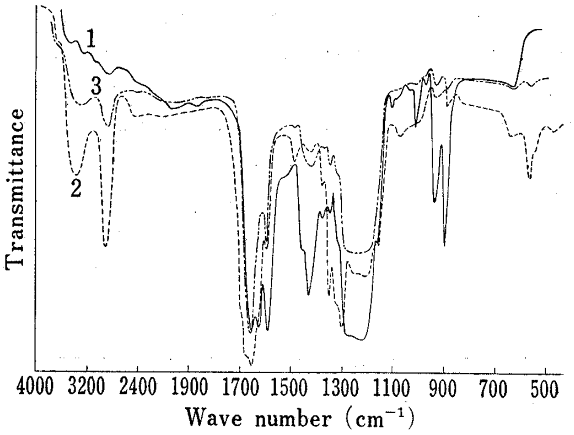

Fig. 17. IR Spectra of the Chloroform Solutions of Vitamin K_3 prepared from Various Samples

sample 1 vitamin K_3
2 the mixture of PVP K15 and vitamin K_3 in the ratio of 9: 1 by weight
3 the powders obtained by the extraction of the aqueous suspension of the sample No. 15 in Table I with carbon tetrachloride

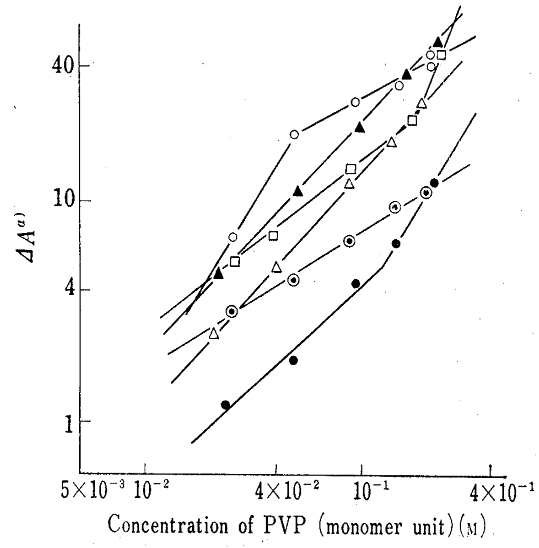

Fig. 18. Influence of the Content of Chloranil in the Mixture with PVP on Solubility of Chloranil from the Ball-Milled Mixture in Distilled water

The equilibrium solutions were obtained by suspending various amounts of the following samples tabulated in Table I in 3 ml of distilled water.
the sample number in Table I
▲: 8 ●: 9 △: 11 ○: 12 ⊙: 13 □: 14
a) the difference of absorbance of the equilibrium solution of chloranil at 295 nm from that of the aqueous solution of the same concentration of PVP

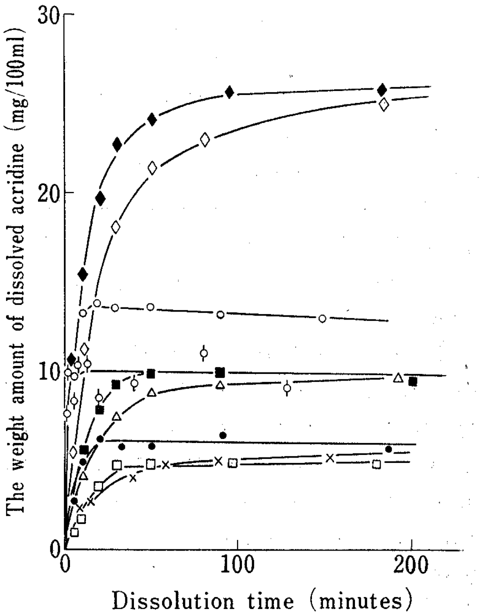

Fig. 19. Dissolution Rate of Acridine in Distilled water from Various Samples

Each of the samples containing 50 mg of acridine was added to 100 ml of distilled water at 30°.
sample
×: acridine ●: ball-milled acrdine
the mixture of acridine and PVP or α-pyrrolidone in the ratio of 1: 9 by weight.
□: α-pyrrolidone ◇: PVP K15
■: PVP K30 △: PVP K90
The mixture of ball-milled acridine and PVP K15 in the ratio of 1: 9 by weight ◆
the sample number of the samples in Table I
ϕ: 2 ○: 4

The absorbance was large when molecular weight of PVP decreased remarkably by ball-milling or when the content of chloranil in the mixture was large in case of the content below 40 w/w%. But an increase of the absorbance with an increase of the concentration of PVP was small in case of the content of chloranil above 20 w/w%. In case of 70 w/w% of the content of chloranil, the absorbance was small and an increase of the absorbance with an increase of the concentration of PVP was also small. The molecular weight of PVP K15 did not decrease by ball-milling and violet powders were obtained by ball-milling the mixture with chloranil for a short time. An increase of the absorbance with an increase of the concentration of PVP was more remarkable in case of the violet mixture of PVP K90 than in case of the mixture of PVP K15.

3) The Dissolution Rate of Slightly Soluble Substances in Distilled Water from Various Samples

As shown in Fig. 19, the dissolution rate of acridine from the physical mixture with PVP in distilled water increased with a decrease of molecular weight of PVP. The dissolution rate of ball-milled acridine was larger than that of the original acridine. But the dissolution rate of acridine from the ball-milled mixture with PVP was identical with or larger than the rate from the physical mixture of PVP K15 and the ball-milled acridine, though solubility of acridine in the equilibrium solution of the ball-milled mixture was smaller than the solubility in the solution of the physical mixture. In case of the other substances, the dissolution rate of them from the ball-milled mixture with PVP was larger than the rate from the other samples. In case of chloranil and phenothiazine, the dissolution rate of the original material, the material ball-milled individually and the rate from the physical mixture with PVP was small and even after six days from the time of the addition of the sample to distilled water, they continued to dissolve very slowly. But the dissolution rate of them from the ball-milled mixture with PVP was large and, within ten minutes from the time of the addition of the ball-milled mixture to distilled water, dissolution of them was equilibrated. Nakai, *et al.* also reported that the dissolution rate of organic powders such as phenacetin in distilled water increased by vibro-milling in the presence of microcrystalline cellulose.[5,12,13] The equilibrium concentration of the slightly soluble substances other than acridine obtained within ten minutes from the time of the addition of the ball-milled mixture with PVP to distilled water did not drop even after six days. The concentration of acridine dissolved from the ball-milled mixture with PVP was the largest after 10—20 minutes from the time of the addition of the mixture to distilled water and after 20 minutes decreased slightly with the lapse of the time, but after 200 minutes the concentration was equilibrated and did not drop any more even after six days.

It was reported in the previous paper that the rate of an increase of the surface area of sulfadimethoxine and white alundum by ball-milling was proportional to $J_b^{\alpha}\ J_s^{-\beta}$ in case of J_b below 0.5, where J_b and J_s were the ratio of the volume of the balls and the materials inserted in a mill to the capacity of a mill, respectively. The value of α was 1.8—2.1 and the value of β was 1.3—1.7 in case of the revolving velocity of a mill of 0.70—0.85 times of the critical velocity.[3] It was reported in our another paper that the particle size of the organic powders such as sulfadimethoxine and acetanilide was approximately equilibrated within 30 hours of ball-milling in a ceramic mill with ceramic balls of true density of 2.4 g/cm^3, and the equilibrated particle size by the air permeability method was 1—2 μm.[14] It is considered from the above facts that the particle size of the organic substances was equilibrated after ball-milling under the conditions in Table I. The dissolution rate of the slightly soluble substances increased by ball-milling in the presence of PVP, whether interaction of them with PVP was

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[12] Y. Nakai, E. Fukuoka, S. Nakajima, and K. Yamamoto, The 93 th Annual Meeting of Pharmaceutical Society of Japan, Tokyo. Apr., 1973, p. 5N2-1.

[13] Y. Nakai, S. Nakajima, and K. Sugiyama, The 94 th Annual Meeting of Pharmaceutical Society of Japan, Sendai, Apr. 1974, p. 5S10-5.

[14] A. Ikekawa, K. Imagawa, T. Omori, and N. Kaneniwa, *Chem. Pharm. Bull.* (Tokyo), **19**, 1027 (1971).

caused or increased by ball-milling or not. It may be probable that the particle size of the slightly soluble substances obtained by ball-milling with PVP is smaller than the size obtained by ball-milling separately.

4) The Change in Crystallinity of the Organic Powders by Ball-milling in the Presence of PVP

As shown in Fig. 20, the signals of acridine in the X-ray diffraction diagram of the physical mixture with PVP of amorphous structure deteriorated gradually and disappeared by ball-milling, without concern in a decrease of molecular weight of PVP. The same phenomenon was also observed for the mixture of PVP and phenothiazine or vitamin K_3. But the X-ray diffraction diagrams of acridine, phenothiazine and vitamin K_3 ball-milled separately were nearly identical with those of the original substances, respectively. It was also found by Nakai, *et al.* that crystalline powders such as acetylsalicylic acid turned amorphous by vibro-milling in the presence of microcrystalline cellulose.[12,13,15,16]

The depth of water was approximately 1.5 cm, when 3 ml of water was added to the test tube in the inside diameter of 1.5 cm. According to the Stokes'es law, it takes approximately five days for the particles of diameter of 0.1 μm and with true density of 1.5 g/cm^3 to fall from the surface of the water to the bottom of the test tube. Accordingly, it is expected to take more than five days for the particles of the slightly soluble substance in diameter of 0.1 μm in the mixture with PVP because of the viscosity of the solution higher than that of distilled water, Brown's movement of the particles and so on. A small part of the particles of vitamin K_3 in the ball-milled mixture with PVP were still suspended in the solution after five days from the time of the preparation of the suspension, but the large part of them precipitated within five days. Almost all the particles of the other slightly soluble substanses in the ball-milled mixture with PVP also precipitated within five days. The resolution ability of X-ray diffraction for the particles below 0.1 mμ is low. Accordingly, the signals are broadened and the diffraction intensity of the signals is extremely small in the diffraction diagram of the

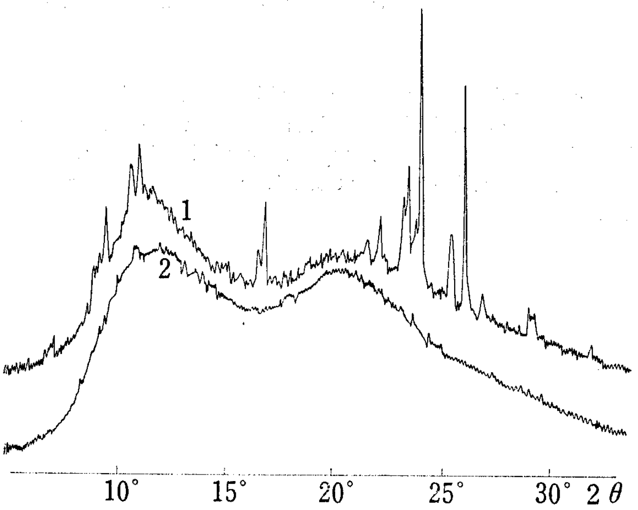

Fig. 20. Influence of Ball-Milling on X-Ray Diffraction Diagram of the Mixture of PVP and Acridine

1 the physical mixture of PVP K90 and acridine in the ratio of 9:1 by weight
2 the mixture of "1" ball-milled in air for 207 hours (the sample No. 5 in Table I)

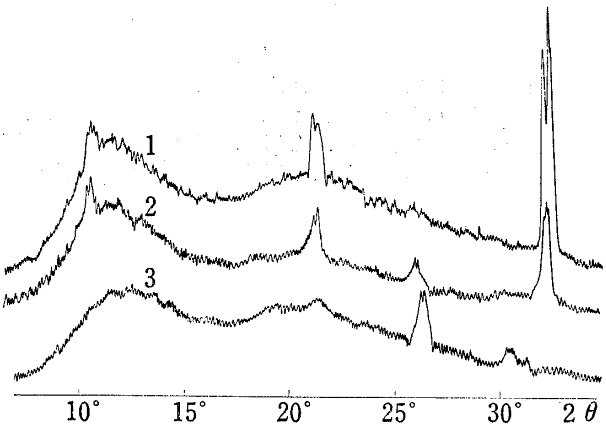

Fig. 21. Influence of Ball-Milling on X-Ray Diffration Diagram of the Mixture of PVP and Chloranil

1 the physical mixture of PVP K90 and chloranil in the ratio of 9:1 by weight
2 the sample No. 9 in Table I
3 the sample No. 10 in Table I

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15) Y. Nakai, E. Fukuoka, S. Nakajima, and K. Yamamoto, The 92 th Annual Meeting of Pharmaceutical Society of Japan, Osaka, Apr. 1972, p. 5B10-2; Y. Nakai, S. Nakajima, and K. Sugiyama, The 95 th Annual Meeting of Pharmaceutical Society of Japan, Nishinomiya, Apr., 1975, p. 5P1-5; Y, Nakai, S. Nakajima, Y. Miyajima, and N. Miyamoto, *ibid.*, p. 6P3-3.

16) Y. Nakai, S. Nakajima, and Y. Iida, The 94 th Annual Meeting of Pharmaceutical Society of Japan, Sendai, Apr. 1974, p. 5S10-4; *idem.*, The 95 th Annual Meeting of Pharmaceutical Socity of Japan, Nishinomiya, Apr., 1975, 5P1-4.

particles below 0.1μm. But, it is considered from the above fact that crystallinity of acridine and phenothiazine decreases by ball-milling in the presence of PVP, though it is not clear whether this phenomenon contributes to an increase of solubility and the dissolution rate of these substances in distilled water by ball-milling in the presence of PVP or not.

As shown in Fig. 21, a new signal appeared around 26° of 2θ in the X-ray diffraction diagram of the mixture of PVP and chloranil by ball-milling for the time below the induction period, which was approximately 210 hours under the condition for the samples No. 9 and 10 in Table I. After the lapse of the induction period, the signals of the original chloranil disappeared and another small new signal appeared around 30.5° of 2θ. The same tendency was also observed by ball-milling chloranil alone, but it did not seem to be so remarkable as in the case of ball-milling with PVP. More details will be reported in the separated paper concerning this phenomenon.

The four substances slightly soluble in distilled water were much soluble in benzene or carbon tetrachloride. But these substances dissolved little in these solvents from the ball-milled mixture with PVP. Vitamin K_3 and acridine dissolved in these solvents by shaking the mixture of the aqueous suspension of the ball-milled mixture with PVP and these solvents, though even by this procedure, chloranil and phenothiazine dissolved little in these solvents because of the interaction with PVP. Nakai, *et al.* also found the similar phenomena. Vibro-milling easily sublimated powders such as *d*-camphor in the presence of microcrystalline cellulose prevented them from sublimation.[16] They also found that microcrystalline cellulose had a porous structure and that the number of the pore in diameter around 40 Å increased in the microcrystalline cellulose after the removal of benzoic acid from the vibro-milled mixture by dissolution in a solvent.[12] It is probable from these findings that the slightly soluble substances disperse in the solid of PVP in fine particles by ball-milling with PVP. An increase of the solubility, the dissolution rate in distilled water and the change in the crystal structure of these substances are probably due to dispersion of them in the solid of PVP in fine particles by ball-milling with PVP.

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