Molecular State of Methyl *p*-Hydroxybenzoate in the Solid Dispersion Prepared by Grinding with α-Cyclodextrin

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The molecular interaction in a ground mixture of α-cyclodextrin (α-CD) and methyl *p*-hydroxybenzoate (MPHB) has been studied as a function of the mixing molar ratio. The states of MPHB molecules were investigated by means of powder X-ray diffraction, differential scanning calorimetry measurement and the determination of remaining MPHB after sublimation. The results indicated that in the ground mixture the MPHB molecules could exist in a mono-molecular dispersed state in the hydrogen bonding network of α-CD as well as in the α-CD cavity. It was suggested that two types of crystalline MPHB, fine crystals embedded in the α-CD matrix and intact crystals, were also present in the ground mixture of molar ratio 5 (MPHB/α-CD) or above.

Keywords grinding; crystallinity; amorphous; α-cyclodextrin; molecular dispersion; sublimation

Among the unit processes of pharmaceutical technology, grinding is useful for reducing the particle size or the crystallinity of medicinals for the purpose of enhancing the dissolution rate. Nakai *et al.* reported that the co-grinding with an additive, such as microcrystalline cellulose or cyclodextrins, could change crystalline drug into amorphous state and demonstrated the improvements of pharmaceutical properties.[2–4]

We described previously[5] the molecular interaction in binary (drug and additive) freeze-dried products and the effects of freezing condition on the interaction mode. In this paper, the changes of crystalline properties of methyl *p*-hydroxybenzoate (MPHB) by grinding with α-cyclodextrin were investigated in comparison with those in the freeze-drying process.

Experimental

Materials MPHB was of special reagent grade. α-Cyclodextrin (α-CD) (Nakarai Chem. Co., Ltd.) was stored in a desiccator containing P_2O_5, *in vacuo*.

Preparation of Ground Mixture A vibrational mill (Heiko Seisakusho TI-200), which was made of tungsten carbide, was used. The volume of the mill was 140 cm^3, and the height of the rod was 55 mm. The total weight of specimen was 2.0 g.

Preparation of Freeze-Dried Sample The apparatus and procedure were the same as those reported in the previous paper.[5] Liquid nitrogen was used as the freezing medium.

Powder X-Ray Diffraction A Rigaku Denki 2027 diffractometer was used. The measurement conditions were as follows: target Cu, filter Ni, voltage 30 kV, current 5 mA, scintillation counter.

Differential Scanning Calorimeter (DSC) A Perkin Elmer 1B differential scanning calorimeter was used. Samples were sealed in aluminum pans for liquid samples and were measured at the scanning speed of 8 K/min.

Sublimation Treatment[5] For estimating the amorphous fraction of MPHB in freeze-dried samples, the crystalline MPHB was removed by sublimation. The samples were evacuated at 110 °C below 10^{-2} Torr for 4 h, and then were dissolved in Clark Lubs' buffer solution (pH = 1.45, $\mu = 0.09$). The amount of remaining MPHB was determined by using an ultraviolet (UV) spectrophotometer (Shimadzu UV-200S).

Results and Discussion

The crystallinity of cyclodextrins is decreased by mechanochemical treatment or freeze-drying. Figure 1 shows the powder X-ray diffraction patterns of physical mixtures and 12-min-ground mixtures of α-CD–MPHB. In 1 : 1 (MPHB/α-CD) ground mixture, the X-ray diffraction peaks of α-CD crystals and MPHB crystals disappeared completely and the diffractogram changed to a halo pattern. On the other hand, the diffraction peaks of MPHB crystals were found in 5 : 1 (MPHB/α-CD) ground sample, though no diffraction peaks of α-CD crystals were found. In the 5 : 1 ground sample, however, a small quantity of MPHB was in the amorphous state, as a decrease of the peak intensity was observed in comparison with that of the physical mixture. It was reported that the sublimation of a drug from co-ground samples was suppressed owing to the mono-molecular dispersion of the drug into the additive matrix.[3] In the previous paper,[5] Nakai *et al.* reported that in an MPHB–α-CD (1 : 2) freeze-dried sample all MPHB

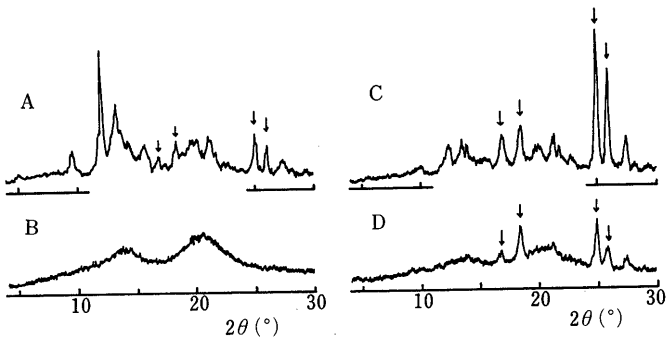

Fig. 1. Powder X-Ray Diffraction Patterns of α-CD and MPHB Mixtures

A, MPHB–α-CD (molar ratio 1 : 1) physical mixture; B, ground sample of A (ground for 12 min); C, MPHB–α-CD (molar ratio 5 : 1) physical mixture; D, ground sample of C (ground for 12 min). The diffraction peaks due to MPHB crystals are indicated by arrows.

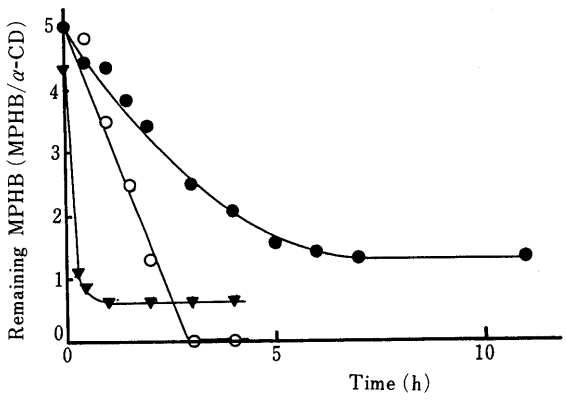

Fig. 2. MPHB Sublimation from MPHB–α-CD (Molar Ratio 5 : 1) Systems

●, ground mixture; ○, physical mixture; ▼, freeze-dried sample.

molecules remained in the matrix after the heating at 110 °C *in vacuo* for 4 h.

Sublimation treatment was carried out to investigate the interaction between MPHB and α-CD in co-ground samples. Figure 2 shows the time courses of MPHB sublimation behavior from different preparations of MPHB–α-CD (5 : 1) systems. Sublimation of MPHB from the freeze-drying sample was rapid in comparison with that from the physical mixture. On the other hand, the ground mixture showed slower sublimation and a certain amount of MPHB remained even after evacuation for 11 h. Rapid sublimation of MPHB from the freeze-dried sample may be attributed to the formation of extremely fine MPHB crystals. The slow sublimation from the ground mixture was concluded to be the result of fine MPHB crystals having become embedded in the α-CD matrix. Some fraction of MPHB was found to remain after heating *in vacuo* for 24 h of the ground mixture and the freeze-dried sample. It was concluded that the remaining MPHB molecules were dispersed into the α-CD cavity or into the hydrogen-bonding network formed by α-CD molecules, mono-molecularly.[3,4,6]

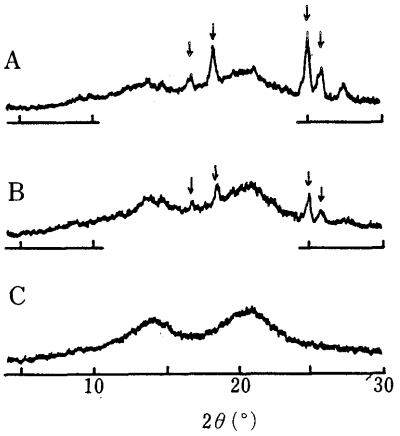

Fig. 3. Changes of Powder X-Ray Diffraction Pattern of MPHB–α-CD Ground Mixture (Molar Ratio 5 : 1) after Storage at 110 °C *in Vacuo*

A, before storage; B, stored for 4 h; C, stored for 12 h. The peaks due to MPHB crystals are indicated by arrows.

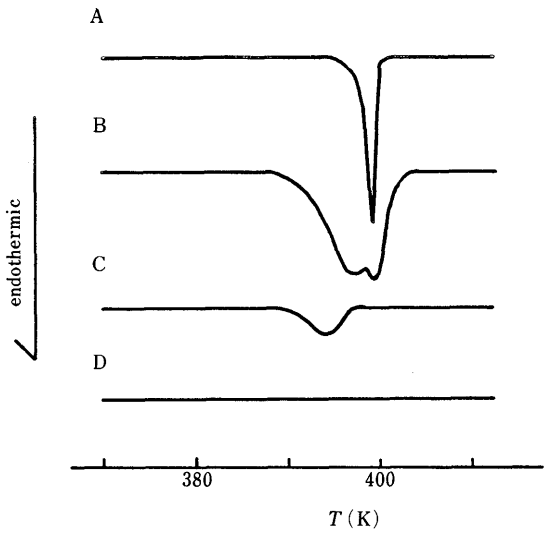

Fig. 4. Changes of DSC Curves of MPHB–α-CD (5 : 1) Ground Mixture during Storage at 110 °C *in Vacuo*

A, intact MPHB; B, before storage; C, stored for 4 h; D, stored for 12 h.

Changes of powder X-ray diffraction pattern of the ground mixture (5 : 1) during storage at 110 °C *in vacuo* are shown in Fig. 3. The diffraction peaks of MPHB crystals decreased in intensity with storage time, indicating the removal of MPHB crystals by sublimation. In a 12-h-stored sample, the diffraction peaks due to MPHB crystals were no longer detected, while the sample still contained 26% MPHB.

The thermal behavior of the ground mixture was investigated by DSC to clarify the sublimation properties of MPHB from α-CD ground mixture. Figure 4 shows the effects of sublimation treatment on the DSC curve of MPHB–α-CD (5 : 1) ground mixture. The melting peak of MPHB crystals was observed in the DSC curve, and consisted of two peaks in the ground mixture, that is, one at 396 K, the melting point of intact MPHB crystals, and the other (broad) at six degrees below the melting point. After heat-treatment for 4 h, the melting peak at 396 K disappeared while the endothermic peak at 390 K still remained. After heat-treatment for 12 h, no endothermic peak due to the melting of MPHB was observable. Consequently, the slow sublimation of MPHB from the ground mixture was considered to result from MPHB crystals dispersed within the matrix and showing a lower melting point than intact MPHB crystals. The depression of melting point may be ascribed to enhanced free energy of MPHB crystals arising from pulverization by grinding.[7,8]

After the removal of sublimable MPHB from the ground mixture, the remaining amount of MPHB was plotted as a function of initial mixing molar ratio (MPHB/α-CD) as shown in Fig. 5. In the systems of initial mixing ratio 2—15, the amounts of remaining MPHB were 1.2—1.3 in molar ratio. For samples of initial mixing ratio above 20, the values were almost unity. It was supposed in systems of initial mixing ratio 2—15 (MPHB/α-CD) that after the sublimation, remaining MPHB molecules could exist mono-molecularly in the hydrogen-bonding network of α-CD as well as in the α-CD cavity. In systems with a mixing molar ratio of above 20 (MPHB/α-CD), a large amount of MPHB molecules existed in comparison with α-CD molecules, so presumably a rigid hydrogen-bonding network could not be formed between α-CD molecules. In other words, the α-CD molecules was dispersed in MPHB medium, differently from the low MPHB content mixtures. Hence, the retention

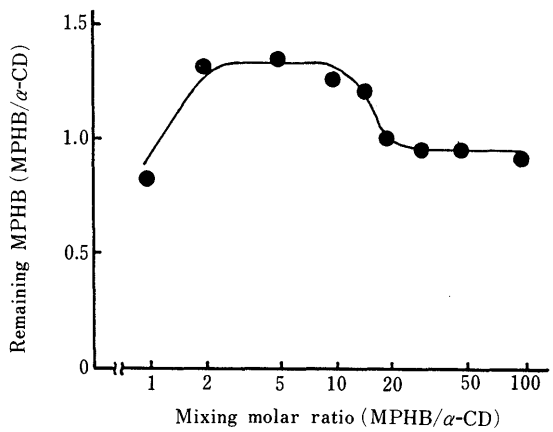

Fig. 5. Remaining Amount of MPHB in Ground Mixture with α-CD after Storage at 110 °C *in Vacuo* for 24 h.

of MPHB molecules after sublimation was caused only by inclusion in the α-CD cavity.

The results of this study demonstrated that in ground mixtures of α-CD and MPHB, MPHB molecules could be present in four states as follows: (a) included in the α-CD cavity, (b) as a stable mono-molecular dispersion in the hydrogen-bonding network formed by α-CD molecules, (c) as comparatively stable fine crystals embedded in an α-CD matrix, (d) in a crystalline state similar to that of intact MPHB crystals. By means of sublimation treatment, MPHB in state (d) was readily sublimed, while that in state (c) was quite slowly sublimed. On the other hand, no sublimation took place from state (a) or (b).

References and Notes

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