

Studies on Whisker Growth in Solid Preparations. VI.¹⁾ Whisker Growth in Mixtures Composed of Aspirin and Porous Glass Powder²⁾

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Effects of the pore size of controlled pore glass (CPG) on whisker growth in mixtures composed of aspirin and CPG were studied. When the powder mixture and the tablets, both composed of five kinds of the CPG having different pore sizes, aspirin and micro-crystalline cellulose, were preserved in glass containers under various temperatures for 5 d, whisker growth was observed in some samples. The main component of whisker was salicylic acid, and the amount of whisker was measured using high-performance liquid chromatography at fixed time intervals. The pore size distribution was determined by mercury intrusion porosimetry. The growth rate and amount of whisker were both larger with a higher preservative temperature. Furthermore, the amount of whisker was almost proportional to the surface area of samples under the same preservative temperature above 60 °C, except for the samples containing CPG350, while in the samples containing CPG350, a larger amount and a higher growth rate than expected were observed. These results suggest the participation of a particular pore size in the whisker growth.

Keywords controlled pore glass; mercury intrusion porosimetry; whisker; aspirin; salicylic acid; pore size

Whisker growth in powders and granules is known to cause aggregation among the powder and granule particles, thus lowering the flowability of these preparations. In tablets, it is known that the whisker markedly lowers the market value and mars external beauty because it is mistaken for mold. We have reported in our previous paper³⁾ that the mechanical ability of tablets decreased, reflecting a decrease in hardness and an increase in friability in the experiments using tablets containing aspirin (ASP), activated carbon and microcrystalline cellulose (MCC), and that the component of whisker which appeared on the tablet surface was determined to be salicylic acid (SA). Further, the capillary structure had been presumed to be one of the factors for the whisker growth.⁴⁾

The present study was undertaken to clarify the relationship between whisker growth and pore size on the basis of the observation of whisker growth behavior during storage of the powder mixture and tablets composed of five kinds of controlled pore glass (CPG) having different pore sizes, ASP and MCC.

Experimental

Materials ASP purchased from Maruishi Pharmaceutical Co., Tokyo, was of pharmacopoeial grade (JP XII), and was used after sieving (355–425 μm). CPG was obtained from Electro-Nucleonics, Ltd., and was used after drying in a vacuum at 120 °C for 2 h. The physical properties of CPG are listed in Table I. MCC used as an excipient was Avicel® PH101 obtained from Asahi Kasei Kogyo Co., Tokyo, and was used after sieving (150–212 μm).

TABLE I. Mean Pore Diameter, Specific Surface Area and Particle Size of Used CPG Powder

CPG	Mean pore diameter (Å)	Specific surface area (m ² /g)	Particle size (μm)
CPG 75	74	152.7	125–425
CPG 170	156	90.9	125–425
CPG 350	324	79.0	125–425
CPG 700	729	24.9	125–425
CPG 1400	1273	24.0	125–425

Preparation of Samples The powder samples were prepared by mixture in the composition ratios shown in Table II, where P-W samples contain the same amount of CPG, and P-S samples contain an amount of CPG having the same surface area. The tablet samples were prepared by tableting after mixing the materials in the composition ratios shown in Table III, where T-W samples contain the same amount of CPG, and

TABLE II. Mixing Ratio of Powder Samples

	CPG (mg)					ASP (mg)
	75	170	350	700	1400	
P-W 75	140	—	—	—	—	140
P-W 170	—	140	—	—	—	140
P-W 350	—	—	140	—	—	140
P-W 700	—	—	—	140	—	140
P-W 1400	—	—	—	—	140	140
P-S 75	26	—	—	—	—	140
P-S 170	—	44	—	—	—	140
P-S 350	—	—	51	—	—	140
P-S 700	—	—	—	161	—	140
P-S 1400	—	—	—	—	167	140
Control	—	—	—	—	—	140

W and S mean a constant weight and surface area, respectively.

TABLE III. Mixing Ratio of Tablet Samples

	CPG (mg)					ASP (mg)	MCC (mg)
	75	170	350	700	1400		
T-W 75	140	—	—	—	—	140	220
T-W 170	—	140	—	—	—	140	220
T-W 350	—	—	140	—	—	140	220
T-W 700	—	—	—	140	—	140	220
T-W 1400	—	—	—	—	140	140	220
T-S 75	26	—	—	—	—	140	220
T-S 170	—	44	—	—	—	140	220
T-S 350	—	—	51	—	—	140	220
T-S 700	—	—	—	161	—	140	220
T-S 1400	—	—	—	—	167	140	220
Control	—	—	—	—	—	140	220

W and S mean a constant weight and surface area, respectively.

T-S samples contain the amount of CPG having the same surface area.

Tableting The powder mixture was compressed at a compression pressure of 500 kg/cm² into tablets by the direct compression method, using a tensile and compression testing machine (Minebea Co., Ltd., model TCM-5000C) with a single flat punch of 1 cm² cross section.

Storage of Samples The samples were each sealed in a 5 ml glass container immediately after mixing or tableting, and stored in constant temperature ovens at 40, 50, 60, 70 and 80 °C.

Observation of Whisker Growth An optical microscope (Nikon, type SMZ-10) was used to observe whisker growth on the tablet surface. A scanning electron microscope (JASCO, model JSM T-200) was used to observe the whiskers in the powder mixture.

Quantitative Analysis of Whisker We have already reported that the component of the whisker developed in the mixture containing ASP was SA,³⁾ and in the present study the amount of SA was measured as the whisker by high-performance liquid chromatography (HPLC).⁵⁾ Formic acid solution (0.5%) was added to the powder and tablet samples up to 100 ml immediately after the preparation and after storage. After 280 mg of citric acid was added to this, the suspension was ultrasonicated for 3 h to dissolve ASP and SA, and the supernatant solution after filtration with a 0.45 μm filter (Toyo Roshi Kaisha, Ltd.) was used as the sample for measurement by HPLC. The HPLC equipment consisted of a

Hitachi 655 high-performance liquid chromatograph and a Hitachi 638 spectrophotometer. The separations were achieved on a silica-gel normal-phase column (Kaseisorb LC 60-5, particle size 5 μm, 250 × 4.6 mm i.d.; Tokyo Kasei Kogyo Co., Ltd., Tokyo). The mobile phase consisted of chloroform, dichloromethane, acetonitrile and formic acid (700 : 300 : 30 : 2). A flow rate of 2.5 ml/min was used. The absorbance at 300 nm for SA was determined. Peak areas were calculated with a Hitachi 833 chromatointegrator.

Measurement of Pore Size Distribution The pore size distribution in each sample immediately after mixing and tableting was measured by mercury intrusion porosimetry, employing a mercury porosimeter (Quantachrome Co., Autoscan-33). The principle of the mercury intrusion porosimetry is as follows; when mercury is forced into a pore in a solid material, the relationship between the pressure required to fill the pore completely and the size of the pore is expressed by Washburn's equation⁶⁾:

$$Pr = -2\phi \cos \theta \quad (1)$$

where P is the pressure; r , the pore radius; ϕ , the surface tension of mercury and θ , the contact angle of mercury with the solid material. When ϕ and θ are regarded as 480 dyn/cm and 140°, respectively, the Eq. 1 was reduced to the following Eq. 2.⁷⁾

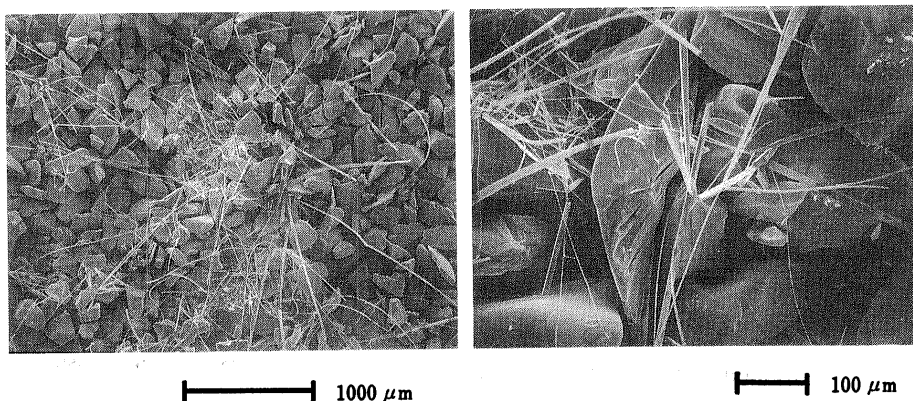


Fig. 1. Scanning Electron Micrographs of Whisker Growth in Powder Mixture Containing ASP and CPG

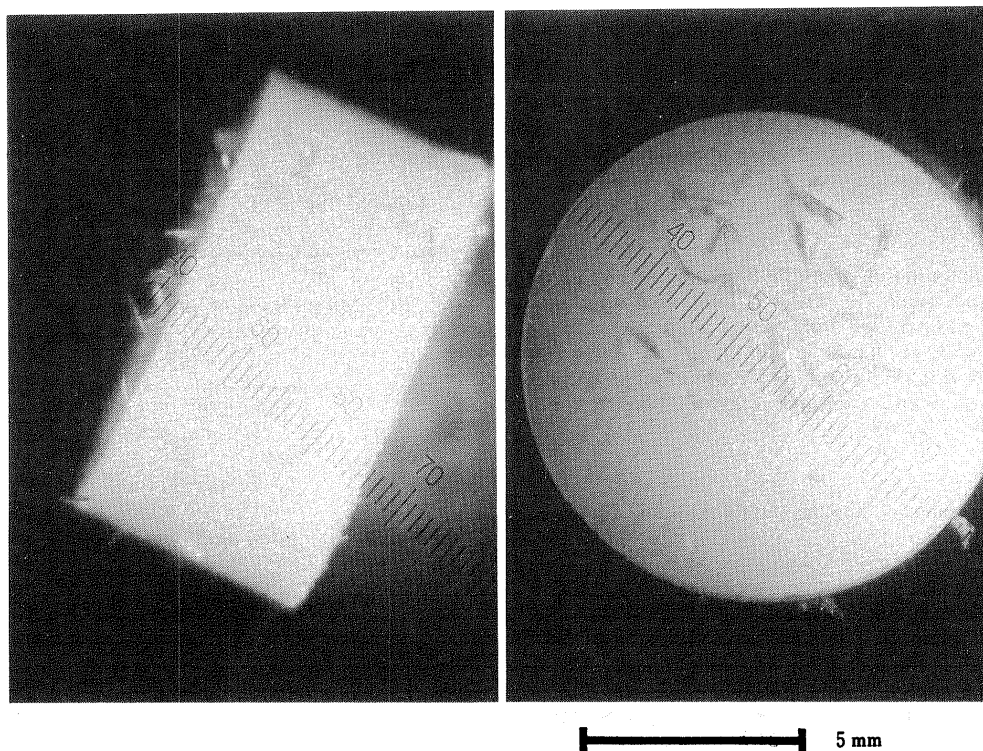


Fig. 2. Optical Micrographs of Whisker Growth on Tablet Surface Containing ASP, CPG and MCC

$$D=213/P$$

(2)

where D is the pore diameter in microns and P is the absolute pressure in psia.

Results and Discussion

Whisker Growth in Powder and Tablets Containing ASP and CPG The whisker growth in the powder mixture and a tablet containing ASP and CPG which were preserved at 80 °C for 5 d is shown in Figs. 1 and 2. Whisker growth was observed in both the powder and the tablet containing CPG and ASP. Then, the time course of the whisker growth behavior of the powder mixture and tablets at various mixing ratios and storage conditions was investigated to clarify the effects of CPG on whisker growth.

Figure 3 shows the time course of whisker growth of P-W samples and controls which were preserved under

various temperatures for 5 d.

The initial rate of whisker growth was larger with a higher preservative temperature in the mixture with CPG having the same pore size, while a bit of whisker was observed at 40 and 50 °C, and controls showed no whisker growth under any temperature. A trace amount of SA was measured in the samples before preservation, probably because a slight amount of ASP had already been hydrolyzed into SA and acetic acid before its use for the experiment at the time of the classification and the pretreatment of the samples for HPLC.

As shown in Table I, the specific surface area of CPG was larger with the decrease in the CPG pore diameter. When the surface area for CPG in P-W75, P-W170, P-W350, P-W700 and P-W1400 was calculated using the figures in Table I, these values corresponded to 21.4, 12.7, 11.1, 3.5 and 3.4 m², respectively. In P-W samples, the

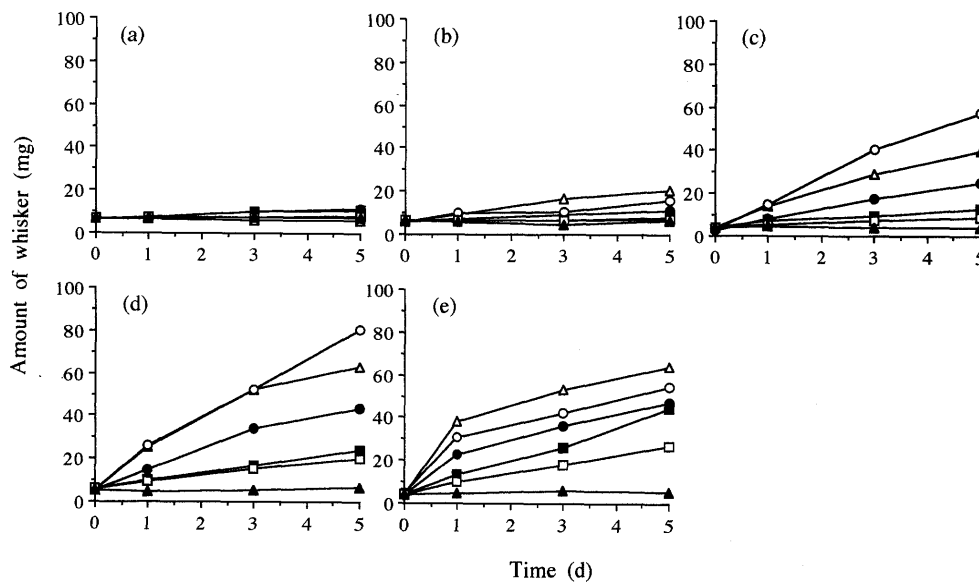


Fig. 3. Time Course of Whisker Growth in P-W Samples Preserved at 40 °C (a), 50 °C (b), 60 °C (c), 70 °C (d) and 80 °C (e)
 △, P-W75; ●, P-W170; ○, P-W350; ■, P-W700; □, P-W1400; ▲, control.

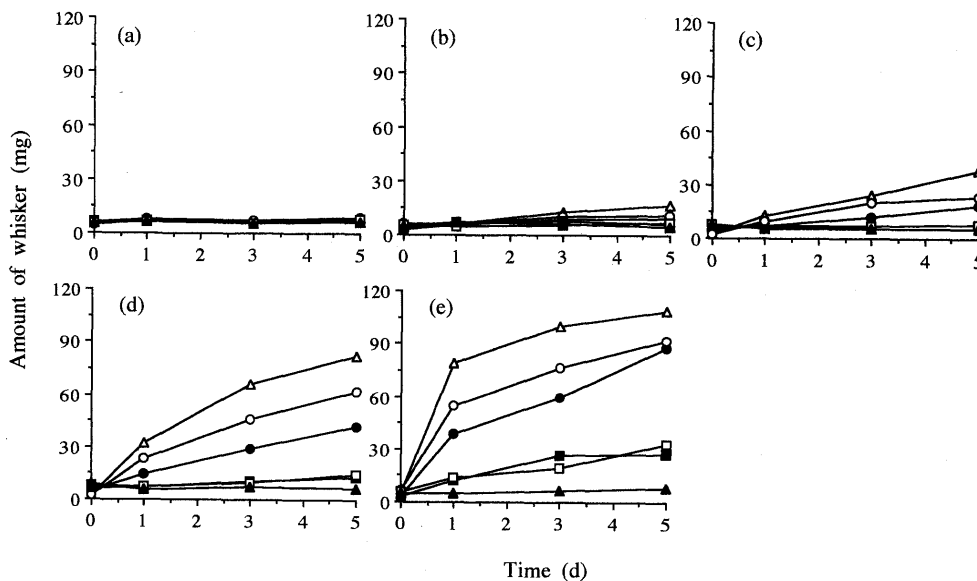


Fig. 4. Time Course of Whisker Growth in T-W Samples Preserved at 40 °C (a), 50 °C (b), 60 °C (c), 70 °C (d) and 80 °C (e)
 △, T-W75; ●, T-W170; ○, T-W350; ■, T-W700; □, T-W1400; ▲, control.

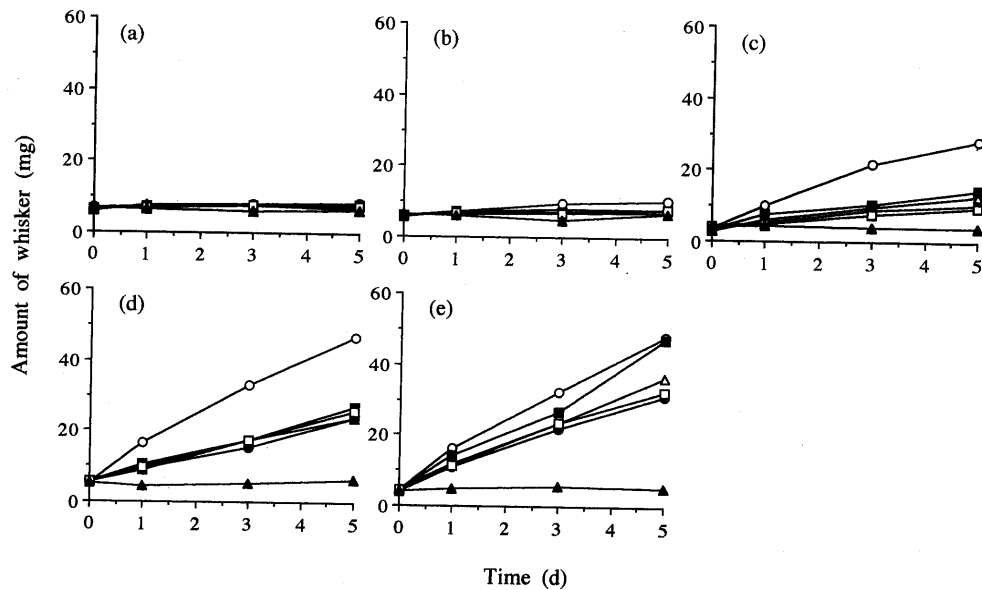


Fig. 5. Time Course of Whisker Growth in P-S Samples Preserved at 40 °C (a), 50 °C (b), 60 °C (c), 70 °C (d) and 80 °C (e)
 Δ , P-S75; \bullet , P-S170; \circ , P-S350; \blacksquare , P-S700; \square , P-S1400; \blacktriangle , control.

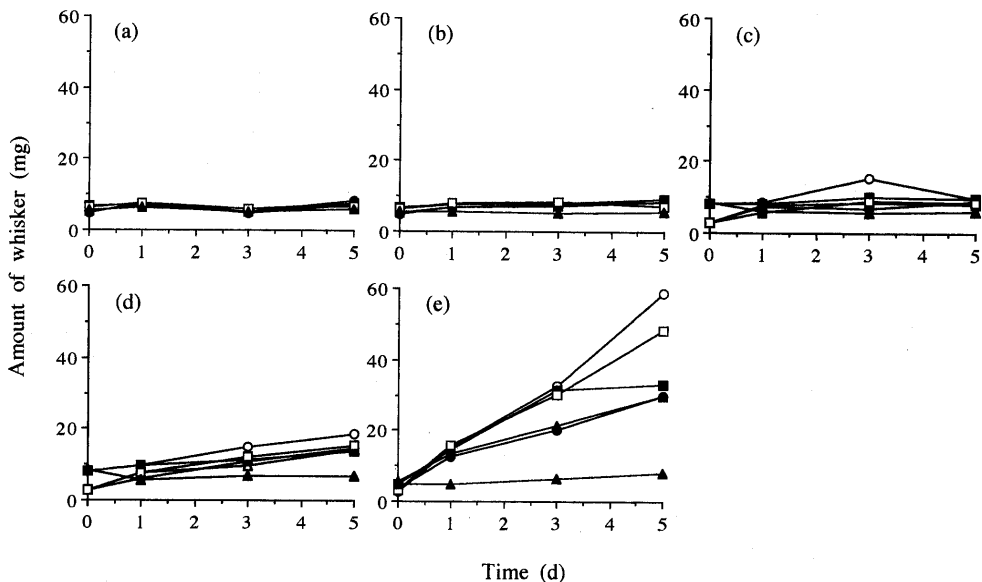


Fig. 6. Time Course of Whisker Growth in T-S Samples Preserved at 40 °C (a), 50 °C (b), 60 °C (c), 70 °C (d) and 80 °C (e)
 Δ , T-S75; \bullet , T-S170; \circ , T-S350; \blacksquare , T-S700; \square , T-S1400; \blacktriangle , control.

amount of whisker was increased in the order of the CPG surface area in the mixture except for P-W350. A large amount of whisker was observed in P-W350.

Figure 4 shows the time course of whisker growth of T-W samples and controls which were preserved under various temperatures for 5 d. The whisker growth behavior in T-W samples was approximately similar to that in P-W samples. Controls also showed no whisker growth under any temperature, suggesting that MCC did not affect the whisker growth.

In P-W and T-W samples, the amount of whisker and its growth rate were assumed to be affected by the surface area of CPG in the samples. Then, the powder mixture and tablets containing the amount of CPG having 4 m² of the surface area were prepared, and the same preservative experiments as in the cases of P-W and T-W samples were

carried out to clarify the effects of the pore diameter of CPG.

The time courses of whisker growth of P-S samples and controls, and T-S samples and controls, which were preserved under various temperatures for 5 d, are shown in Figs. 5 and 6, respectively.

P-S75, P-S170, P-S700 and P-S1400 showed a similar whisker growth behavior at the same preservative temperature. This result suggests that the amount of whisker and its growth rate were affected by the surface area of CPG. However, the largest amount of whisker was observed in P-S350 at the preservative temperature of more than 60 °C.

T-S samples at the preservative temperature of less than 70 °C showed a smaller amount of whisker than P-S samples did. It was thought that the contact points and

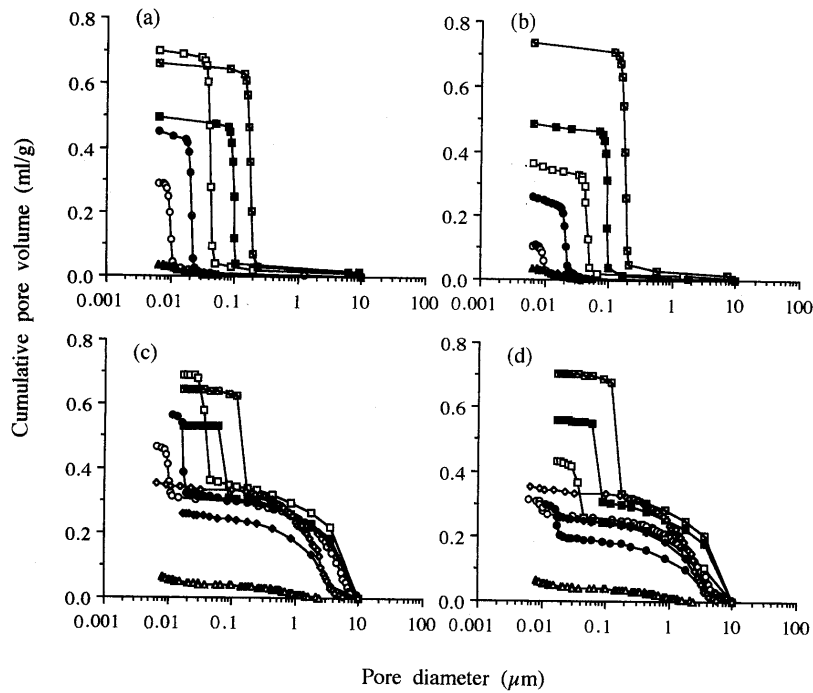


Fig. 7. Pore Size Distribution in Powder Mixture (a, b) and Tablets (c, d) Containing ASP and CPG

(a) P-W samples; (b) P-S samples; (c) T-W samples; (d) T-S samples. ○, P-W75, P-S75, T-W75, T-S75; ●, P-W170, P-S170, T-W170, T-S170; □, P-W350, P-S350, T-W350, T-S350; ■, P-W700, P-S700, T-W700, T-S700; ▤, P-W1400, P-S1400, T-W1400, T-S1400; ▲, ASP powder (control); △, tablet composed of ASP; ◇, tablet composed of MCC; ◆, tablet composed of ASP and MCC (control).

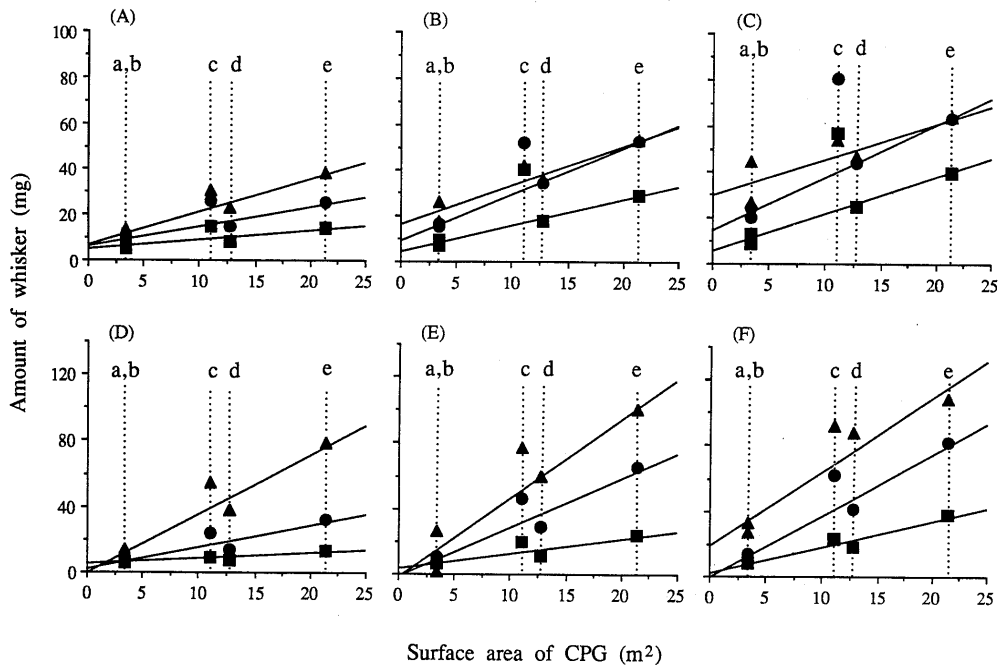


Fig. 8. The Relationship between Whisker Growth and Surface Area of CPG

A, B and C are P-W samples and D, E and F are T-W samples. From the start of preservation; A and D 1st day, B, E 3rd day, C, F 5th day. a, CPG1400; b, CPG700; c, CPG350; d, CPG170; e, CPG75. Preservative temperature; ■, 60 °C; ●, 70 °C; ▲, 80 °C.

area formed by ASP and CPG particles decreased by the addition of MCC in T-S samples. The largest amount of whisker was observed in T-S350 at 70 and 80 °C as in the case of the P-S350 samples.

Pore Size Distribution in Samples Containing CPG The pore size distribution of the samples listed in Tables II and III immediately after mixing and tableting are shown in Fig. 7.

The intrinsic pore size distribution of CPG contained in each powder sample was observed and is shown in Figs. 7a and 7b. ASP powder had almost no pores in powder particles. On the other hand, in tablet samples, pores having a pore diameter of 3–10 μm, except for the intrinsic pores of CPG, were observed. It was thought that these pores were interparticle pores formed by formulated CPG, ASP and MCC particles. Especially, in the T-W

samples (Fig. 7c), all the tablet containing CPG showed the same shape of pore size distribution and pore volume in the pore size range of 3–10 μm . It was probably because the T-W samples had the same formulation and each composing powder particle in the formulation had the same particle size. In T-S samples (Fig. 7d), different pore size distributions were observed in the pore size range of 3–10 μm . It was assumed that these differences were caused by a difference in the amount of contained CPG particles in each T-S sample. However, the T-S samples had the same surface area, probably because the powder particles formulated had the same surface area, even though the amount of CPG particles was different.

Mechanism of Whisker Growth Using the results in Figs. 3 and 4 at 60, 70 and 80 $^{\circ}\text{C}$, the relationship between whisker growth and the surface area of CPG is shown in Fig. 8, in which the ordinate shows the amount of whisker and the abscissa shows the surface area of contained CPG in the samples.

It was observed that the amount of whisker was almost proportional to the surface area of contained CPG, except for P-W350 and T-W350, while the plots for the samples containing CPG350 were located above these proportional lines in Fig. 8.

These results support our previous speculations about the presence of the optimum pore diameter in the whisker growth for ethenzamide and caffeine anhydride,⁴⁾ the acceleration of whisker growth by the pores in activated carbon in the mixture of ASP and activated carbon, and the whisker growth caused by capillary condensation.³⁾ Yonemochi *et al.* reported that the rate constant for the hydrolysis of ASP depended on the pore diameter of the

pores in CPG.⁸⁾ It was assumed that if the capillary condensation caused a supersaturation of SA vapor in the CPG pores and the nucleation of SA whisker, the whisker growth rate would be larger as the CPG pore diameter became smaller, thus in the order of samples containing CPG75, CPG170 and CPG350. However, in the present experiment, in the samples containing CPG75 and CPG170 having pores with a pore diameter smaller than 324 \AA (CPG350), a smaller amount of whisker was observed than in the case of CPG350. The study of these points is now under way.

References and Notes

- 1) We now designate this article as Part VI of "Studies on Whisker Growth in Solid Preparations"; Parts III, IV and V of the series are "Effects of Compression Force on Growth of Whisker" published in *Yakuzaigaku*, **41**, 155 (1981), "Quantitative Measurement and Mechanism of Whisker Growth" published in *Yakuzaigaku*, **41**, 161 (1981) and "Studies on Whisker Growth on the Tablet Surface. III. Mechanism of Whisker Growth on Aspirin Tablet and Its Effect on the Mechanical Strength of the Tablet" published in *Chem. Pharm. Bull.*, **34**, 850 (1986), respectively.
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