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Properties of Crystal Water of α-, β-, and γ-Cyclodextrin

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The water vapor sorption isotherms have been established for α-, β-, and γ-cyclodextrin at 40 °C. The powder X-ray diffraction patterns of crystal forms of cyclodextrins stored at various levels of relative humidity (RH) were examined and the results are discussed in terms of the hydration numbers. α-Cyclodextrin hydrate was stable at RH as low as 11%. The water vapor desorption isotherm of β-cyclodextrin showed pronounced hysteresis, which extended to lower RH. The hydrate form of β-cyclodextrin was stable over a wide range of RH in the desorption process, like that of α-cyclodextrin. The crystal form of γ-cyclodextrin $7H_2O$ was obtained in addition to the dehydrate form and the $17H_2O$ hydrate form.

Keywords——cyclodextrin; crystal water; water vapor adsorption; dehydration; X-ray diffraction; crystal form

Cyclodextrins are known to form inclusion compounds with many kinds of drugs and are extensively employed to improve the solubility and stability of drugs.[2] Cyclodextrin may also be useful as a disintegrating agent for tablets.[3] As stable hydrate forms, the $6H_2O$, $12H_2O$, and $17H_2O$ hydrates are known for α-, β-, and γ-cyclodextrin, respectively.[4] Some water molecules in cyclodextrin crystals are present as co-ordinating water and some as structural water.[5] Evans suggested that the structural water plays only a subordinate part whereas the co-ordinating water acts primarily on the arrangement of the water molecules which determines the crystal structure.[5a] The difference between these two types, however, is still not clear except in the case of α-cyclodextrin. Crystal water of additives exerts an influence on the physicochemical properties and the stability of a drug in a formulation.[6]

In the present study, the water vapor sorption isotherms of cyclodextrins were examined in detail and the influence of hydration number on the crystal form of cyclodextrins was investigated.

Experimental

Materials——α-Cyclodextrin (Nakarai Chemicals, Ltd.), β-cyclodextrin (Ando Kasei Co., Ltd.), γ-cyclodextrin (Nakarai Chemicals, Ltd.) were recrystallized from water and used as hydrates. The dehydrates of cyclodextrins were prepared by drying at 110 °C for 3 h *in vacuo*.

Water Vapor Sorption Study——About 2 g of a cyclodextrin dehydrate was weighed into a weighing bottle and exposed to the desired relative humidity (RH) at 40 °C. The sample weight was measured at intervals of a few days. The water vapor sorption was regarded as having reached equilibrium when the weight changed by less than 2 mg as compared to the previous measurement. Saturated salt solutions which maintain 11.0, 22.8, 31.3, 48.3, 61.5, 79.0, and 93.6% RH were used.[7] Sorption was investigated from lower values of RH and then the desorption study was conducted.

Powder X-Ray Diffraction——Powder X-ray diffraction patterns at room temperature were measured as described previously.[8] Heating apparatus was used when necessary to obtain a desired temperature.

Thermogravimetry (TG)——A Shimadzu TG-20 thermogravimeter was used at a heating rate of 1 K/min. Sample weight was 10.0 mg. Dry nitrogen was passed at a rate of 10 ml/min.

Results and Discussion

α-Cyclodextrin

Figure 1 shows the water vapor sorption isotherm of α-cyclodextrin. The determination of water content by the Karl Fisher method showed that the dehydrate molecule contains less than one molecule of water. The α-cyclodextrin molecule adsorbed 4 molecules of water at RH 11% and then the hydration number increased with increasing RH. The water content of α-cyclodextrin became constant at about $6.6H_2O$ molecules above RH 79%. The desorption isotherm was similar to the adsorption isotherm. Figure 2 shows the powder X-ray diffraction patterns of α-cyclodextrin stored at various levels of RH. Figure 2(a) shows the X-ray diffraction pattern of the dehydrate form of α-cyclodextrin. In Fig. 2(b), the characteristic peaks of the dehydrate form ($2\theta = 13.0$, 13.7, and 14.7°) are diminished or decreased in intensity and new peaks due to the hydrate form were observed at $2\theta = 11.7$, 13.3, and 14.0°. The dehydrate form of cyclodextrin changed into the hydrate form during storage at RH 11% (Fig. 2(b)), but the crystallinity was lower than that of the recrystallized hydrate form. The crystallinity increased with increasing RH and the same diffraction pattern as for the recrystallized hydrate was observed above RH 79%. Thus, α-cyclodextrin exists in a stable hydrate form above RH 11%. Figure 3(a) shows the TG curve of α-cyclodextrin $6H_2O$. Klar *et al.* determined the crystal structure of α-cyclodextrin $6H_2O$ and indicated that two of the six water molecules are included in the cavity of α-cyclodextrin and the other four hydration water molecules are located outside of the α-cyclodextrin cavity.[4a)] Stepwise dehydration was observed in the TG curves, indicating that distinctly different energy levels of water were present in the α-cyclodextrin $6H_2O$ molecule. In order to investigate the transition process between hydrate and dehydrate forms, the powder X-ray diffraction of α-cyclodextrin was also measured during heating as shown in Fig. 4(A)—(C). The diffraction peaks due to the

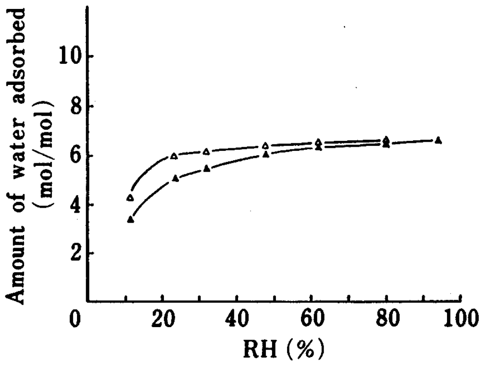

Fig. 1. Water Vapor Sorption Isotherm for α-Cyclodextrin at 40 °C

▲, adsorption; △, desorption.

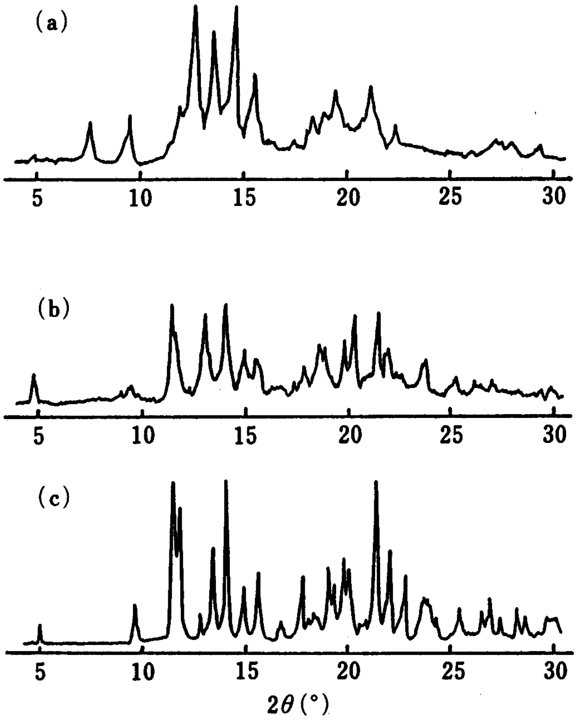

Fig. 2. X-Ray Diffraction Patterns of α-Cyclodextrin Stored at Various Levels of Relative Humidity at 40 °C

(a) dehydrate; (b) RH 11%; (c) RH 79% (recrystallized).

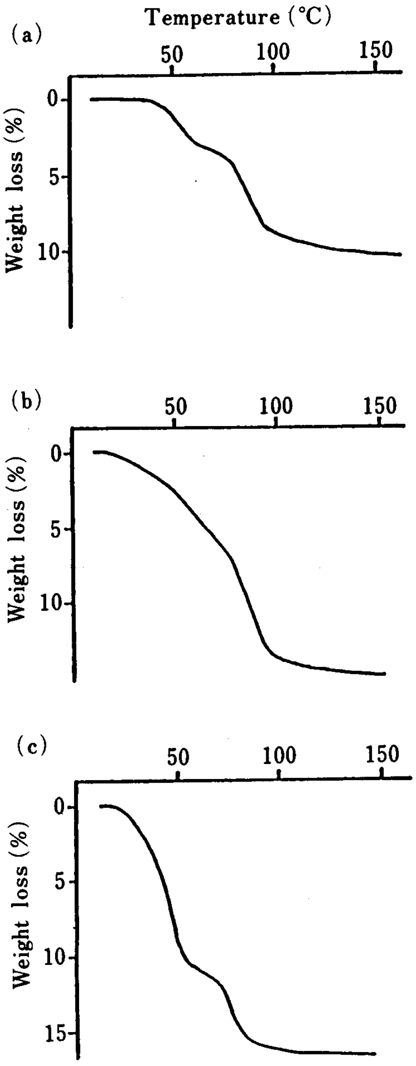

Fig. 3. TG Curves of Cyclodextrins Recrystallized from Water

(a) α-cyclodextrin; (b) β-cyclodextrin; (c) γ-cyclodextrin.

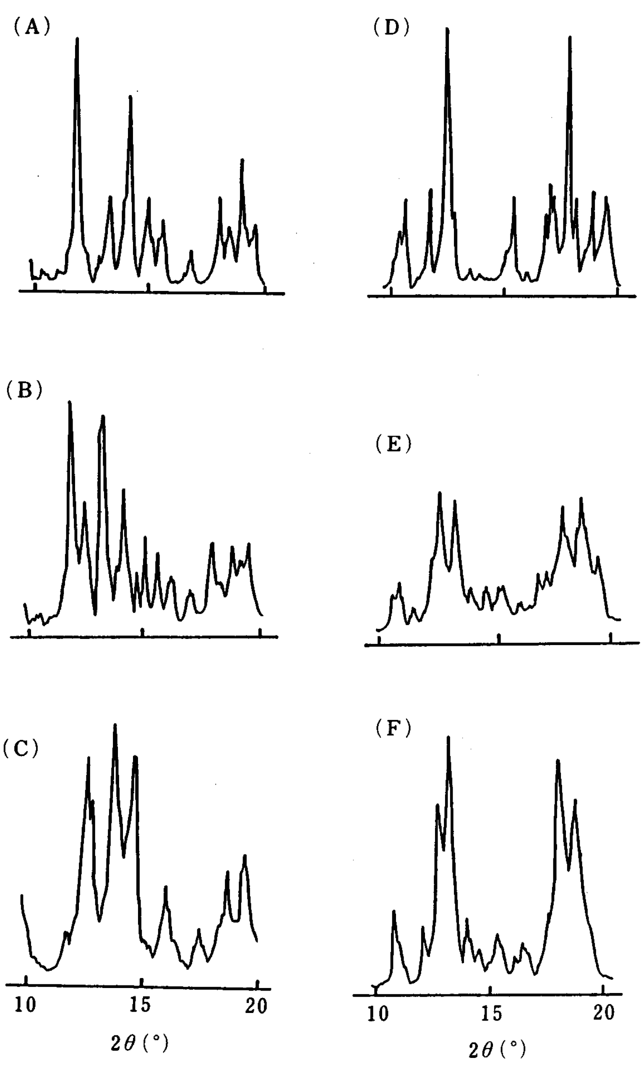

Fig. 4. X-Ray Diffraction Patterns of α- and β-Cyclodextrin on Heating

(A)—(C): α-cyclodextrin. (A) 60 °C; (B) 60 °C for 10 min; (C) 120 °C.

(D)—(F): β-cyclodextrin. (D) 60 °C; (E) 60 °C for 25 min; (F) 120 °C.

dehydrate form ($2\theta = 13.0$, 13.7, and 14.7°) appeared after 10 min at 60 °C and the peak intensities increased with storage time. The hydrate form was transformed into the dehydrate form immediately at 120 °C. Dehydration of α-cyclodextrin was thus a fast, reversible process.

β-Cyclodextrin

Figure 5 shows the water vapor sorption isotherm of β-cyclodextrin. The water content of β-cyclodextrin increased with increasing RH, passing through a plateau region at about RH 23—31% where the water content corresponded to 5—6 water molecules. Lindner and Saenger reported a $12H_2O$ hydrate and Fujiwara *et al*. reported an $11H_2O$ hydrate, but the two forms were not distinguishable in terms of sorption isotherm at higher RH.[4b)] However, the desorption isotherm was quite different from the adsorption isotherm and showed pronounced hysteresis which extended to lower RH. Figure 6 shows the powder X-ray diffraction patterns of β-cyclodextrin stored at various levels of RH. The dehydrate and hydrate forms of β-cyclodextrin showed different powder X-ray diffraction patterns (Fig. 6(a), (d)), and low crystallinity was observed at RH 31% (Fig. 6(b)). At RH 48.3%, β-cyclodextrin

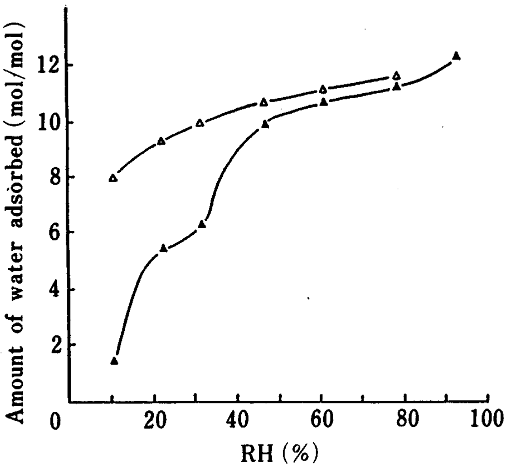

Fig. 5. Water Vapor Sorption Isotherm for β-Cyclodextrin at 40 °C

▲, adsorption; △, desorption.

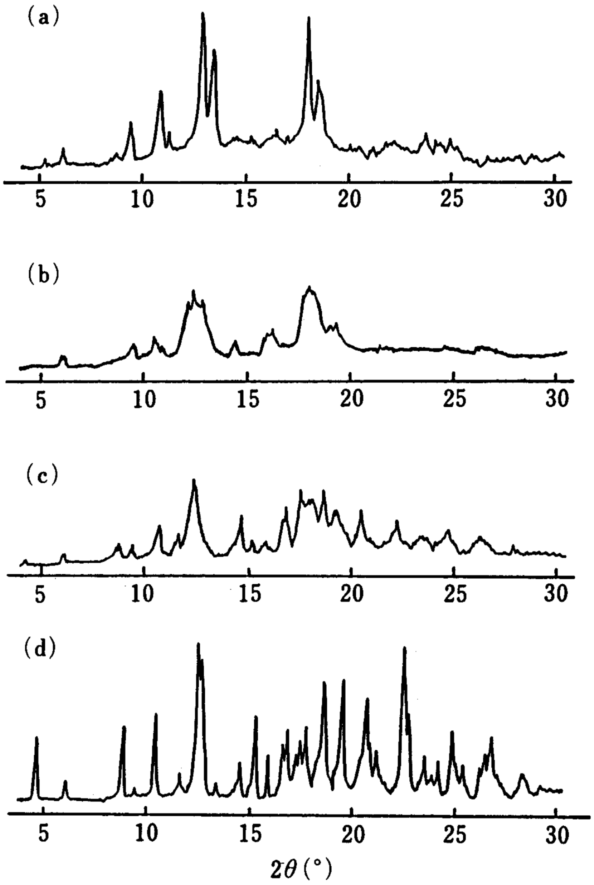

Fig. 6. X-Ray Diffraction Patterns of β-Cyclodextrin Stored at Various Levels of Relative Humidity at 40 °C

(a) dehydrate; (b) RH 31%; (c) RH 48%; (d) RH 79% (recrystallized).

dehydrate was transformed into hydrate form, though the crystallinity was lower than that of a recrystallized sample. The crystallinity increased with increasing RH and the same diffraction pattern for the recrystallized sample was obtained above RH 79%. The powder X-ray diffraction of β-cyclodextrin was also measured on heating as shown in Fig. 4(D)—(F). A low crystallinity was observed when the hydrate form was transformed into the dehydrate form. The hydrate form did not turn into the dehydrate form after storage at 40 °C and RH 11% for 3 months. This indicates that the hydrate form is stable over a wide range of RH, as in the case of α-cyclodextrin, and suggests different pathways for the adsorption and desorption processes. The TG curve of recrystallized β-cyclodextrin indicates continuous dehydration of the hydrate form as shown in Fig. 3(b). This result corresponds to the continuous curve in the desorption isotherm.

γ-Cyclodextrin

Figure 7 shows the water vapor sorption isotherm of γ-cyclodextrin. The isotherm shows a hysteresis effect, and had a plateau region at about RH 20—30%. The number of crystal water molecules was almost 17 at RH 93.6%. Figure 8 shows the powder X-ray diffraction patterns of γ-cyclodextrin after storage at various levels of RH. Patterns (a) and (c) in Fig. 8 are characteristic diffractograms of the dehydrate form and the hydrate form of γ-cyclodextrin, respectively. It is clear that the diffraction pattern of (b) is not a superimposition of the patterns of (a) and (c), but corresponds to a different crystal structure. Thus, it could be

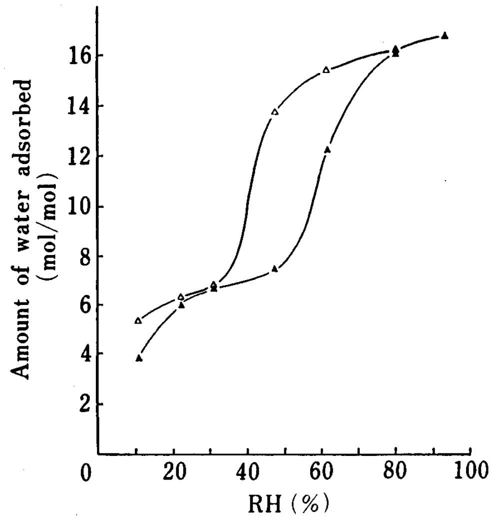

Fig. 7. Water Vapor Sorption Isotherm for γ-Cyclodextrin at 40 °C .

▲, adsorption; △, desorption.

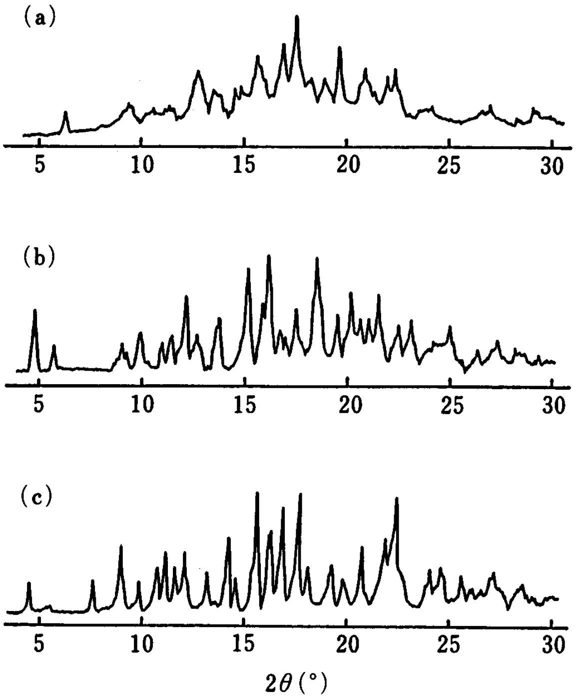

Fig. 8. X-Ray Diffraction Patterns of γ-Cyclodextrin Stored at Various Levels of Relative Humidity at 40 °C

(a), dehydrate; (b) RH 31%; (c) RH 79% (recrystallized).

appropriate to consider that γ-cyclodextrin has an intermediate form, which contains 7 water molecules, between (a) and (c). The hydrate form and the dehydrate form both pass through the intermediate form during dehydration and hydration, respectively. The TG curve in Fig. 3(c) shows the two-step dehydration of γ-cyclodextrin hydrate and supports the involvement of intermediate γ-cyclodextrin $7H_2O$ form.

References and Notes

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