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Binding of Mequitazine with Polyvinylpyrrolidone and Sodium Alginate and Its Effect on the Precipitate Formation of Mequitazine in an Aqueous Phase

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Mequitazine (Meq; 10-(3-quinuclidinylmethyl)phenothiazine) disolved in water formed a complex with polyvinylpyrrolidone (PVP) due to hydrophobic interaction and with sodium alginate (NaAlg) by virtue of ion–dipole and/or –ion interaction between carboxylate groups and quinuclidinyl groups. The binding ratio of Meq to NaAlg was higher than that to PVP, while the adsorption amount of PVP by solid Meq was higher than that of NaAlg. It was shown by electrophoresis that a positive charge of Meq particles was reversed to a negative one after the adsorption of alginate. The degree of crystallinity of Meq recrystallized from an aqueous solution of these polymers was examined by an X-ray powder diffractometry. It decreased with polymer concentration owing to the complex formation and adsorption onto its crystal nuclei and/or embryos.

Keywords mequitazine; sodium alginate; polyvinylpyrrolidone; complex formation; crystallization; adsorption; phenothiazine

Since sodium alginate (NaAlg) is an anionic polysaccharide, it binds cationic and basic chemical species dissolved in water through ion–ion or ion–dipole interaction. It easily captures Ca^{2+}, for example, and gells with the formation of intermolecular egg-box junction.[1] On the other hand, piperazinium cation competes for its binding sites on alginate (Alg) with monovalent alkali metal cation (*i.e.*, Na^+, K^+, and Li^+) without the gelation, although piperazinium cation is bivalent.[2] Specific affinity of bivalent Ca^{2+} for gluronate residues of Alg is responsible for the gelation through the formation of an egg-box junction. The interaction of Alg with organic drugs has been well studied to date by means of the complex/adduct formation method and the mixture kneading method in an attempt to sustain release, prolong absorption, and/or improve the dissolution properties.[3–7]

It is wellknown that polyvinylpyrrolidone (PVP) forms a complex with a cosolute in an aqueous phase through hydrophobic effect, dipole–dipole interaction, and hydrogen bonding.[8,9] The cosolute often forms amorphous solid solution with PVP when it coprecipitates from an aqueous solution of the mixture. Solubility and dissolution rate of a solid solution or an amorphous coprecipitate are usually higher than those of the original crystalline substance itself.[10–13] PVP also behaves as a stabilizing agent for an aqueous colloidal suspension of β-carotene when a solid solution of β-carotene in PVP is re-dissolved in water.[14] This solid solution was prepared from a chloroform solution by evaporating the solvent. In fact, PVP is often used as a dispersing agent in various suspensions,[15] because it behaves as a protecting colloid after the adsorption.

The large and almost planar nature of hydrophobic phenothiazines such as chlorpromazine hydrochloride and promazine hydrochloride is conductive to stacking of the monomers. The self-association has been studied by a time-average light scattering method and a ultrasound velocity measurement method, where two or three inflection points were observed in plots of light scattering intensity and ultrasound velocity against molarity.[16] These phenothiazines are also known to be included in a cavity of β-cyclodextrin (β-CyD), forming a inclusion complex. According to a report by Otagiri *et al.*,[17] the spectral changes strongly suggested that the aromatic portion was included in the hydrophobic cavitiy of β-CyD, while the N-substituent interacted with the outside group of the cavity. Mequitazine (10-(3-quinuclidinylmethyl)phenothiazine; Meq, shown in Fig. 1), which is of interest in this paper, also showed spectroscopic data suggesting complex formation with β-CyD in an aqueous solution in our preliminary experiment. Unfortunately, however, the signal was too weak to analyze quantitatively.

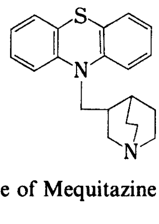

Fig. 1. Molecular Structure of Mequitazine

In the present paper, formation of another type of complex with polymers (PVP and NaAlg) as well as adsorption of these polymers on pulverized Meq was studied. Since Meq is hydrophobic and basic owing to its quinuclidinyl group, the interaction with hydrophobic PVP and anionic Alg was expected in an aqueous solution. The affinity of these polymers toward Meq dissolved in water was compared with that toward the solid suspended in a water phase. One of the interesting points in this paper is that the data of both complex formation and adsorption were obtainable because molar absorption coefficient of Meq is high but its solubility is low. Taking these experimental results into account, the effect of these polymers on crystallinity of Meq recrystallized from an aqueous phase was discussed. The effect varied depending on species and concentration of the added polymer.

Experimental

Materials Meq ($C_{20}H_{22}N_2S = 322.47$) was a gift from Nippon Shoji Kaisha, Ltd. (Osaka). It was a fine and white powder freely soluble in methanol but very slightly soluble in water. The solubility in distilled water at 25 °C was *ca.* 2.1×10^{-4} M. This sample was used as it was without further purification.

NaAlg was the same sample as that used in the previous paper.[2] It was kindly provided by Sakai Chemical Industry Co., Ltd. (Osaka). The viscosity average molecular weight was 4.65×10^5.[2] An apparent degree of dissociation of Na^+ from NaAlg was 42%,[2] which was close to the literature value (=45%) reported by Yonese *et al.*[18] The fractions of gluronate (F_G) and mannuronate (F_M) were 0.55 and 0.45, while those of the consecutive gluronate block (F_{GG}), the consecutive mannuronate block

(F_{MM}), and alternative block composed of gluronate and mannuronate (F_{GM}) were 0.40, 0.31, and 0.29, respectively, as mentioned elsewhere.[2]

PVP was purchased from Nakarai Chemicals Ltd. (Kyoto). The viscosity average molecular weight of PVP K-90, K-30, and K-25 was 111×10^4, 4.21×10^4, and 2.81×10^4, respectively. PVP K-90 was mainly used in the present study.

All other reagents used here were analytical grade and were used without further purification.

Concentration Determination Concentrations of PVP and NaAlg in stock solutions were determined by weighing the residue after drying at 105—110 °C. As the formula weight of a repeating unit of PVP and that of a sugar unit of NaAlg are 111 and 198, 1 mM PVP and 1 mM NaAlg are equivalent to 111 mg/l and 198 mg/l, respectively. Equilibrium concentration of NaAlg for the adsorption experiments was determined by colorimetry according to the method of Disch, Bitter, and Muir at 530 μm.[19] That of PVP was also determined by colorimetry at 470 μm after formation of a brownish red complex with tri-iodide (I_3^-) when PVP was at low concentration,[20] while by iodometry toward I_2 contained in the complex when the concentration of PVP was rather high.[21]

Meq concentration was determined by optical absorption of ultraviolet light ($\lambda = 253$ μm), where, according to the supplier, the molar absorption coefficient, ε, is 3.05×10^4. It was confirmed that salts such as NaCl and $CaCl_2$ do not interfere with the determination of Meq.

Dialysis Equilibrium Dialysis equilibrium was attained with gentle shaking at 4 °C for 7 d using a Visking cellulose tubing (Union Carbide Co.). The initial solution in the tubing (inner solution) was of Meq containing known amount of polymer (NaAlg or PVP K-90) and salt (NaCl or $CaCl_2$). The tubing was soaked in an aqueous solution of a simple salt (outer solution), of which the initial concentration was the same as that in the inner solution. It was confirmed that polymer does not precipitate in the presence of Meq and a salt through the concentration range studied here. After attaining an equilibrium with respect to membrane-permeable cosolute, Meq in the outer solution was determined. Binding ratio of Meq to a polymer was obtained as a molar ratio of Meq to a repeating unit of PVP or to a sugar unit of NaAlg. It was shown as a function of free concentration of Meq in an outer solution.

Polymer Adsorption Powder Meq (1 g) was suspended in an aqueous solution (20 ml) of a known concentration of PVP or NaAlg without a simple salt at 25 °C for 24 h. Concentration of a polymer in a supernatant of a mother solution at adsorption equilibrium was determined after centrifugation. The effect of added salt on the adsorption amount was not studied here in order to save the Meq sample by avoiding repeating similar measurements. The adsorption amount was determined as weight of bound polymer per unit weight of added Meq (mg/g) from a difference in polymer concentration before and after the adsorption without correction for loss of solid Meq, although the apparent solubility of Meq might increase with a concentration of polymer owing to the complex formation. Therefore, the adsorption isotherm obtained here is an apparent one. Loss of solid Meq due to the dissolution/complex formation was not corrected in the present paper, because the dissolved amount and/or the amount of complex formation are insignificant.

Zeta Potential Zeta potential of Meq particles in an aqueous suspension was measured using a Laser Zee TM (model 501, Pen Kem Inc.) at room temperature (*ca.* 25 °C). The particle size of raw Meq was too coarse to measure. Therefore, a suspension of fine particles of Meq was prepared as follows: 2 ml of a methanol solution of Meq (2.5%) was added by drops to an aqueous solution of NaCl (50 ml) containing a known amount of the polymer (PVP or NaAlg). Immediately after the mixing, fine white particles were formed. It was subsequently diluted with the same diluent to form *ca.* 10^{-2}% suspension, which was subjected to measurement. The solution pH was 8.8—9.2.

Particle Size Measurement by a Coulter Counter Mean diameter (d) and number concentration (n) of Meq particles in a suspension were measured by a Coulter counter (Coulter Electronics, Inc., type TA II, aperture size 100 μm) at room temperature (*ca.* 25 °C). A sample for the measurement was prepared *via* two step dilution as follows: 4 ml of 8% Meq solution in methanol was added by drops into 100 ml of an aqueous solution of NaCl (0.9%) containing known amount of polymer, resulting in an aqueous suspension of Meq. It was diluted again 100-fold with a NaCl solution (0.9%) at given time intervals (t), and immediately subjected to measurement to obtain the time courses for d and n of the secondary particles of the precipitate.

X-Ray Powder Diffraction Particles were examined with a diffractometer (Toshiba ADO-301, CuK_α radiation at 35 kV and 10 mA) at room temperature.[22] Samples for the diffraction measurement were prepared at room temperature after treatment with dry ice and acetone by means of freeze-drying of a suspension which was obtained by pouring 10 ml of a methanol solution of Meq (*ca.* 8%) into 250 ml of an aqueous solution of the additive of a known concentration with stirring. Typical diffraction peaks for Meq crystallites were observed at two diffraction angles, $2\theta = 11.6$ and 18.3 deg. However, they were not assigned to the specific crystal lattice faces, because crystallographic data for Meq were not found even in the Cambridge Crystallographic Data Bank (1990). Reproducibility of the diffraction within a range of experimental error was confirmed.

Results

Binding Isotherm of Meq to a Polymer in an Aqueous Phase Figure 2 shows binding isotherms of Meq to NaAlg and PVP. The binding ratio to Alg was remarkably higher than that to PVP. The former decreased with a concentration of added salt. The effect of $CaCl_2$ was more conspicuous than that of NaCl.

These results show the following facts: hydrophobic interaction of Meq with PVP is rather weak although PVP is a typical hydrophobic polymer; on the other hand, the binding of Meq with Alg is due mainly to ion–dipole and/or –ion interaction because the binding ratio decreases with a salt concentration. Nitrogen atom in the quinuclidinyl group is known to be easily protonated. Solution pH was weakly basic (*ca.* pH 9), as expected. That is, Meq electrostatically competes for carboxylate groups of Alg with Na^+ and Ca^{2+}. Calcium ion particularly shows high affinity for Alg,[1,18,23] and this results in selective binding of Ca^{2+} to Alg and, concomitantly, in exclusion of Meq from the polymer domain with an increase in concentration of added $CaCl_2$.

Adsorption Isotherms of Polymers to Solid Particles of Meq The adsorption isotherms of PVP and Alg to solid Meq are shown in Fig. 3. It is interesting that the adsorption amount of PVP by unit weight of Meq (solid) is markedly higher than that of NaAlg, whereas the binding ratio of Meq (soln) to the former was remarkably lower than that to the latter (shown in Fig. 2).

Zeta Potential Zeta potential of Meq particles is shown

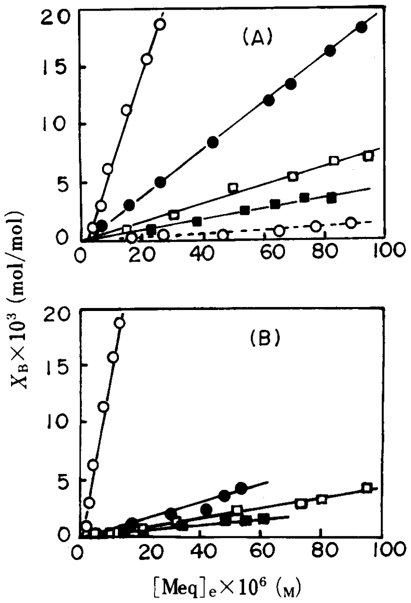

Fig. 2. Binding Ratio of Meq to NaAlg and PVP in an Aqueous Phase

Binding ratio (X_B) of Meq to a sugar residue of NaAlg (——) and to a repeating unit of PVP K-90 (– – –) is shown as a function of equilibrium concentration of Meq, $[Meq]_e$.

(A) [NaCl] (mM) = 0 (○), 1 (●), 2 (□), 5 (■). (B) [$CaCl_2$] (mM) = 0 (○), 0.75 (●), 1.5 (□), 2.5 (■).

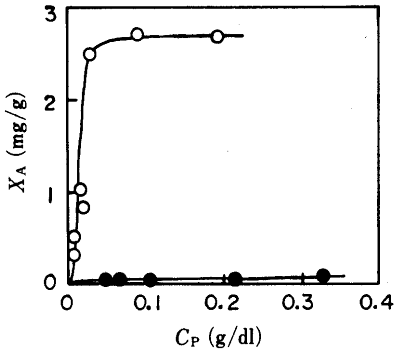

Fig. 3. Amount of Polymer Absorbed by Solid Meq

Amount (X_A) of PVP K-90 (○) and NaAlg (●) absorbed by Meq particles is shown as a function of an equilibrium concentration of a polymer, c_P.

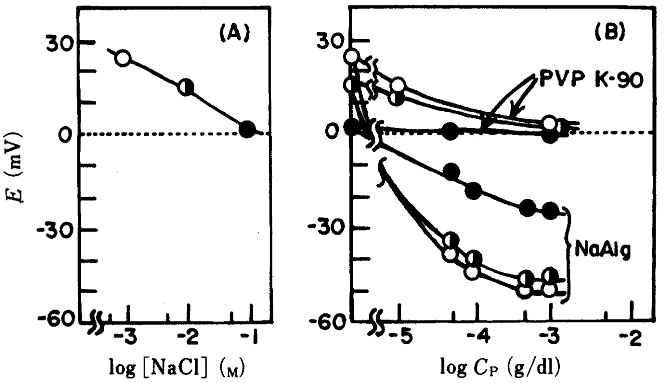

Fig. 4. Zeta Potential of Meq Particle

[NaCl] (mM) = 10^{-3} (○), 10^{-2} (◑), 10^{-1} (●).

Zeta potential (E) is shown as a function of a concentration of added NaCl in the absence of polymer (A), and as a function of a concentration of added polymer (c_P) in the presence of NaCl (B).

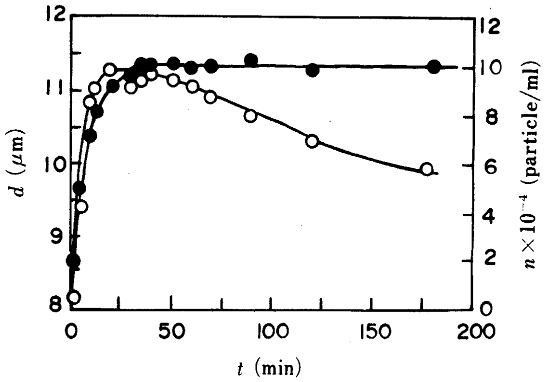

Fig. 5. Time Courses of Mean Diameter and Number Concentration of Meq Particles

Mean diameter (d; ●) and number concentration (n; ○) shown in this figure are those after the 100-fold dilution (see text).

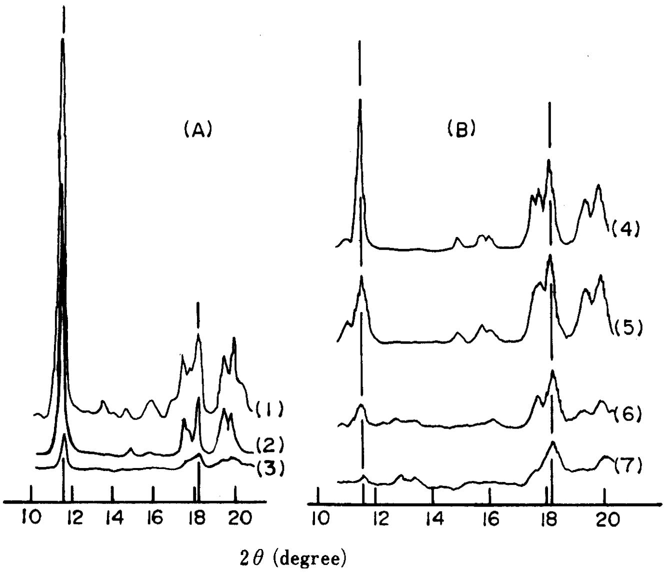

Fig. 6. X-Ray Powder Diffraction Patterns of Meq in the Presence of PVP K-90

Samples: (1) raw Meq, (2) Meq recrystallized from water, (3) physical mixture of Meq and PVP K-90 at 1 : 1 weight ratio, (4) recrystalized Meq from an aqueous solution of 10^{-3}% PVP, (5) from 10^{-2}% PVP, (6) from 10^{-1}% PVP, and (7) from 1% PVP. Patterns (2) and (4)—(7) were those of the samples obtained 2 h after the precipitation.

in Fig. 4 as a function of additive concentration. It was positive in an aqueous solution of NaCl but decreased with NaCl concentration. It also decreased with increase in a concentration of PVP at a given concentration of NaCl, because the slipping plane moved outside by virtue of protruding loops of adsorbed PVP. In contrast, it was reversed from positive to negative value at a certain concentration of added NaAlg owing to the negative charges of adsorbed Alg.

These electrophoresis data show that the bare particles carry positive charges because quinuclidinyl groups on the surface are protonated even at around pH 9. Alg was, therefore, adsorbed through electrostatic interaction between its carboxylate groups and quinuclidinyl groups on the surface of those particles probably with rather flat conformation. On the other hand, PVP was adsorbed *via* hydrophobic and van der Waals interaction between some of the segments of PVP and hydrophobic domain of the particles. The other segments are unattached on the surface but protrude into the solution, forming loops. Consequently, the adsorption amount of PVP was larger than that of NaAlg (PVP/Meq > NaAlg/Meq in Fig. 3). This is consistent with the result that the higher the affinity of Meq (soln) for polymer, the higher the ratio of the bound Meq to polymer (Meq/NaAlg > Meq/PVP in Fig. 2).

Formation of Secondary Particles of Recystallized Meq Figure 5 shows time courses of mean diameter (d) and number concentration (n) of Meq particles formed in an aqueous phase (0.9% NaCl) in the absence of polymer. The particle size increased monotonously with time and levelled off ($d = 11.3\,\mu$m, $t \geq 90$ min), while the particle number decreased after attaining a maximum. These results mean that large secondary particles of Meq were formed after aggregation of small particles. When polymer was added to an aqueous solution of 0.9% NaCl, the value of d decreased with its concentration (*i.e.*, dispersing effect) after attaining a maximum at $c_P = ca.\ 10^{-3}$% (*i.e.*, flocculating effect). Maximums of d at $t = 120$ min were 47 μm for PVP K-90, 35 μm for PVP K-30, and 32 μm for NaAlg (compare with $d = 11.3\,\mu$m for a suspension in the absence of a polymer). The d at the maximum in the presence of NaAlg was smaller than that in the presence of PVP K-90 or K-30 because the polymer chain of adsorbed Alg causes interparticle electrostatic repulsion synchronously with interparticle bridging.

X-Ray Powder Diffraction by Recrystallized Meq Meq particles prepared under various conditions were examined

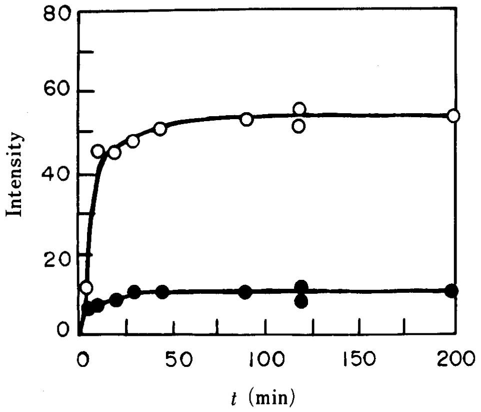

Fig. 7. Time Courses of Diffraction Intensity

2θ(deg) = 11.6 (○) and 18.3 (●). Diffraction intensity is in arbitrary units, directly read from the scale of a recording chart.

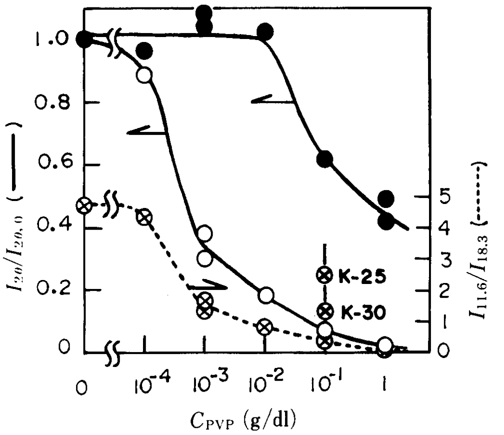

Fig. 8. Effect of PVP K-90 Concentration on Diffraction Intensity

—●—: $I_{2\theta}/I_{2\theta,0}$ at $2\theta = 18.3$ deg, —○—: $I_{2\theta}/I_{2\theta,0}$ at $2\theta = 11.6$ deg, --⊗--: $I_{11.6}/I_{18.3}$. Plots (⊗) on $c_{PVP} = 10^{-1}$ g/dl with terms of K-25 and K-30 are those for PVP K-25 and PVP K-30, respectively.

by X-ray powder diffractometry. Diffraction patterns (1), (2), and (3) in Fig. 6A are of raw material supplied from the company, of a recrystallized material from water without any additive ($t = 120$ min), and of a physical mixture of dry raw Meq with dry PVP K-90 at 1 : 1 weight ratio in a mortar with a pestle, respectively. Diffraction patterns (4)—(7) in Fig. 6B are those of Meq recrystallized from an aqueous solution containing various concentrations of PVP K-90 ($t = 120$ min).

Figure 7 shows time courses of the diffraction intensity at $2\theta = 11.6$ and 18.3 deg for the sample recrystallized from water. Strictly speaking, the diffraction angles immediately after the preparation of the sample were slightly smaller than those at the equilibrium: 11.3 and 18.1 deg at 5 min, 11.5 and 18.2 deg at 20 min, and 11.6 and 18.3 deg at 45 min and longer, for example. This transient deviation was due to the loose and unstable molecular array immediately after the precipitation. In any event, diffraction angles as well as mean diameter of the particle (Fig. 5) had attained equilibrium within 2 h after the mixing. Therefore, the samples for measurements were obtained 2 h after their preparation.

In Fig. 6, the diffraction intensity (or crystallinity) of (1) was the highest among the samples examined here. The shape of diffraction pattern of (2) was quite similar to that of (1). The ratio of diffraction intensity at $2\theta = 11.6$ deg ($I_{11.6}$) to that at $2\theta = 18.3$ deg ($I_{18.3}$) was 4.8 and 4.7 for (1) and (2), respectively. The half width of (1) at $2\theta = 11.6$ deg was almost the same as that of (2). These results mean that crystallinity or total number of crystallites in the raw material is higher than that in the recrystallized material, but the size of each crystallite is almost the same between these samples.

Diffraction intensities at $2\theta = 11.6$ and 18.3 deg in the diffraction pattern (3) were lower than those in (1) and (2). The decrease in $I_{11.6}$ was more remarkable than that in $I_{18.3}$, resulting in $I_{11.6}/I_{18.3} = 2.8$. This is smaller than 4.7—4.8 for (1) and (2), and shows that the diffraction at $2\theta = 11.6$ deg is more easily interfered by PVP than that at $2\theta = 18.3$ deg. For Meq recrystallized from a PVP solution, the PVP effect becomes more conspicuous, as is mentioned later.

Comparison of diffraction patterns among (4) through (7) revealed the following facts: the diffraction intensity decreased with a concentration of PVP (c_{PVP}); the diffraction at $2\theta = 11.6$ deg almost disappeared at $c_{PVP} = 1\%$ while that at $2\theta = 18.3$ deg was still clearly observable, although the diffraction at 11.6 deg was stronger than that at 18.3 deg in the case of (1)—(4). These diffraction angles were invariable irrespective of the PVP concentrations studied. Therefore, we need not consider the intercalation by PVP[24] but must to consider the effect of PVP on molecular array of Meq and on diffraction intensity. Because the diffraction peak at $2\theta = 11.6$ deg diminishes rapidly with c_{PVP} and the shape of the diffraction peak at $2\theta = 18.3$ deg is rather complicated, it is difficult to discuss a crystallite size from the half width.

Figure 8 shows relative diffraction intensity ($I_{2\theta}/I_{2\theta,0}$) at $2\theta = 11.6$ (○) and 18.3 deg (●) as a function of c_{PVP}, where $I_{2\theta}$ and $I_{2\theta,0}$ are the diffraction intensity of Meq prepared in the presence and absence of PVP K-90, respectively. $I_{18.3}$ decreased with c_{PVP} after remaining almost constant up to $c_{PVP} = ca.\ 10^{-2}\%$, whereas $I_{11.6}$ decreased more steeply with c_{PVP}. This shows again that the effect of PVP on diffraction at 11.6 deg was more remarkable than that at 18.3 deg. Therefore, the ratio $I_{11.6}/I_{18.3}$ also decreased with c_{PVP} (⊗). However, the ratio at $c_{PVP} = 10^{-1}\%$ increased in the order of PVP K-90, K-30, and K-25; that is, the effect of PVP weakened with decrease in the molecular weight.

These results show that diffraction intensity and/or crystallinity of Meq was significantly affected by the concentration and molecular weight of added PVP. PVP seems to interfere with crystallite formation by its adsorption on the surface of crystal nuclei as well as by its complex formation with Meq on the nuclei surface. The thickness of adsorption layer (*i.e.*, size of the loops) and the adsorption amount of PVP (*i.e.*, segment density on the surface) are significant factors for the interference. However, we do not know whether PVP, which interacts with Meq, is eventually included in the amorphous domain of the primary particles of Meq to disturb the molecular array.

Effect of other additives on $I_{2\theta}/I_{2\theta,0}$ ($2\theta = 11.6$ and 18.3 deg) and $I_{11.6}/I_{18.3}$ is shown in Figs. 9, 10. These parameters decreased with an added concentration in a similar way to that shown in Fig. 8. However, the rate of decrease was different depending on the species added. In the case of sucrose (◐) and NaCl (△), $I_{2\theta}/I_{2\theta,0}$ decreased in almost the same manner in these two additives and the

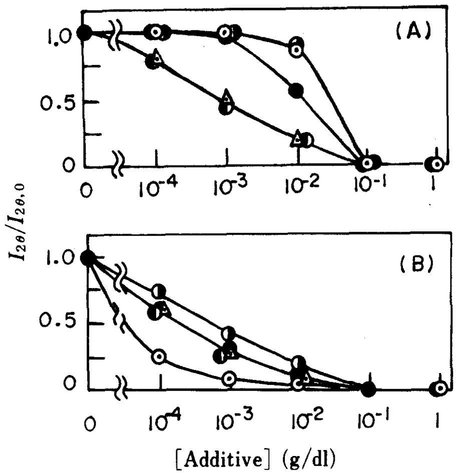

Fig. 9. Effect of Concentration of Additive on Relative Diffraction Intensity, $I_{2\theta}/I_{2\theta,0}$

$2\theta=18.3$ deg (A) and 11.6 deg (B). Additives are NaAlg (⊙), NaCl (△), NaMan (◑), sucrose (◐), and NaHMPi (●; mean degree of condensation, n, was 6.9).

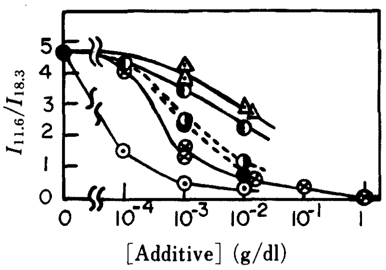

Fig. 10. Effect of Concentration of Additive on the Ratio of Diffraction Intensity, $I_{11.6}/I_{18.3}$

Additives are PVP-K-90 (⊗), NaAlg (⊙), NaCl (△), NaMan (◑), sucrose (◐), and NaHMPi (●; $n=6.9$).

two diffraction angles, $2\theta=11.6$ and 18.3 deg (Fig. 9). That is, the decrease in crystallinity was almost uniform and isotropic with respect to these two diffraction angles. Therefore, the rate of decrease in $I_{11.6}/I_{18.3}$ with the concentration of additive was the smallest among all additive studied here (see Fig. 10).

On the other hand, $I_{2\theta}/I_{2\theta,0}$ ($2\theta=18.3$ deg) for sodium mannuronate (NaMan, ◑) and sodium hexametaphosphate (NaHMPi, ●) was higher than that for NaCl and sucrose, while the trend of decrease in $I_{2\theta}/I_{2\theta,0}$ ($2\theta=11.6$ deg) was quite similar to that of NaCl and sucrose. The ratio of $I_{11.6}/I_{18.3}$ for NaMan and NaHMPi was, therefore, lower than that for NaCl and sucrose, but higher than that for NaAlg (⊙) and PVP K-90 (⊗). The decrease in $I_{2\theta}/I_{2\theta,0}$ was not uniform but rather anisotropic with respect to these two angles.

The value of $I_{2\theta}/I_{2\theta,0}$ ($2\theta=18.3$ deg) for NaAlg was almost the same as that for NaMan, but that at $2\theta=11.6$ deg was the lowest among the additives over the concentration range studied here. Consequently, $I_{11.6}/I_{18.3}$ was the lowest, and the anisotropy was the strongest. According to the result shown in Fig. 10, the effect of additives is classified into three catagories: NaCl and sucrose (almost isotropic), NaMan and NaHMPi (anistoropic), and NaAlg and PVP (extremely anisotropic).

Discussion

There are several factors affecting diffraction intensity; degree of crystallinity, size and number of crystallites, degree of crystallite orientation, and interference of the additive with diffracted X-ray. Actually, PVP in physical mixture interfered with the diffraction at $2\theta=11.6$ deg more than that at 18.3 deg ($I_{11.6}/I_{18.3}=2.8$), as shown in Fig. 6A. Therefore, we should consider that PVP, which had been entrapped in the Meq aggregate formed during the preparation by freeze-drying, also interferes in the intensity of diffracted X-ray. The diffraction intensity at $2\theta=11.6$ deg in (6) and (7) of Fig. 6 was too weak when we compare it with the diffraction intensity in (3), taking the PVP content into account (*viz.*, 0.1—1% *vs.* 50%). Anisotropy in the diffraction intensity must be caused by the specific interference of an additive with the diffracted X-ray as well as anisotropic growth of crystallite. Keeping these factors in mind, we will discuss here the effect of additives on the crystallite formation.

Sucrose and NaCl do not exhibit any specific effect except simple physical disturbance on the crystal growth because these substances are not bound to molecular Meq in solution or its crystal surface. On the other hand, NaAlg and PVP K-90 markedly disturbed/interfered with the diffraction corresponding to $2\theta=11.6$ deg, while that corresponding to $2\theta=18.3$ deg was not much affected up to *ca.* 10^{-2}%. Simple conjecture that anionic species such as HMPi, Man, and Alg were bound to the quinuclidinyl group on the crystal nucleus while PVP was bound to the hydrophobic group of Meq seems insufficient to explain the fact that effects of NaAlg and PVP on $I_{2\theta}/I_{2\theta,0}$ and $I_{11.6}/I_{18.3}$ are qualitatively similar. Additional factor involved in the anisotropic effect must be sought.

Molecular array and crystallite formation of Meq with respect to the lattice corresponding to $2\theta=11.6$ deg seems to be sensitively disturbed and broken down by the interference/interaction with PVP or NaAlg (*i.e.*, polymer effect), because $I_{2\theta}/I_{2\theta,0}$ ($2\theta=11.6$ deg) in the presence of these polymers was less than that in the presence of nonspecific additives, NaCl or sucrose. Polymer interaction here refers to the complex formation and adsorption. The disturbing effect of polymer at $2\theta=11.6$ deg increased with molecular weight of the additive homolog: see the effect of molecular weight of PVPs (⊗) in Fig. 8, and compare the effect of NaMan (◑) with that of NaAlg (⊙) in Figs. 9B and 10, where NaMan is one of the monomeric components of NaAlg. The higher the molecular weight was, the weaker the diffraction intensity became owing to the disturbance of the molecular array of Meq (with respect to $2\theta=11.6$ deg) through the interference of the bulky polymer coil in the growth/formation of the crystal lattice.

On the other hand, $I_{2\theta}/I_{2\theta,0}$ ($2\theta=18.3$ deg) in the presence of these polymers was still retained at almost unity up to 10^{-2}%, where it decreased to less than 0.25 in the case of NaCl or sucrose. This suggests that the molecular array and/or crystallite formation of Meq with respect to the lattice face corresponding to $2\theta=18.3$ deg was enforced by the polymer in contrast to the effect on the lattice for $2\theta=11.6$ deg. Unfortunately, we cannot discuss the microscopic molecular mechanism for the interaction of polymer with the crystal lattices (for $2\theta=11.6$ and 18.3 deg), because we do not have the crystallographic data for Meq at present.

Needless to say, however, the molecular array in the crystallite is attained under the competitive effects of the intermolecular force among Meq molecules and of the disturbance due to the complex formation and adsorption with the additives. The balance between them and/or their competitive effect determine the crystallinity and the size and number of the crystallites for the respective crystal lattices.

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