Interaction of Medicinals and Porous Powder. III. Effects of Pore Diameter of Porous Glass Powder on Crystalline Properties

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The physicochemical properties of drug molecules in a mixture with controlled-pore glass (CPG) were studied by using differential scanning calorimetry (DSC) and powder X-ray diffraction. The DSC data indicated the presence of three states of benzoic acid in the CPG mixtures below 500 Å CPG pore diameter. The proportions of the three states of benzoic acid in the CPG mixture varied with the content of benzoic acid and also with the pore diameter of CPG. The amount of crystalline fraction in the mixture increased with increasing pore diameter of CPG. When benzoic acid was mixed with different pore diameters of CPG (CPG120 and CPG1000), it was found that benzoic acid molecules preferentially interacted with CPG of small pore diameter.

Keywords benzoic acid; controlled pore glass; differential scanning calorimetry; powder X-ray diffraction; pore size; amorphous; interaction

The interactions between medicinals and excipients in a dosage form are closely related to the stability, dissolution behavior and bioavailability of the medicinals.[1–4] We have already investigated the interaction between medicinals and either controlled pore glass (CPG)[5] or pillar interlayered montmorillonite (PILM).[6] CPG has a large surface area and many pores with a narrow pore size distribution. It was found that the medicinal crystals mixed with CPG showed a broad and small endothermic peak of melting on differential scanning calorimetry (DSC) thermograms. At a lower mixing ratio of medicinals, the DSC endothermic peak due to the fusion disappeared and the powder X-ray diffractograms showed no crystalline diffraction peaks. In the previous paper, we reported on the sublimation of benzoic acid and the improvement of benzoic acid dissolution from the mixture with CPG.[7]

In this paper, the effects of pore diameter from 75 to 1000 Å on the crystalline properties of benzoic acid were investigated by using DSC and powder X-ray diffraction. CPG powder mixtures were used to elucidate the distribution mode of benzoic acid molecules in relation to different pore diameters during heating.

Experimental

Materials CPG was obtained from Electro-Nucleonics Ltd. The pore diameter and the specific surface area of CPGs are listed in Table I. The CPGs were used after drying in vacuum at 120 °C for 2 h. Benzoic acid (Koso Chemical Co., Ltd.) was used as received from the supplier.

Preparation of the Mixture The mixtures of crystalline drug and the CPG were prepared with a mortar and pestle in various mixing ratios.

TABLE I. Mean Pore Diameter and Specific Surface Area of Various CPGs

CPG	Mean pore diameter[a] (Å)	Specific surface area[b] (m^2/g)
CPG75	70	207
CPG120	116	155
CPG240	226	94.0
CPG350	347	68.4
CPG500	546	43.1
CPG1000	962	26.1

a) Nominal. *b*) Calculated from nitrogen gas adsorption data.

DSC The samples of the mixtures were sealed into liquid sample pans and DSC measurements were made on a Perkin-Elmer DSC-1B instrument. The heating rate was 4 K/min under a nitrogen atmosphere. The temperature was increased from 323 K to 405 K then allowed to decrease to 323 K, and the measurement was repeated. The first temperature increase was named the 1st run and the repeated increase was the 2nd run.

Powder X-Ray Diffraction Powder X-ray diffraction patterns were measured using a Rigaku Denki 2027 diffractometer with Ni filtered Cu-K_α radiation. The scanning speed was 2 °/min.

Preparation of CPG120–CPG1000 Mixtures CPG120 and CPG1000 of different particle sizes were used, *i.e.*, CPG120 (mesh size: 80/120 (passing/retaining)), CPG120 (200/400), CPG1000 (80/120) and CPG1000 (200/400). Two mixtures of CPG120 and CPG1000 were prepared from these powders of different particle sizes; one CPG mixture was composed of CPG120 (80/120) and CPG1000 (200/400), and the other mixture of CPG120 (200/400) and CPG1000 (80/120). The CPG mixture of CPG 120–CPG1000 was prepared by simple blending in various mixing ratios. After benzoic acid was added to the mixture of CPGs at the concentration of 20%, the DSC measurements were carried out in the same way as above. After DSC measurement, the samples were sieved using 150 and 200 mesh screens. The fraction retained on a 150 mesh screen and the fraction that passed through a 200 mesh screen were used for the determination of the amount of benzoic acid contained in the CPG powders.

Measurement of the Concentration of Benzoic Acid Accurately weighed CPG–benzoic acid mixture was dispersed in 10 ml of JP XI 1st fluid of the disintegration test and sonicated. The suspension was centrifuged then the supernatant solution was passed through a Millipore filter (Millipore Corp., pore size 0.22 μm). The concentration of benzoic acid was determined spectrophotometrically at 273 nm on a Shimadzu ultraviolet (UV) 200S doublebeam spectrophotometer.

Results and Discussion

Figure 1 shows the DSC curves and the powder X-ray diffraction patterns for benzoic acid and the physical mixture of 5% benzoic acid and 95% CPG120. An endothermic peak was observed at 392 K in the DSC curve of benzoic acid crystals due to fusion, while the mixture showed no such peak. In the powder X-ray diffraction patterns, only the halo pattern was observed for the physical mixture of 5% benzoic acid and 95% CPG120. This result suggested that benzoic acid molecules were dispersed in an amorphous state in the CPG mixture. Figure 2 shows the DSC curves of benzoic acid–CPG120 mixtures with various mixing ratios of benzoic acid. In the case of 10% benzoic acid physical mixture, the endothermic peak due to the fusion of benzoic acid was not observed. Before the DSC measurement, the 10% physical mixture showed X-ray diffraction peaks at $2\theta = 8.0$ and 17.0° due

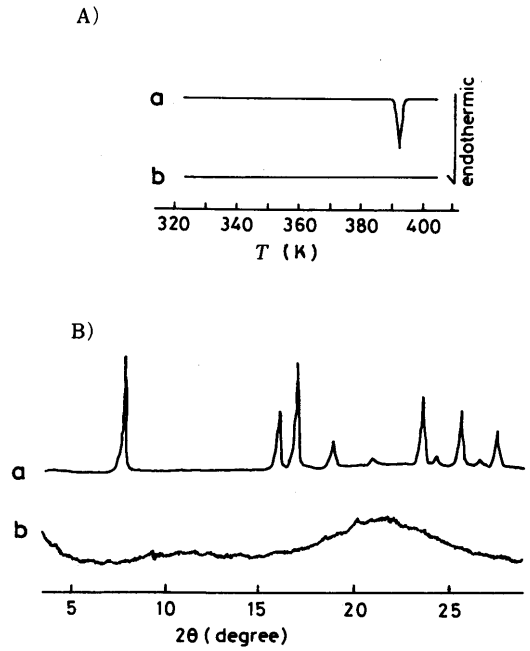

Fig. 1. DSC Curves and Powder X-Ray Diffraction Patterns of Benzoic Acid, and the Physical Mixture of 95% CPG120 and 5% Benzoic Acid

A) DSC curves; B) powder X-ray diffraction patterns; a) benzoic acid; b) physical mixture of 95% CPG120 and 5% benzoic acid.

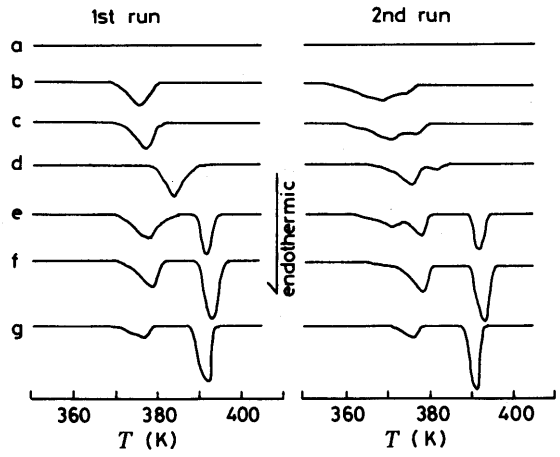

Fig. 2. DSC Curves of CPG120–Benzoic Acid Systems

a) 10% benzoic acid; b) 20% benzoic acid; c) 30% benzoic acid; d) 40% benzoic acid; e) 50% benzoic acid; f) 60% benzoic acid; g) 70% benzoic acid; heating rate, 4 K/min.

to benzoic acid crystals. The pattern was different from that of the 5% physical mixture shown in Fig. 1B. After the 1st run of DSC measurement, however, the X-ray diffraction peaks of benzoic acid disappeared. From this result, it follows that benzoic acid molecules in the mixture entered the pore spaces of the CPG and became amorphous in state during the heating process. As the mixing ratio of benzoic acid increased, a broad endothermic peak appeared at lower temperature than the melting point of benzoic acid. In the mixtures with low contents of benzoic acid, all the benzoic acid molecules seemed to exist in the pores of CPG because crystalline character of benzoic acid was not observed. In the cases of mixing ratios of above 50%, each curve showed two endothermic peaks. The shape of the first

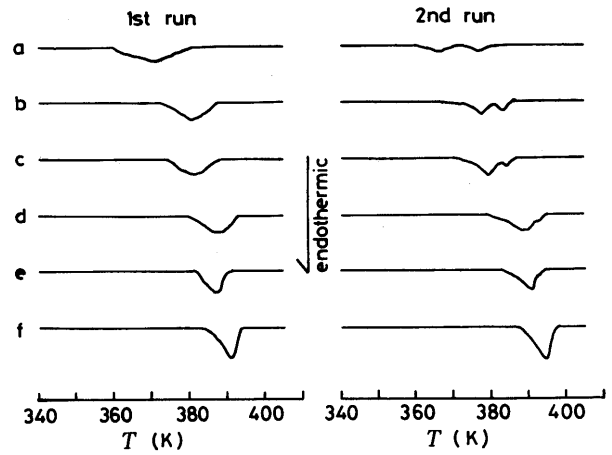

Fig. 3. DSC Curves of the Mixtures of 30% Benzoic Acid and 70% Various CPGs

a) CPG75; b) CPG120; c) CPG240; d) CPG350; e) CPG500; f) CPG1000; heating rate, 4 K/min.

peak that appeared at a lower temperature was similar to that of the broad peak seen at low benzoic acid contents. The second peak corresponded to the fusion of benzoic acid crystals. In the 2nd runs of the 20% and 30% mixtures, the broad endothermic peak began to appear from 355 K, which was 12 K lower than that of the 1st run. In addition, the peak of the 2nd run had two tops. These results suggested that a part of the benzoic acid molecules in the mixture penetrated into the pores of CPG during the heating process. Figure 3 shows the DSC curves of the mixtures of 30% benzoic acid and 70% CPGs having pore diameters were from 75 to 1000 Å. The broad endothermic peak position shifted to higher temperature with the increase of the CPG pore diameter. Three phases of benzoic acid molecules in the CPG mixture were proposed in the previous paper, *i.e.*, crystal (phase 1), disordered structure (phase 2) and amorphous or adsorbed state on the pore wall (phase 3).[5] In the cases of the mixtures of the CPGs having mesopore size (20—500 Å),[8] the presence of phase 2 was revealed by the endothermic peaks at lower temperatures than the melting point of benzoic acid.

The DSC pattern of the CPG1000 mixture was similar to that of benzoic acid–glass beads mixture and no pore effects were observed. In the mixture of the CPG1000, therefore, phase 2 of benzoic acid was no longer detectable in the DSC thermograms. It seems reasonable to assume that the three phases of benzoic acid in the mixture actually reflect a continuous state change from phase 3 to phase 1, and that phase 2 is an intermediate state between phase 3 and phase 1. Phase 2 was considered to correspond to the condensed molecules in pore spaces. In the CPG1000 mixture, it was not possible to differentiate between the condensed molecules in pore spaces (phase 2) and the crystals (phase 1).

Through the measurements of heat of fusion, the amounts of phase 1 and phase 2 of benzoic acid were calculated to elucidate the difference in the interaction between CPG120 and CPG1000, respectively. It was assumed that the specific heat of melting of the broad peak was equal to that of the crystals. The amount of phase 3 was derived by subtracting the sum of the calculated amounts for phase 1 and phase 2 from the amount of benzoic acid initially

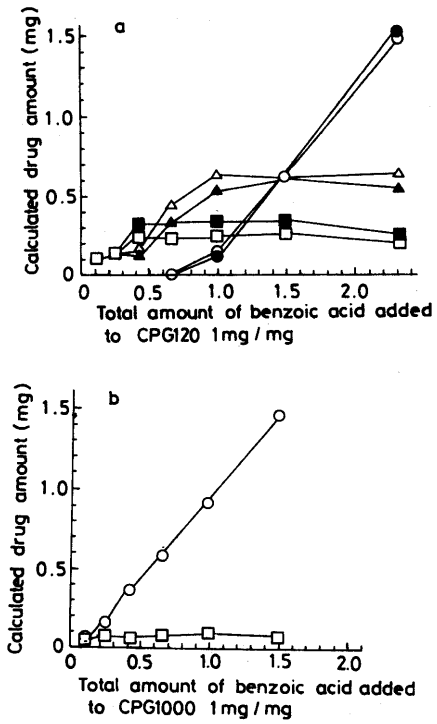

Fig. 4. Relationship between Total Amount of Benzoic Acid Added to the CPGs and Calculated Amounts of the Three Phases

a) CPG120 mixture; b) CPG1000 mixture; ○, phase 1 1st run; △, phase 2 1st run; □, phase 3 1st run; ●, phase 1 2nd run; ▲, phase 2 2nd run; ■, phase 3 2nd run.

contained in the mixtures. Figure 4 shows the relationship between the total amount of benzoic acid added to CPG120 or CPG1000 and the calculated amounts of the three phases. In the case of CPG120 mixtures, the calculated amount of phase 1 was zero up to the concentration of 0.65 mg of benzoic acid in 1 mg of CPG120, and then increased linearly with increase of the added amount of benzoic acid. The amount of phase 2 increased sharply with increase of the added amount of benzoic acid up to the concentration of 1.0 mg of benzoic acid, then became a constant value suggesting saturation for phase 2. The amount of phase 3 was almost constant except below the concentration of 0.45 mg. The amount of phase 1 showed no apparent change between the 1st run and the 2nd run. The amount of phase 2 in the 2nd run decreased as compared to the 1st run, while that of phase 3 increased. It was suggested that benzoic acid molecules transferred from phase 2 to phase 3 after heating in the 1st run. In the case of CPG1000 mixtures shown in Fig. 4b, the amount of phase 1 increased linearly with increase of the amount of benzoic acid. The amount of phase 1 calculated from the peak areas of the DSC thermogram was less than the initial amount of benzoic acid, indicating the presence of phase 3. The amount of phase 3 in CPG1000 mixtures was less than that in CPG120 mixtures.

Using mixtures of benzoic acid and two CPGs of different pore sizes, we investigated whether benzoic acid molecules transferred to small pores or large pores of CPGs during the heating process. Figure 5 shows the DSC curves of the mixture containing 20% benzoic acid and 80% CPG120–CPG1000 mixture (previously prepared in various mixing ratios). The broad endothermic peak at about 380 K

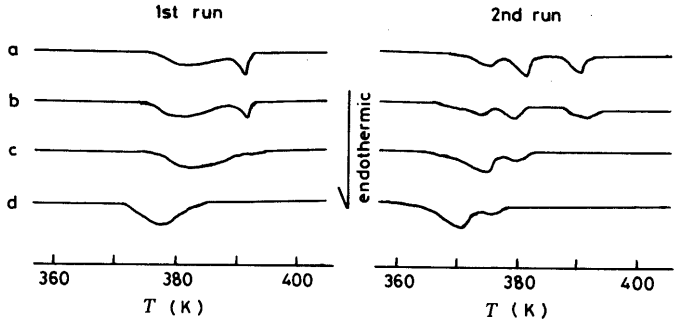

Fig. 5. DSC Curves of the Mixtures of 20% Benzoic Acid and 80% CPG120–CPG1000 Mixtures

a) CPG120:CPG1000=2:8; b) CPG120:CPG1000=3:7; c) CPG120:CPG1000=4:6; d) CPG120:CPG1000=6:4; heating rate, 4 K/min.

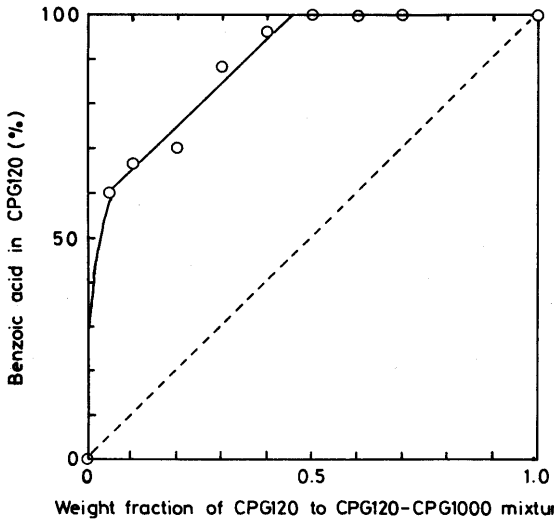

Fig. 6. Percent of Benzoic Acid in CPG120 in CPG120–CPG1000 Mixture

CPG120, 80/120 mesh; CPG1000, 200/400 mesh; concentration of benzoic acid, 20%. The broken line assumes a uniform distribution of benzoic acid in each of the CPGs.

represents the phase 2 of benzoic acid in CPG120 and the sharp peak at 390 K represent benzoic acid crystals. The DSC patterns varied with the mixing ratio of CPG120 and CPG1000. When the CPG120 concentration was less than 30%, two endothermic peaks were observed in DSC curves. When the concentration was above 40%, however, only one endothermic peak was observed, indicating that the most of the benzoic acid molecules in the mixture had interacted with CPG120. It was suggested that benzoic acid preferentially interacted with CPG120 in the CPG120–CPG1000 mixtures. The heat of fusion was also calculated from the peak areas to determine the amounts of benzoic acid in the CPGs. When the weight fraction of CPG120 was 0.1 in the CPG120–CPG1000, over 50% of benzoic acid in the mixture interacted with CPG120. As the amount of phase 3 in each CPG was neglected in the above discussion, the exact amounts of benzoic acid in each CPG were determined by a UV method as shown in Fig. 6. The addition of CPG120 at 0.05 weight fraction made it possible for about 60% of benzoic acid to exist in the CPG120. When the weight fraction of CPG120 was 0.50, all the benzoic acid molecules existed in CPG120. This result showed that the drug molecules mixed in porous materials

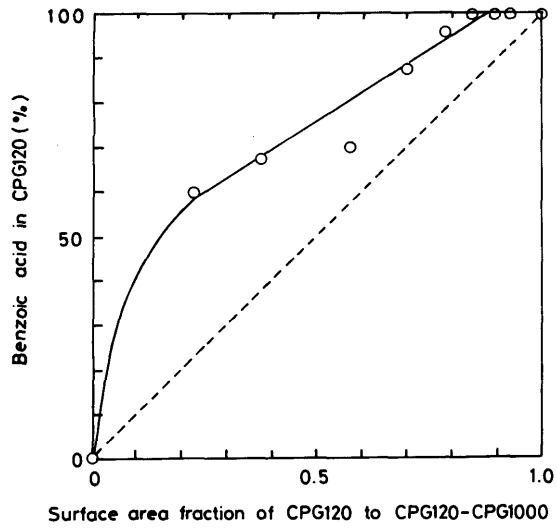

Fig. 7. Percent of Benzoic Acid in CPG120 in CPG120–CPG1000 Mixture

CPG120, 80/120 mesh; CPG1000, 200/400 mesh; concentration of benzoic acid, 20%. The broken line assumes a uniform distribution of benzoic acid in each of the CPGs.

of various pore sizes tended to interact with small pores. No particle size effect was observed between CPG120 and CPG1000 because the results were the same in either 80/120 mesh size or 200/400 mesh size. Taking into account the effects of the surface area of CPGs, the relationship between the surface area fraction and the amount of benzoic acid in CPG120 is shown in Fig. 7. When the surface area fraction of CPG120 was 0.25, about 60% of the benzoic acid existed in CPG120. The broken line was drawn by assuming that benzoic acid in the CPG120–CPG1000 mixture was distributed to each of the CPGs homogeneously. The observed amount of benzoic acid in CPG120 was always above the broken line, which indicates that benzoic acid was predominantly distributed to CPG120.

In conclusion, we found that low contents of benzoic acid in porous powder of mesopore size showed no crystalline properties. In addition, benzoic acid molecules tended to be concentrated in CPG having a small pore diameter rather than in that having a large pore diameter.

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