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Inclusion Complexes of Cyclodextrins with Cinnamic Acid Derivatives: Dissolution and Thermal Behavior[1]

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Typical B_S type phase solubility diagrams were obtained for α- and β-cyclodextrins (α-CyD and β-CyD) with methyl cinnamate, ethyl cinnamate, and cinnamaldehyde in water at 25°. Solid complexes for α- and β-CyDs with three guest molecules were obtained and their molar ratios were found to be 2:1 (α-CyD/guest molecule) and 1:1 (β-CyD/guest molecule), respectively. In sharp contrast, apparent stability constant (K_c') and dissolution rate (k_c') of α-CyD complexes were larger than those of β-CyD complexes. The thermal gravimetric analysis thermogram showed that the volatility of the guest molecule was lowered by the formation of CyD inclusion complex.

Keywords——inclusion complex; α- and β-cyclodextrins; methyl cinnamate; ethyl cinnamate; cinnamaldehyde; phase solubility diagram; stability constant; thermal gravimetry; dissolution rate

Inclusion complexes of cyclodextrins (CyDs) with various drugs have been extensively applied in pharmaceutical formulations to enhance the solubility,[3] chemical stability,[4] and absorption characteristics[5] of the drugs. Studies on physical properties of the cyclodextrin complexes in solid state, however, are limited.[6] In our previous papers,[7] cinnamic acids and their related compounds have been shown to be adequate guest molecules toward cyclodextrin cavity to gain insight into inclusion mechanism in aqueous solution. In these continuing investigations, some solid complexes of α- and β-cyclodextrins (α-CyD, β-CyD) with methyl cinnamate (MC), ethyl cinnamate (EC), and cinnamaldehyde (CA) were prepared and their dissolution and thermal behaviors were examined.

Experimental

Materials——α- and β-CyDs were favored from Teijin Ltd. MC, EC, and CA were obtained commercially, analytical reagent grade, and used without further purification. Deionized, double-distilled water was used throughout the study. All other materials and solvents were analytical reagent grade.

Solubility Studies——These were carried out according to Higuchi and Lach.[8] Excess amounts of guest molecule (MC, EC, or CA) were added to aqueous α- or β-CyD solution and were shaken at 25±0.5°.

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[1] A part of this study was presented at the 2nd Symposium on Stabilization and Evaluation Methodology of Pharmaceutical Preparations, Okayama, October 1977.

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[8] T. Higuchi and J.L. Lach, *J. Am. Pharm. Assoc., Sci. Ed.*, 43, 349 (1954).

After equilibration was attained (about 2 weeks), an aliquot was centrifuged and pippetted through a cotton filter. A 0.5 ml aliquot of the sample solution was diluted with suitable amounts of 0.1 M phosphate buffer (pH 7.0) and analyzed spectrophotometrically. Apparent stability constant, K_c', was calculated from the initial straight line portion of phase solubility diagram according to following equation.[9]

$$K_c' = \frac{\text{slope}}{\text{intercept}\cdot(1-\text{slope})} \qquad (1)$$

Preparation of Solid Complexes——An adequate mixing ratio of CyD and guest molecule in water was referred to descending curvature of phase solubility diagram (an arrow in Fig. 1). For example, 0.4 g of MC and 3.4 g of β-CyD in 200 ml water were sealed in a flask and shaken at 25° for two weeks. The complex precipitated as a microcrystalline powder was filtered and dried under vacuum at 40° for 24 hr. This powder corresponded to 1 : 1 β-CyD–MC complex which has a molecular weight of 1296 g ± 5%. Other CyD complexes were prepared in the same manner.

Dissolution Studies——The sample powder was compressed into cylindrical tablet (diameter, 20 mm; thickness, 1.4 mm; and weight, 500 mg ± 2%) in a vacuum at high pressure (about 150 kg/cm^2). Release of the guest molecule was measured using a rotating disk apparatus in 150 ml of water at 58 rpm and 25° over 2 hr. Samples were assayed spectrophotometrically at ultraviolet (UV) absorption maximum of the guest molecule. Corrections were applied for cumulative dilution caused by replacement of samples by equal volumes of the original medium. The tablets maintained a constant shape throughout the measurements.

Thermal Gravimetric Analysis (TGA)——This was carried out by a Shimadzu DT-20B thermal analyzer. The sample weight was 2—8 mg, and a scanning speed of 10°/min was employed.

Results and Discussion

Solubility Study

All the solubility curves for α- and β-CyDs–three guest molecules studied showed a B_S type phase diagram[9] in water. Fig. 1 shows a typical example of β-CyD–MC system, where precipitation of solid complex was accompanied in the higher concentration range of β-CyD. Stoichiometry of the complexes in solid state was analyzed chemically, and found to be 2 : 1 for α-CyD system and 1 : 1 for β-CyD system, respectively (Table I). The results were in good accordance with that analyzed from the data in plateau region of the solubility diagrams. Apparent stability constants, K_C', were calculated from initial straight line portion of solubility diagram. In all cases, K_C' values for α-CyD complexes were larger than those for β-CyD complexes. These may be rationalized in the following way. α-CyD is capable to interact with not only phenyl moiety but also substituent group of cinnamic acid derivatives. This may substantially result in 2 : 1 complex formation with larger stability constant. On the other hand, cavity size of β-CyD may be too large to include the substituent group of cinnamic acid derivatives. This explanation was supported by ^{13}C-nuclear magnetic resonance (NMR) study,[10] and similar results have been obtained for the complexation of sulfonylureas with α- and β-CyDs in aqueous solution.[11] Interactions between CyDs and guest molecules

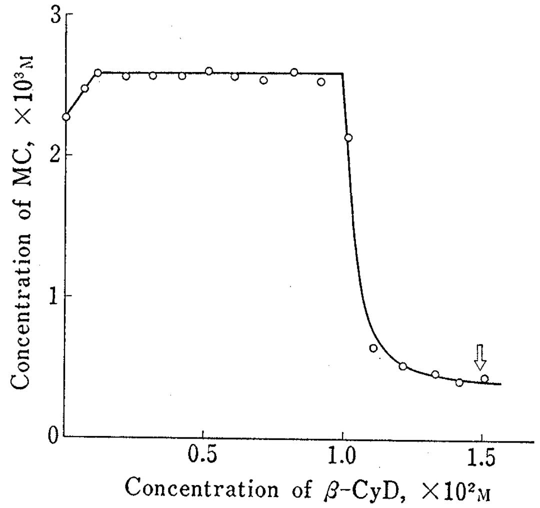

Fig. 1. Phase Solubility Diagram of β-CyD–MC System in Water at 25°

An arrow showing experimental condition of the preparation of solid complex (see text).

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in solid state was further ascertained by powder X-ray diffraction patterns12) and infrared (IR) spectra13) of the prepared complexes in the comparison with those of physical mixtures.

TGA Thermogram

Figure 2 shows TG curves of three cinnamic acid derivatives and their β-CyD complexes. The volatility of the complex was found to be significantly lower than that of guest molecule

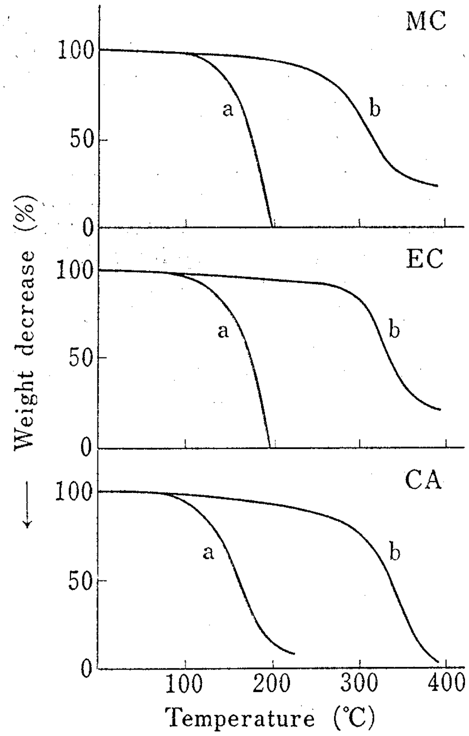

Fig. 2. TGA Thermograms of Cinnamic Acid Derivatives and Their β-CyD Complexes

a: cinnamic acid derivative alone,
b: β-CyD complex.

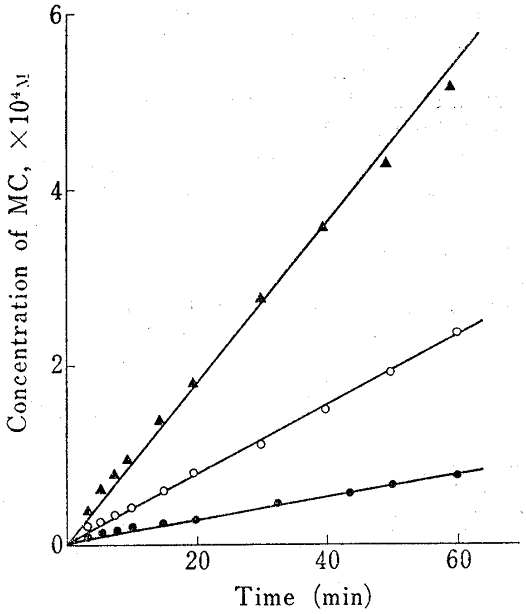

Fig. 3. Dissolution Curves of MC and Its α-CyD and β-CyD Complexes in Water at 25° by Rotating Disk Method

○: MC, ▲: α-CyD complex, ●: β-CyD complex.

TABLE I. Results for Solubility and Dissolution Rate Studies in Water at 25°

Complex	Molar ratio a)	K_c' b) (M^{-1})	k_c' c) ($\times 10^6$ M/min)	S_c d) ($\times 10^3$ M)	S_o e) ($\times 10^3$ M)
α-CyD–MC	2:1	1360	9.03 (3.59) f)	4.43	2.16
α-CyD–EC	2:1	1100	3.12	2.05	1.10
α-CyD–CA	2:1	70	8.10	8.82	10.02
β-CyD–MC	1:1	200	1.30	0.415	
β-CyD–EC	1:1	430	0.93	0.288	
β-CyD–CA	1:1	60	3.30	6.88	

a) CyD: guest molecule.
b) Apparent stability constant (see text).
c) Apparent dissolution rate, calculated from initial dissolution curve.
d) Saturated solubility of the complex, estimated from descending curvature of B_s type phase solubility diagram.
e) Solubility of the corresponding guest molecule.
f) Apparent dissolution rate (k_o') of MC. The k_o' values for EC and CA could not be determined because of the viscous oil.

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12) Measured by Geiger Flex 2012 X-ray Diffraction Analyzer (Rigaku Denki Co., Ltd.).
13) Measured by KBr disk method.

itself. Similar tendency in TGA thermograms was obtained for α-CyD system. This type of complex was nonglassy and ease of handling. Thus, crystallinity and thermal stability of the CyD complex would make it easier to formulate with prolonged storage time than viscous oil, particularly for EC and CA.

Dissolution Behaviors of Complexes

Figure 3 shows dissolution behaviors of MC and its α- and β-CyD complexes in water, as an example, where sharp contrast in dissolution rate changes were noted. The change in dissolution rate appears to depend upon the solubility of the complexed guest molecule, since solubilities of α-CyD–MC, MC, and β-CyD–MC decreased in that order (see Table I). In the cases of EC and CA, the dissolution rates of α-CyD complexes were also larger than those of β-CyD complexes. Dissolution rate of the complex is known to be dependent upon various factors such as intrinsic solubility, diffusion coefficient, ionization, and dissociation of the complex.[14] As is seen in Fig. 4A, a linear correlation between dissolution rate of the complex (k_C') and solubility of the complex (S_C) was obtained for CyD-cinnamate (MC and EC) system. It also appeared that k_C' was rather correlated with K_C' of CyD–cinnamate complexes (Fig. 4B). In Fig. 4, data for CA complexes were excluded because the physico-chemical property of CA is apparently different from that of cinnamate as is expected from their smaller K_C' values (see Table I). Assuming that diffusion coefficient of the complex is almost same as that of guest molecule, above facts indicate that not only solubility of the complex but also dissociation of the complex in dissolution medium may affect the k_C' value in CyD–cinnamate system. However, wettability of the complexing agent will not be excluded because aqueous solubility of α-CyD is about eight times larger than that of β-CyD. Further investigations should be made to elucidate the dissolution mechanism of CyD complexes, particularly for CA–CyD system.

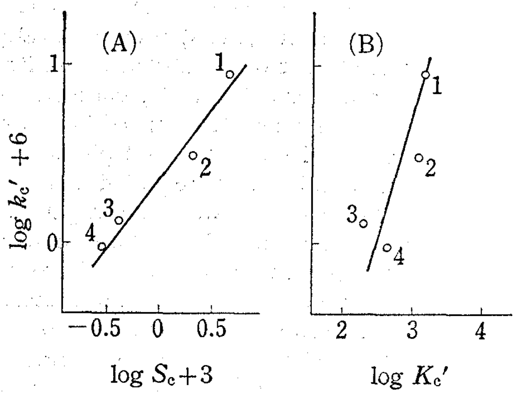

Fig. 4. Correlations of log k_c' with log S_c (A) and log K_c' (B)

1: α-CyD–MC, 2: α-CyD–EC, 3: β-CyD–MC, 4: β-CyD–EC.

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