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Effects of Solid Dispersion with Heptakis-(2,6-di-*O*-methyl)-*β*-cyclodextrin on the Dissolution and Sublimation of Naphthalene

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The solid dispersion of naphthalene with heptakis-(2,6-di-*O*-methyl)-*β*-cyclodextrin (DMCD) has been studied by using X-ray diffraction and thermal methods. The influence of the solid dispersion on the dissolution and sublimation of naphthalene were studied. X-Ray diffraction and thermal data indicated the amorphous state of naphthalene and DMCD. Enhanced dissolution and reduced sublimation characteristics were observed in the ground mixture and the coprecipitate. The sublimation rate of naphthalene from the ground mixture and the coprecipitate increased during storage at high relative humidity due to crystallization.

Keywords——di-*O*-methyl-*β*-cyclodextrin; naphthalene; grinding; solid dispersion; dissolution; sublimation; X-ray diffraction; thermal analysis

A number of solid dispersion techniques are known to enhance the dissolution and the absorption rates of drugs.[2)] As carriers in such solid dispersions, polyvinylpyrrolidone,[3)] polyethylene glycol,[4)] microcrystalline cellulose[5)] and cyclodextrins are used. In particular, cyclodextrins form inclusion compounds with various drug molecules, and the utilization of complexation with cyclodextrins is widespread in the pharmaceutical field.[6)] The effects of drug dispersion into cyclodextrins on the stability and sublimation behavior were described by Nakai *et al.*[7)] Recently, heptakis-(2,6-di-*O*-methyl)-*β*-cyclodextrin (DMCD) has received considerable attention, because its physicochemical properties and inclusion behavior are different from those of *β*-cyclodextrin.[8)]

In this work, naphthalene, which sublimes readily and has a low solubility in water, was chosen to prepare a solid dispersion with DMCD.[9)] The aim of this study was to investigate the interaction between DMCD and naphthalene and to determine whether the sublimation and dissolution characteristics of naphthalene were improved in the solid dispersion with DMCD.

Experimental

Materials——DMCD was purchased from Toshin Chemical Co., and used as received. Naphthalene (Wako Chemical Co.) was of special reagent grade. All other materials and solvents were of analytical reagent grade. Double distilled water was used.

Ground Mixture——A tungsten carbide vibrational mill (Heiko Seisakusho TI-200) was used for preparing the ground mixture. Total weight of the sample was 2.10 g. The mixing molar ratio of naphthalene to DMCD was 1 : 1.

Preparation of Coprecipitate——The coprecipitate was prepared by dissolving equimolar amounts of naphthalene and DMCD in ethanol and then evaporating the solvent, as described by Nagai *et al.*[10)]

Solubility Study——Solubility measurements were carried out according to the method of Higuchi and Connors.[11)] An excess of naphthalene (76.8 mg) was added to 10 ml of distilled water containing various concentrations of DMCD, and the solutions were shaken constantly at 25.0 °C for 7 d. The naphthalene

concentrations were determined spectrophotometrically using a double-beam spectrophotometer (Shimadzu UV-200S) at 276 nm. The molar absorptivity of naphthalene was not affected by DMCD under the present analytical conditions.

X-Ray Diffractometry——The powder X-ray diffractometer and the procedures were the same as those reported in the previous paper.[8a)]

Thermal Measurements——Thermogravimetry (TG; Shimadzu TG-20B) was done at a heating rate of 10 °C/min over the temperature range of 25—200 °C under N_2 gas flow. The sample weight was 10.0 mg. A differential scanning calorimeter (DSC; Perkin-Elmer DSC-1B) was also used; the scanning speed was 8 °C/min and the measurements were carried out under N_2 gas flow. The sample weight was about 4.5 mg.

Dissolution Study——A powder sample containing 250 mg of naphthalene was put into a beaker containing 200 ml of distilled water maintained at 37.0 °C. A glass propeller was stirred at 50 rpm. At appropriate intervals, 5 ml of the solution was withdrawn by the use of a pipette fitted with a cotton wool filter. The assay procedure for naphthalene was the same as that in the solubility study.

Measurement of Naphthalene Sublimation——Each naphthalene–DMCD dispersed sample (about 500 mg) was placed in a vacuum glass vessel at 70 °C for 1 h. The remaining amount of naphthalene was determined spectrophotometrically using ethanol as a solvent.

Measurement of Naphthalene Content Variation——The various dispersion samples were stored at 40 °C and at 11, 31, 48 and 79% relative humidity (RH) for definite time periods. The naphthalene contents were determined spectrophotometrically.

Results and Discussion

Complexation in Aqueous Solution and in the Solid State

The complexation of naphthalene with DMCD in water was investigated by the solubility method. Figure 1 shows a phase solubility diagram obtained for the naphthalene–DMCD system at 25.0 °C. This solubility curve was classified as type A_p, showing a positive deviation from linearity.[11)] With the addition of DMCD, the concentration of naphthalene increased owing to the inclusion complex formation. The stability constant for the 1 : 1 complex $K_{1:1}$ was calculated as 569 M^{-1} from the slope of the initial straight portion of the curve. The A_p diagram indicates that the soluble complexes contained more than one molecule of ligand at higher DMCD concentrations.[12)] Therefore, the stability constant for the 1 : 2 complex $K_{1:2}$ was calculated by the iteration method reported by Higuchi and Kristiansen.[11)] After 100 iterations, the $K_{1:1}$ and $K_{1:2}$ values were determined as 564 and 24.0 M^{-1} respectively.

The coprecipitate and the ground mixture of naphthalene with DMCD were prepared using a mixture of 1 : 1 molar ratio. Figure 2 shows the powder X-ray diffraction patterns of

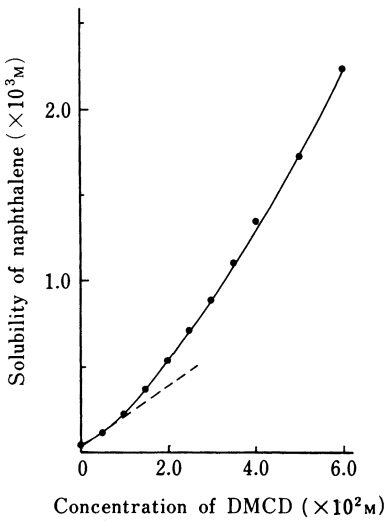

Fig. 1. Phase Solubility Diagram of Naphthalene and DMCD in Water at 25.0 °C

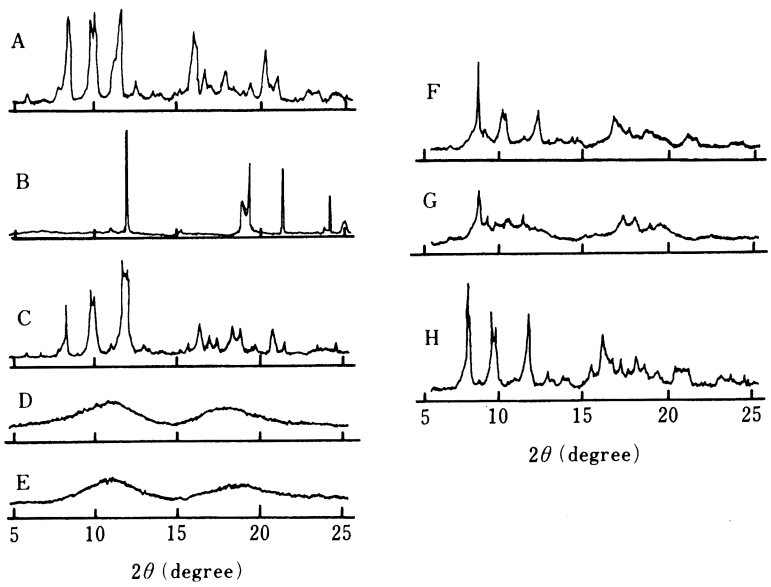

Fig. 2. Powder X-Ray Diffraction Patterns of Naphthalene DMCD Systems

A, DMCD; B, naphthalene; C, physical mixture; D, ground mixture; E, coprecipitate; F, ground mixture stored at 79% RH, 40 °C for 15 d; G, coprecipitate stored at 79% RH, 40 °C for 15 d; H, ground mixture heated at 100 °C for 1 h.

the various naphthalene–DMCD systems. It was found that crystalline naphthalene and DMCD changed into the amorphous state in the ground mixture and the coprecipitate (curves D and E). When the two amorphous samples were stored at 40 °C and 79% RH for 15 d, crystalline powders were obtained giving the X-ray diffraction patterns shown by curves F and G. From a comparison of the X-ray diffraction patterns of the physical mixture and the crystallized powders, it was concluded that the crystalline powders were crystalline DMCD. The naphthalene molecules dispersed in amorphous samples were eliminated from the system after water vapor adsorption, and then the crystallization of DMCD could occur. Hall and Lim reported the crystalline complex formation of naphthalene with DMCD by applying the C^{13} cross polarization magic angle spinning nuclear magnetic resonance (NMR) method and showed that the host guest molar ratio was not stoichiometric.[13] In our study, the molar ratio of naphthalene to DMCD varied with storage time and conditions as shown later. For samples F and G in Fig. 2, the molar ratio was about 0.15 : 1. The heating at 100 °C for 1 h of the amorphous samples also caused crystallization. The X-ray diffraction patterns also coincided with that of DMCD crystals, showing the sublimation of naphthalene from the system (Fig. 2-H).

Figure 3 shows the TG curves of the naphthalene–DMCD systems. The beginning of weight loss due to the sublimation of naphthalene was observed at higher temperatures in the ground mixture and the coprecipitate than in the physical mixture. This fact was ascribed to presence of molecular interaction between naphthalene and DMCD molecules.

Figure 4 shows the DSC patterns of naphthalene–DMCD systems. In the case of the physical mixture, an endothermic peak due to the melting of naphthalene was observed at 350 K. In contrast, the ground mixture and the coprecipitate showed no appreciable endothermic peak of naphthalene within the melting range revealing the amorphous state of naphthalene. The ground mixture showed, however, an exothermic peak due to the crystallization of DMCD, although the coprecipitate did not show any peak in this

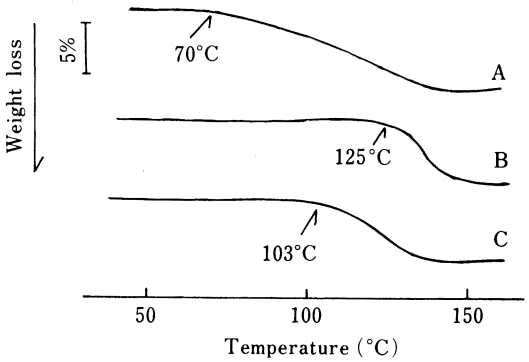

Fig. 3. TG Curves of Naphthalene DMCD Systems

A, physical mixture; B, ground mixture; C, coprecipitate.

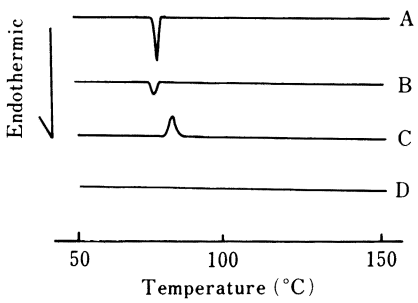

Fig. 4. DSC Curves of Naphthalene DMCD Systems

A, naphthalene crystals; B, physical mixture; C, ground mixture; D, coprecipitate.

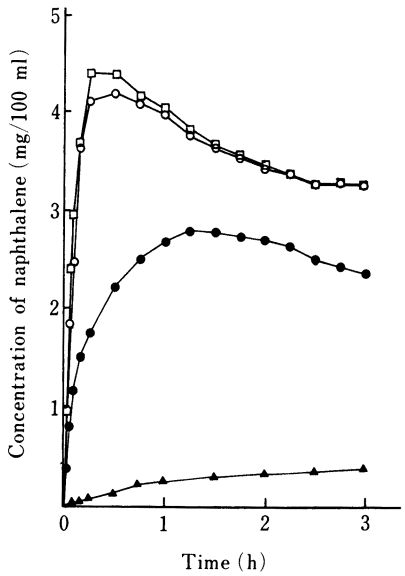

Fig. 5. Dissolution Profiles of Naphthalene from Naphthalene DMCD Systems at 37.0 °C

▲, naphthalene crystals; ●, physical mixture; ○, ground mixture; □, coprecipitate.

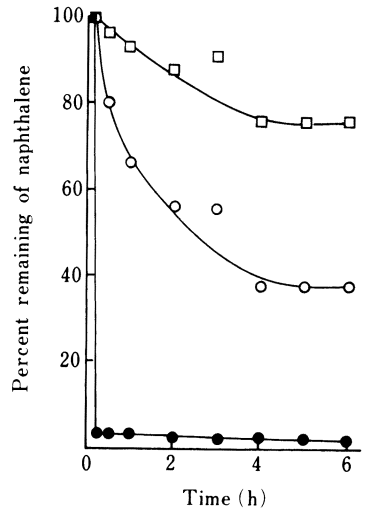

Fig. 6. Effects of Heating at 70 °C for 1 h on the Remaining Amounts of Naphthalene

●, physical mixture; ○, ground mixture; □, coprecipitate.

temperature range. This difference could be attributed to the differences in the amount and the mode of existence of adsorbed water on the amorphous solid.

Dissolution Behavior

The dissolution profiles of naphthalene crystal, physical mixture, ground mixture and coprecipitate in water at 37.0 °C are shown in Fig. 5. From the ground mixture and the coprecipitate, naphthalene dissolved about 40 times faster than from naphthalene crystals at 10 min. The physical mixture showed a significant increase in the dissolution rate in comparison with naphthalene crystals due to the improvement of wettability and to the solubilization effect. Supersaturation of naphthalene was observed for the ground mixture and the coprecipitate in the initial period of the dissolution, as all of the DMCD and

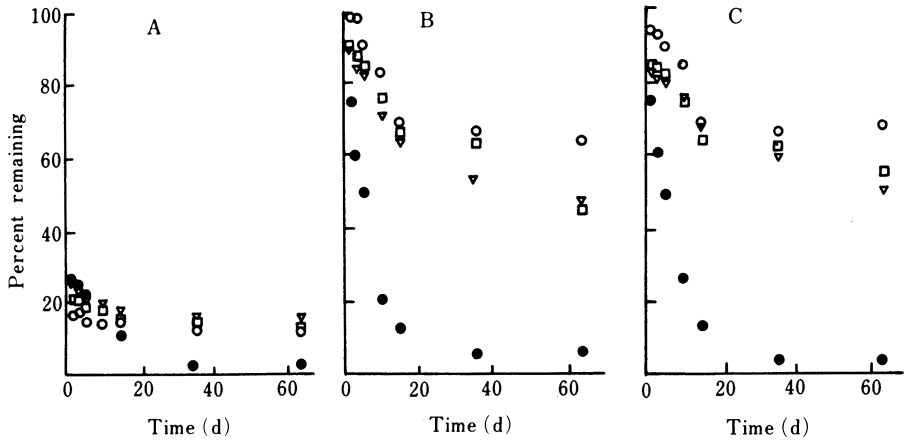

Fig. 7. Effects of Relative Humidity on Naphthalene Contents at 40 °C

A, physical mixture; B, ground mixture; C, coprecipitate.
○, 11% RH; □, 31% RH; ▽, 48% RH; ●, 79% RH.

contained naphthalene were released together to the dissolution medium. After 10 min, however, the dissolution profiles of amorphous samples showed negative curvature with the passage of time, due to the recrystallization of naphthalene.

Sublimation Behavior

The remaining amounts of naphthalene during heating at a constant temperature of 70 C *in vacuo* were measured for the physical mixture, the ground mixture and the coprecipitate. In the case of the physical mixture, naphthalene content decreased abruptly to less than 3% of the content after 1 h of heating (Fig. 6). In the cases of the ground mixture and the coprecipitate, the sublimination of naphthalene occurred gradually and appeared to stop after 4 h of heating. The difference of remaining percentage of naphthalene between the ground mixture and the coprecipitate could be attributed to variability of the complexing mode of naphthalene to DMCD.

Figure 7 shows the time course of remaining naphthalene percentage during storage at 40 C and at 11, 31, 48 and 79% RHs. In the physical mixture (Fig. 7-A), the sublimation of naphthalene was observed at the fastest rate regardless of RHs. In contrast, the ground mixture and the coprecipitate showed slow sublimation of naphthalene. After 65 d of storage, the remaining percentages in both the ground mixture and the coprecipitate were between 50 and 70% except at 79% RH. At 79% RH, the sublimation rates were markedly increased and the percent remaining was less than 15% at 15 d. This rapid decrease of the remaining values could be attributed to the crystallization of DMCD in the ground mixture and the coprecipitate subsequent to uptake of water vapor, as indicated in Fig. 2. The measurement of water content in the amorphous DMCD demonstrated that the amount of water vapor adsorbed increased with increasing RH up to 61% RH and that at 79% RH the amount of water vapor adsorbed abruptly decreased, reflecting the crystallization of DMCD. In this study, crystalline naphthalene–DMCD complex was not obtained, while in the ground mixture and in the coprecipitate molecular interaction was considered to occur between naphthalene and DMCD.

References and Notes

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2) R. Jachowicz, *Int. J. Pharm.*, **35**, 1, 7 (1987).
3) C. Doherty and P. York, *Int. J. Pharm.*, **34**, 197 (1987).
4) W. R. Ravis and C.-Y. Chen, *J. Pharm. Sci.*, **70**, 1353 (1981).
5) K. Yamamoto, M. Nakano, T. Arita, Y. Takayama, and Y. Nakai, *J. Pharm. Sci.*, **65**, 1484 (1976).
6) K. Uekama, *Yakugaku Zasshi*, **101**, 857 (1981).
7) Y. Nakai, K. Yamamoto, K. Terada, and K. Akimoto, *Chem. Pharm. Bull.*, **32**, 685 (1984).
8) *a*) G. A. El-Gendy, K. Terada, K. Yamamoto, and Y. Nakai, *Int. J. Pharm.*, **31**, 25 (1986); *b*) F. Hirayama, M. Kurihara, and K. Uekama, *ibid.*, **35**, 193 (1987).
9) S. Hashimoto and J. K. Thomath, *J. Am. Chem. Soc.*, **107**, 4655 (1985).
10) K. Yamaoka, Y. Yamagishi, K. Takayama, N. Nambu, and T. Nagai, *Yakuzaigaku*, **41**, 231 (1981).
11) T. Higuchi and K. A. Conners, *Adv. Anal. Che. Instrum.*, **4**, 117 (1965); T. Higuchi and H. Kristiansen, *J. Pharm. Sci.*, **59**, 1601 (1970).
12) A. J. Repta, "Techniques of Solubilization of Drugs," ed. by S. H. Yalkowsky, Marcel Dekker, New York, 1981, pp. 139—141.
13) L. D. Hall and T. K. Lim, *J. Am. Chem. Soc.*, **108**, 2503 (1986).