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Interaction of Medicinals and Porous Powder. I. Anomalous Thermal Behavior of Porous Glass Mixtures

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The molecular properties of benzoic acid, ethyl *p*-aminobenzoate and benzophenone mixed with porous glass powder were investigated by differential scanning calorimetry (DSC), powder X-ray diffraction, and gas adsorption measurements. The mixtures had anomalous properties as compared with the mixtures with glass beads, that is, (1) a low concentration mixture (about 5%) did not show the melting heat and X-ray diffraction peaks associated with the medicinal crystals, (2) a high concentration mixture (about 20%) showed only a broad endothermic peak at a lower temperature than the melting point, and (3) a higher concentration mixture (more than 40%) showed an endothermic heat effect at the melting point together with the broad peak at a lower temperature. The peak area at the melting point increased with an increase of drug concentration while the broad peak area remained unchanged. Mixing with medicinals caused a decrease of surface area and a change of pore diameter distribution of the porous glass. From these results it was concluded that the medicinals took three phases in the mixture; phase 1 (crystal structure), phase 2 (disordered structure) and phase 3 (probably adsorbed on the pore walls). The amounts of these phases were calculated from DSC curves.

Keywords——controlled pore glass; differential scanning calorimetry; powder X-ray diffraction; amorphous; adsorption; benzoic acid; ethyl *p*-aminobenzoate; benzophenone

Porous glass has numerous fine pores of 10 to 1000 Å in diameter, and has found many applications: for example, desalting of sea water,[1] separation of hydrogen,[2] and as a catalyst carrier,[3] as well as in studies of superconductivity[4] and photochemical reactions.[5] In particular, controlled pore glass (CPG) is utilized in chromatography[6] and as a solid support for enzymes.[7]

We have been investigating the adsorption properties of drugs on porous materials.[8] The physicochemical properties of drug molecules adsorbed on porous materials are markedly different from those in the crystalline state. In the present study, organic medicinal crystals were mixed with CPG at room temperature, and the state of the medicinals in the mixture was examined by differential scanning calorimetry (DSC), X-ray diffraction and gas adsorption measurements. CPG was used as a model porous material since there are many types having different mean pore diameters and chemical surface characteristics on the market and the properties of CPG are well known.

Experimental

1) Materials——Controlled pore glass of 70 Å pore diameter (CPG) was obtained from Electro-Nucleonics Ltd. and was used after drying in a vacuum at 120 °C for 1 h. Glass beads were used as a reference additive. Benzoic acid (Wako Pure Chemical Industries, Ltd.), mp 122.4 °C, ethyl *p*-aminobenzoate (Nakarai Chemicals, Ltd.), mp 88—90 °C, and benzophenone (Wako Pure Chemical Industries, Ltd.), mp 48.5 °C, were used as crystalline medicinals.

2) Preparation of Mixtures and Melted Mixtures——One of the medicinals and CPG or glass beads were mixed

in various ratios in a mortar and pestle. Then the samples were stored in a desiccator containing silica gel at room temperature. Melted mixtures were prepared by heating the mixture above the melting point of the respective medicinals followed by cooling.

3) Thermal Analysis——A Perkin-Elmer DSC-1B apparatus was used for the measurements of melting point and heat of fusion. The measurements were performed using liquid sample pans at a heating rate of 2 °C/min, range of 2 mcal/s (10 mV) and chart speed of 10 mm/min. Heat of fusion was determined by measuring the peak area on the thermogram by the weighing method.

4) Powder X-Ray Diffraction——A Rigaku Denki 2027 diffractometer was used under the following conditions: target Cu, filter Ni, voltage 30 kV, current 5 mA, time constant 0.5 s, scanning speed 2 °/min, chart speed 40 mm/min.

5) Measurement of Nitrogen Gas Adsorption——The adsorption apparatus was made in this laboratory following the specifications of the technical bulletin of Mellon Institute of Industrial Research. Dead space was measured by using He gas.

Results and Discussion

Characteristics of DSC Curves

DSC curves of the mixture of benzoic acid and CPG are shown in Fig. 1. The mixture containing 20% benzoic acid showed a small broad endothermic peak at 85—100 °C, but no peak was found at 122.4 °C, the melting point of benzoic acid. In the mixture containing 40% benzoic acid, two endothermic peaks were observed at 85—100 and 117 °C. The area of the endothermic peak at 117 °C increased with increasing ratio of benzoic acid, while that of the peak at 85—100 °C scarcely varied. In the second run curves, the endothermic peak at 85—100 °C was separated into two endothermic peaks, but the areas were not changed. On the other hand, the DSC curve of the benzoic acid–glass beads mixture showed only one endothermic peak corresponding to the melting of benzoic acid, although the peak had an irregular shape.

Figure 2 and 3 show the DSC curves for ethyl *p*-aminobenzoate and benzophenone, respectively. In the first run with 20% ethyl *p*-aminobenzoate mixture, there was a small endothermic peak at 90 °C, the melting point of the crystals. The second run showed a broad endothermic peak at a lower temperature of 45—50 °C. Curve (c) in Fig. 2 is for 35% ethyl *p*-aminobenzoate. Both on the first run and the second run, two endothermic peaks appeared at 90 and 45—75 °C. Similar patterns were observed for benzophenone mixtures, as shown in Fig. 3. At 20% content of benzophenone, no endothermic peaks were found on the curve while at higher contents of 40 and 60% there were two endothermic peaks at 45 °C (melting point of benzophenone) and at 15—25 °C (20—30 °C below the melting point). These DSC results indicate that three different states of the drug may exist in drug–CPG mixtures, that is (1) the crystalline state, (2) the state which shows the broad endotherm at-a lower temperature than the melting point, and (3) the state which does not show a peak on the DSC curve. As the

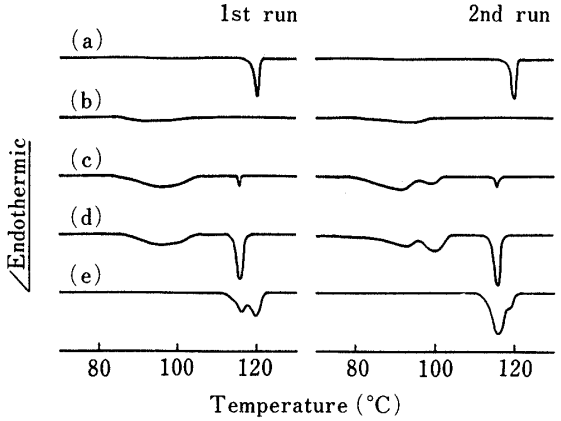

Fig. 1. DSC Curves of Mixtures of Benzoic Acid and CPG or Glass Beads

(a), benzoic acid; (b), 20% benzoic acid, 80% CPG; (c), 40% benzoic acid, 60% CPG; (d), 60% benzoic acid, 40% CPG; (e), 20% benzoic acid, 80% glass beads.

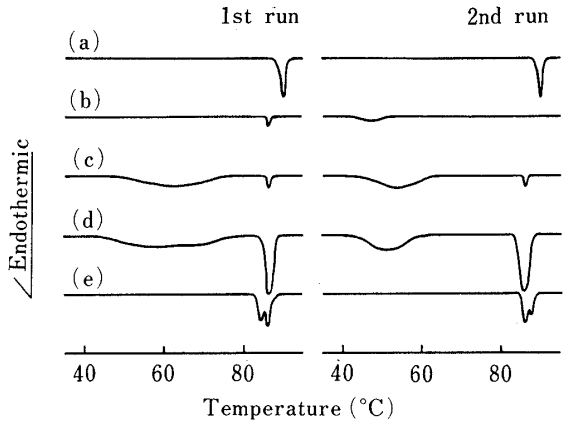

Fig. 2. DSC Curves of Mixtures of Ethyl *p*-Aminobenzoate and CPG or Glass Beads

(a), ethyl *p*-aminobenzoate; (b), 20% ethyl *p*-aminobenzoate, 80% CPG; (c), 35% ethyl *p*-aminobenzoate, 65% CPG; (d), 60% ethyl *p*-aminobenzoate, 40% CPG; (e), 20% ethyl *p*-aminobenzoate, 80% glass beads.

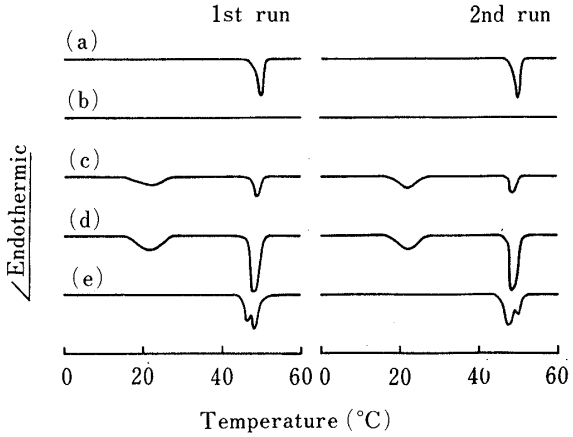

Fig. 3. DSC Curves of Mixtures of Benzophenone and CPG or Glass Beads

(a), benzophenone; (b), 20% benzophenone, 80% CPG; (c), 40% benzophenone, 60% CPG; (d), 60% benzophenone, 40% CPG; (e), 20% benzophenone, 80% glass beads.

mixture of drug and glass beads showed only melting of the crystals, it is thought that the pores of CPG play an important role in these phenomena.

Changes in the Powder X-Ray Diffraction Patterns

Powder X-ray diffraction patterns of the mixture of benzoic acid with CPG or glass beads are shown in Fig. 4. Figure 4(a) shows the diffraction pattern of the 5% benzoic acid and 95% CPG system, in which the peaks due to benzoic acid crystals were not observed. For the mixture of 10% benozic acid (b), the peaks were observed at first, but they decreased in intensity on storage of the mixture for one week (c) and one month (d) at room temperature. Figure 4(e) and (f) show the mixtures of 5% benzoic acid and 95% glass beads before and after storage for one month, respectively. Benzoic acid crystal peaks did not decrease in intensity on storage of the crystals under the same conditions. Figure 5 shows the X-ray diffraction pattern of the mixture of ethyl *p*-aminobenzoate and CPG or glass beads. The CPG mixture with 10% ethyl *p*-aminobenzoate did not show crystalline peaks but mixtures with more than 15% showed the peaks, which decreased in intensity on storage at room temperature as in the case of benzoic acid–CPG. The mixtures, after being melted and then solidified, showed a halo pattern up to the concentration of 15% ethyl *p*-aminobenzoate. A similar pattern was observed for the mixture of 15% benzophenone and 85% CPG. Glass beads mixtures with ethyl *p*-aminobenzoate or benzophenone, on the other hand, did not show any change in peak intensity on storage at room temperature. From the powder X-ray diffraction patterns, it is assumed that the crystalline medicinals changed into a non-crystalline or "amorphous" state on admixture with CPG.

Pore Size Distribution and Specific Surface Area of CPG-Medicinal System

Specific surface area was determined from nitrogen gas adsorption isotherms using the B.E.T. method. The specific surface area values of CPG before and after mixing are shown in Table I. The mixture having no crystalline peaks in the X-ray diffraction patterns showed an appreciable decrease in the surface area.

Figure 6 shows the pore size distributions of these samples determined by the Cranston–Inkley method. When the medicinals were mixed with CPG, the mean pore diameters did not change except in the case of 10% ethyl *p*-aminobenzoate–CPG mixture. Pore volume and the

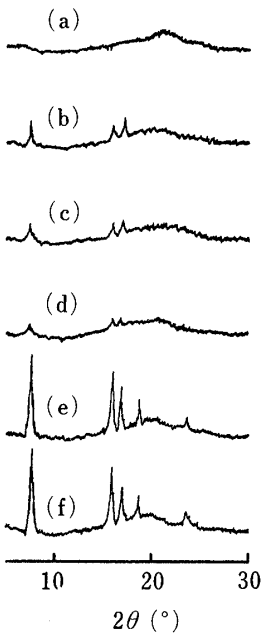

Fig. 4. Powder X-Ray Diffractograms of Mixtures of Benzoic Acid and CPG or Glass Beads

(a), benzoic acid 5%, CPG 95%; (b), benzoic acid 10%, CPG 90%; (c), benzoic acid 10%, CPG 90% (kept for one week at room temperature); (d), benzoic acid 10%, CPG 90% (kept for one month at room temperature); (e), benzoic acid 5%, glass beads 95%; (f), benzoic acid 5%, glass beads 95% (kept for one month at room temperature).

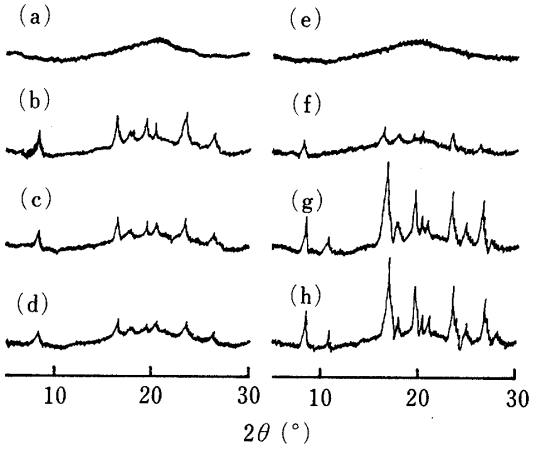

Fig. 5. Powder X-Ray Diffractograms of Mixtures of Ethyl *p*-Aminobenzoate and CPG or Glass Beads

(a), ethyl *p*-aminobenzoate 10%, CPG 90%; (b), ethyl *p*-aminobenzoate 15%, CPG 85%; (c), ethyl *p*-aminobenzoate 15%, CPG 85% (kept for one week at room temperature); (d), ethyl *p*-aminobenzoate 15%, CPG 85% (kept for one month at room temperature); (e), ethyl *p*-aminobenzoate 15%, CPG 85% (melted and then solidified); (f), ethyl *p*-aminobenzoate 20%, CPG 80% (melted and then solidified); (g), ethyl *p*-aminobenzoate 10%, glass beads 90%; (h), ethyl *p*-aminobenzoate 10%, glass beads 90% (kept for one month at room temperature).

TABLE I. Specific Surface Area of Mixtures of Various Medicinals with CPG as Determined by the B.E.T. Method

Mixture	Specific surface area (m^2/g)
CPG alone	171
Benzoic acid–CPG	165
Ethyl *p*-aminobenzoate–CPG	139
Benzophenone–CPG	109

maximum distribution volume at about 145 Å decreased appreciably in all cases. From these results, it is suggested that the medicinals were present in the pores of CPG in the mixture.

Molecular Behavior of Benzoic Acid in a Mixture with CPG

When medicinals were mixed with CPG at a low concentration, the mixtures did not show the heat of melting or the X-ray diffraction peaks associated with the crystals. At a higher concentration such as 20%, a broad endothermic peak was observed at a lower temperature than the melting point. At the high concentration of 40%, an endothermic peak at the melting point appeared in addition to the broad peak. The peak area at the melting point increased with an increase of the concentration of benzoic acid, while the peak area at a lower temperature did not change. From these results, the presence of three phases was deduced for the medicinals contained in the mixture. The first is the crystal phase (phase 1),

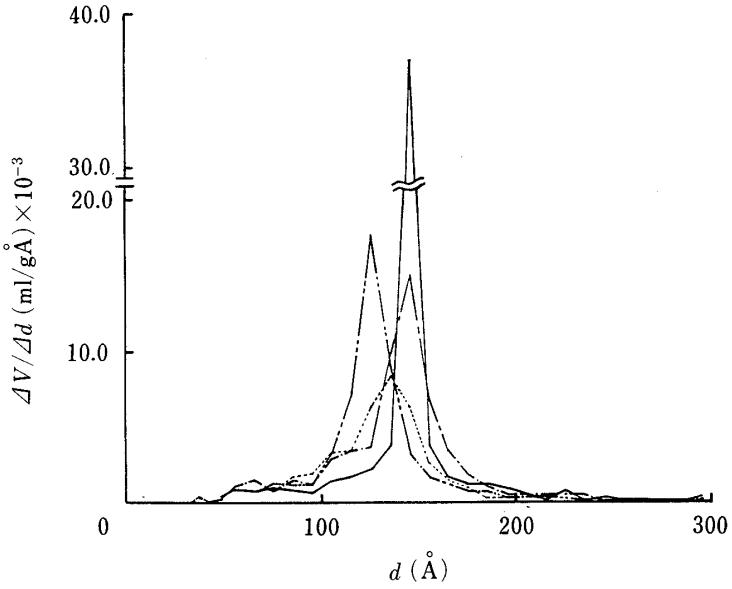

Fig. 6. Pore Size Distribution of Drug–CPG Systems

——, CPG; — - —, 5% benzoic acid and 95% CPG; — -- —, 10% ethyl *p*-aminobenzoate and 90% CPG; ------, 15% benzophenone and 85% CPG.

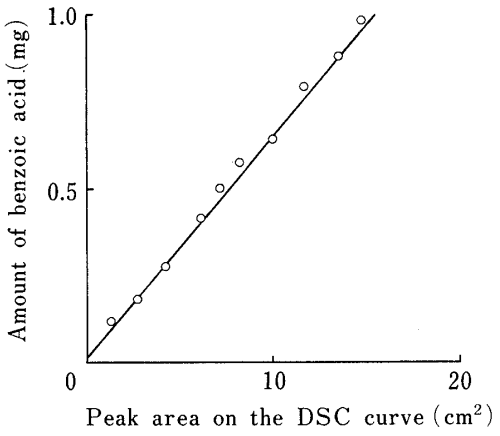

Fig. 7. Regression Line between Amount of Benzoic Acids and Peak Area in the DSC Curves

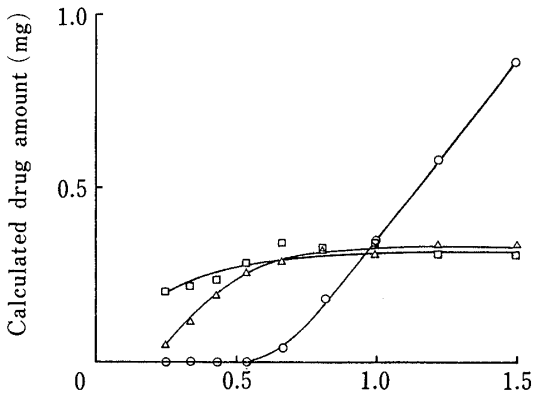

Fig. 8. Relationship between Total Amount of Benzoic Acid and Calculated Amount of the Three Phases

○, phase 1; △, phase 2; □, phase 3.

the second is the phase that shows the broad peak at a temperature lower than the melting point of the crystals (phase 2), and the last is the phase undetectable by the DSC and X-ray diffraction methods (phase 3).

Quantitative Analysis of Benzoic Acid in the Three Phases

The quantities of the three phases in mixtures were obtained from the thermograms. Figure 7 shows the regression line between the amount of benzoic acid and the peak area on thermograms. The quantity of phase 1, m_1, can be calculated from the peak area at the melting point by using the regression line. The quantity of phase 2, m_2, can be calculated by measuring the broad peak area at lower temperature on the assumption that the specific heat of melting is equal to that of the crystals. The quantity of phase 3, m_3, can be calculated as $m_3 = m - (m_1 + m_2)$ where m is the total amount of benzoic acid in the mixture. Figure 8 shows the relationship between total amount of benzoic acid added to 1 mg of CPG and the

calculated amounts of the three phases. The calculated amount of phase 1 was zero up to 0.5 mg of benzoic acid and then increased linearly with an increase of the added amount. In contrast with phase 1, the value of phase 2 increased sharply up to 0.5 mg of benzoic acid and thereafter increased slowly to reach a constant value, and that of phase 3 had a large value even at a low content of benzoic acid and soon reached a constant value on further addition of benzoic acid. The specific heat of melting of phase 2 may be smaller than that of the crystals since lattice disorder is presumed to exist from the DSC and X-ray diffraction patterns. The amount of phase 2, therefore, may be somewhat larger than the calculated values. However, these results lead to the conclusion that benzoic acid is in phase 2 and 3 in the pores of CPG at room temperature when a small amount of benzoic acid is added to CPG. When a large amount of benzoic acid is added to CPG, the excess amount of benzoic acid is in phase 1, which probably exists outside of the pores. The mixtures of ethyl *p*-aminobenzoate and benzophenone with CPG showed similar properties to the benzoic acid–CPG mixture. When such samples were cooled down and a second DSC measurement was carried out, a phase change was no longer recorded on the thermogram. As will be reported in the following paper, the volatile medicinal was retained in the mixture with CPG even when the mixture was heated at moderately high temperature *in vacuo*. From these results, it may be concluded that the molecules in phase 3 are adsorbed tightly on the pore walls through chemical bonding forces such as hydrogen bonding.

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