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Effect of β-Cyclodextrin on the Degradation Rate of Cinnarizine in Aqueous Solution[1)]

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The degradation kinetics of cinnarizine in aqueous solution containing β-cyclodextrin at pH 1.20 and four different temperatures were investigated. The degradation of cinnarizine was found to be a pseudo first-order reaction. The pseudo first-order rate constant with β-cyclodextrin decreased with increase in the concentration of β-cyclodextrin at pH 1.20. From Arrhenius plots, the values of activation energy of the degradation in aqueous solution at pH 1.20 containing 3.26×10^{-3} and 15.32×10^{-3} M β-cyclodextrin were calculated to be 37.0 kcal/mol and 40.1 kcal/mol, respectively.

Keywords——cinnarizine; β-cyclodextrin; stability; Arrhenius plot; activation energy

In a previous paper,[2)] it was reported that the dissolution rate of cinnarizine (CN) could be enhanced by preparing CN–β-cyclodextrin (β-CD) inclusion complex, which was prepared by three different methods, *i.e.*, coprecipitation, neutralization and spray-drying. In the case of the neutralization and spray-drying methods, which were new and efficient methods, it was necessary to dissolve CN in an acidic solution in which degradation might occur. Therefore, the kinetics of degradation of CN in acidic solution, the effect of pH on the degradation rate and the activation energy were investigated.[3)]

Suppressing and accelerating effects of cyclodextrins (CD) on many chemical reactions in aqueous solution have been reported. For example, the rate of hydrolysis of prostacyclin and its methyl ester in aqueous solution were significantly retarded by α-, β- and γ-CD,[4)] and the degradation rate of nitroglycerin in aqueous solution was increased by adding β-CD.[5)]

Following the previous study,[3)] the present study was carried out in order to investigate the effect of β-CD on the degradation rate of CN in acidic solution under heating. It was confirmed that there is no significant degradation of CN in the process of neutralization required for the preparation of CN–β-CD inclusion complex by the spray-drying method.

Experimental

Materials——Cinnarizine (CN) and β-cyclodextrin (β-CD) were obtained from Eisai Co., Ltd., and Nippon Shokuhin Kako Co., Ltd., respectively. Other chemicals were of reagent grade. Deionized water was used in all experiments.

Kinetic Measurement of Degradation of CN——CN was dissolved in the first fluid of JP X (pH 1.20) with β-CD to make a 1.63×10^{-3} M solution. The concentrations of β-CD used were 1.63×10^{-3}, 3.26×10^{-3}, 8.15×10^{-3} and 15.32×10^{-3} M, which corresponded to molar ratios of CN to β-CD of 1:1, 1:2, 1:5 and 1:9.4, respectively. A 5 ml aliquot of the solution containing 1.63×10^{-3} M CN with β-CD was placed in a 10 ml glass ampule, which was sealed and kept in a controlled temperature oven (Yamato Scientific Co., Ltd., Tokyo, Japan) at 60, 70, 80 and 90 °C with ±0.1 °C precision. The ampules were withdrawn at appropriate intervals and cooled to room temperature. Then 10 ml of 10% hydrochloric acid and 15 ml of chloroform were added to 3 ml of the solution taken from the ampule.

The mixture was shaken and the absorbance at 295 nm of the organic layer was measured. The amount of CN remaining in the solution was calculated from a calibration curve prepared in advance.

Results and Discussion

Determination of CN with β-CD in Aqueous Solution

The method for determination of CN in degraded solution was described in the previous paper.[4] In the case of degraded solution containing β-CD, it was necessary to confirm that the presence of β-CD did not interfere with the determination of CN. If there is any interference by β-CD in the process of determination of CN, it may occur during the extraction of CN with chloroform from acidic solution. The following possibilities may be considered: (1) an inclusion complex of chloroform with β-CD is formed and deposited, (2) the partition of CN from aqueous layer to chloroform layer is dependent on the amount of β-CD in the aqueous layer, (3) a degradation product of CN which has an absorption peak at 295 nm may be extracted together with CN by chloroform.

The following results were obtained: (1) no inclusion complex of chloroform with β-CD or other precipitate was observed in 15.32×10^{-3} M β-CD or below, (2) the recovery of CN from the aqueous layer in the presence of β-CD was 98.5% (mean of two experiments), and (3) *N*-cinnamylpiperazine (showing absorption at 295 nm among the degradation products of CN[6]) was not extracted by the method used in this report. These results indicate that the determination of CN in degraded solution containing β-CD can be carried out by the method described in Experimental.

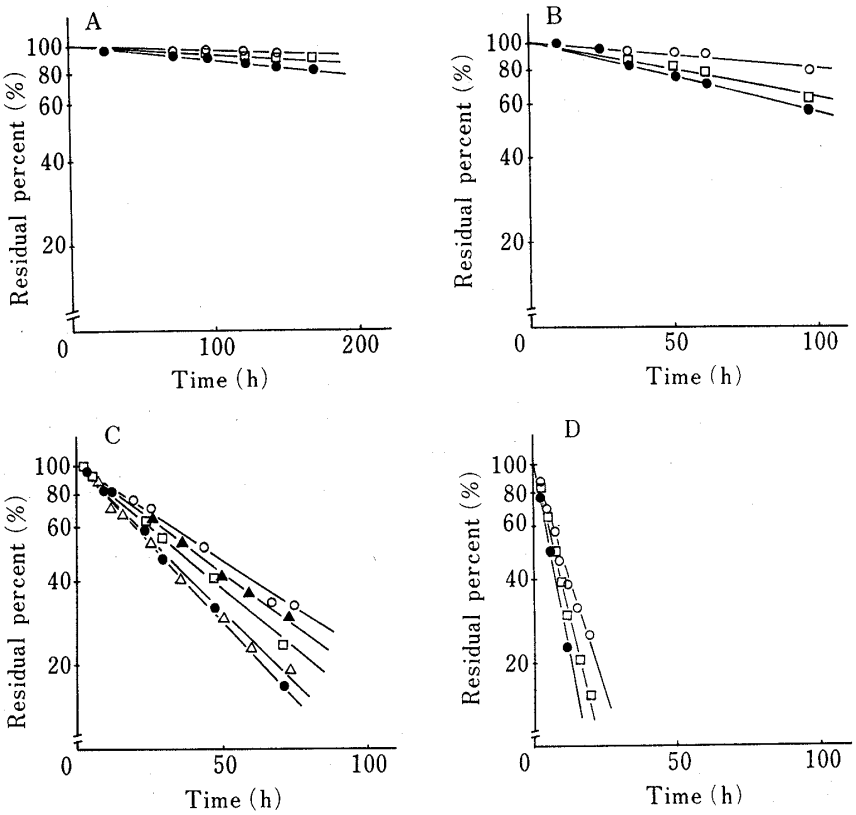

Fig. 1. First-Order Plots for the Degradation of CN in the Presence of β-CD at Four Different Temperatures in Aqueous Solution (pH 1.20)

A, 60 °C; B, 70 °C; C, 80 °C; D, 90 °C.
●, CN alone (1.63×10^{-3} M)[a]; △, β-CD 1.63×10^{-3} M; □, β-CD 3.26×10^{-3} M; ▲, β-CD 8.15×10^{-3} M; ○, β-CD 15.32×10^{-3} M.
a) data from the previous paper.[3]

TABLE I. Rate Constants of the Apparent First-Order Degradation of CN

°C	k (min^{-1})				
	CN[b]	Molar ratio (CN: β-CD)[a]			
		1:1	1:2	1:5	1:9.4
60	1.85×10^{-5}	—	1.07×10^{-5}	—	1.82×10^{-6}
70	1.05×10^{-4}	—	8.56×10^{-5}	—	4.99×10^{-5}
80	4.07×10^{-4}	3.88×10^{-4}	3.46×10^{-4}	2.80×10^{-4}	2.60×10^{-4}
90	1.94×10^{-3}	—	1.68×10^{-3}	—	1.26×10^{-3}

a) Molar ratio of initial concentrations of CN and β-CD in the solution. *b*) Data from the previous paper.[3]

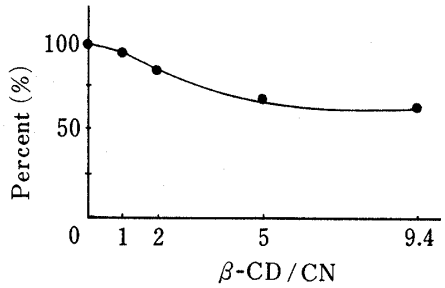

Fig. 2. Effect of β-CD on the Rate Constants for Apparent First-Order Degradation of CN at 80 °C

The *X* axis shows the molar ratio of initial concentrations of CN and β-CD in the solution.
The *Y* axis shows percent decrease of the rate constant compared with that of CN alone.

Study of the Kinetics

The degradation of CN in acidic solution was reported to be a pseudo first-order reaction,[3] in agreement with the results for diphenhydramine[7] and homochlorcyclizine.[8] Therefore, the degradation reaction of CN in acidic solution with β-CD is also assumed to be a first-order type process. Figure 1 shows the relationship between residual percent (logarithmic scale) and time in the degradation of CN at four different temperatures, 60, 70, 80 and 90 °C, in pH 1.20 buffer solution containing various concentrations of β-CD. Each plot in Fig. 1 gives a good straight line. These results indicate that the degradation reaction of CN in the presence of β-CD is apparently a first-order reaction, like the degradation reaction of CN alone. The apparent first-oder rate constant, k, was calculated from the slope of each straight line shown in Fig. 1. The results are shown in Table I.

Effect of β-CD Concentration

When β-CD was present in the reaction system, the apparent first-order rate constant, k, was smaller than that of CN alone at four different temperatures as shown in Table I. The results indicate that the addition of β-CD to the reaction system stabilized, and the degree of stabilizing effect increased with increasing concentration of β-CD in the system.

Figure 2 shows the relationship between the decrease of the degradation rate of CN and the concentration of β-CD at 80 °C. At above 3.26×10^{-3} M β-CD (CN : β-CD = 1 : 2), the reaction rates decreased hyperbolically with increasing β-CD concentration, showing characteristic saturation kinetics.[9,10] Such kinetics are observed when the drug forms a complex with a ligand added in large excess, so this pattern supports the occurrence of inclusion complexation of CN and β-CD. The decrease of the rate constant with 3.26×10^{-3} M β-CD (CN : β-CD = 1 : 2) was larger than that with 1.63×10^{-3} M (CN : β-CD = 1 : 1). This result seemed to be in agreement with the reported stoichiometry of CN–β-CD complex, which was concluded to be 1 : 2 (CN : β-CD) from the data in the plateau region of the solubility diagram,[2] and the stabilizing effect of β-CD thus seems to be the result of formation of an

inclusion complex with a molar ratio of 1 : 2 in the solution. In the case of 1.63×10^{-3} M β-CD (CN : β-CD = 1 : 1), the inclusion complex with a molar ratio 1 : 2 was formed in the solution, but not all the CN molecules could be accommodated, so that the degree of stabilizing effect seemed to be low.

Effect of Temperature

Figure 3 shows Arrhenius plots of the degradation of CN in the system containing β-CD. At two different concentrations of β-CD, the plots at 70, 80 and 90 °C gave good straight lines. The activation energy of the degradation was calculated from the slope of each plot. The results are shown in Table II. The activation energies were 37.0 and 40.1 kcal/mol in 3.26×10^{-3} (CN : β-CD = 1 : 2) and 15.32×10^{-3} M β-CD (CN : β-CD = 1 : 9.4), respectively. The activation energy in the system containing β-CD increased with addition of β-CD but the degree of the increase was small. This result indicates that the stabilizing effect of β-CD on CN was not a result of alteration of the degradation reaction itself. In Fig. 3, the data at 60 °C were not on the straight lines. This result is considered to reflect the β-CD concentration available for the stabilization of CN. The degradation rate of β-CD in acidic solution is about one-half of that of CN at 80 °C.[11] At a lower temperature, 60 °C, the degradation rate of β-CD might be even slower than that of CN. Therefore, the concentration of β-CD available for the stabilization of CN might be apparently higher than at the other three temperatures. However, further investigation seems desirable.

Stabilization of CN in Acidic Solution

The results mentioned above indicate that the addition of β-CD to the reaction system stabilized CN in the acidic solution. It was reported that the stabilization of drugs by CDs occurs by the inclusion of the reacting site of the drug molecule into the cavity of the CD molecule. However, in the case of CN, the reacting site of CN was apparently not included in the cavity of CD on the basis of molecular structure models for CN and CD. The stabilization of CN by β-CD is considered to be an indirect effect caused by the partial inclusion of CN into the CD molecule.

The apparent rate constant, k, of the degradation of CN varied with F of CN^{2+}, where F is the mole fraction, as previously reported.[3] On the other hand, it was reported that the addition of β-CD decreased the degree of dissociation of drugs.[12] In view of the above two reports, the addition of β-CD to the reaction system might decrease the degree of dissociation of CN^{+} to CN^{2+} and thus decrease the F of CN^{2+} with increasing concentration of β-CD at

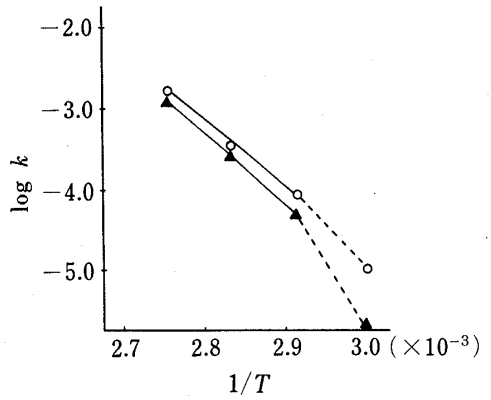

Fig. 3. Arrhenius Plots Based on the Rate Constants Measured at pH 1.20

○, CN: β-CD = 1 : 2; ▲, CN: β-CD = 1 : 9.4. (molar ratio of the initial concentrations of CN and β-CD in the solution).

TABLE II. Activation Energy of Degradation of CN

Molar ratio[a]	E_a (kcal/mol)
CN alone[b]	36.8
CN: β-CD = 1 : 2	37.0
CN: β-CD = 1 : 9.4	40.1

a) Molar ratio of initial concentrations CN and β-CD in the solution. *b*) Data from the previous paper.[3]

the same pH and temperature. Thus, the degradation rate of CN might decrease with increasing concentration of β-CD in the reaction system. However, it is necessary to investigate the effect of β-CD on the pK_{a2} of CN.

In conclusion, these results indicate that there is no great problem in dissolving CN in acidic solution in the presence of β-CD for the preparation of CN–β-CD complex by use of the neutralization method and the spray-drying method.[2b)]

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References and Notes

1) A part of this work was presented at the 104th Annual Meeting of the Pharmaceutical Society of Japan, Sendai, May 1984.
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