

## Release Characteristics of Iodine Encapsulated in Cyclodextrins

TZE-LOON NEOH, YASUHIRO NODA, HIDEFUMI YOSHII and TAKESHI FURUTA  
*Department of Biotechnology, Tottori University, 4-101 Koyamacho-minami, 680-8552, Tottori, Japan*

**Key words:** iodine, modified cyclodextrin, natural cyclodextrin, release, stability constant

### Abstract

The effect of cyclodextrins (CDs) on water solubility of iodine was investigated. Modified CDs greatly enhanced the solubility of iodine. On the contrary, enhancement by natural CDs was rather moderate whereby the solubility was only doubled at the highest  $\beta$ -CD concentration examined. Desorption experiment of iodine from solution was carried out with addition of various CDs to study the effect of CDs on iodine retention.  $\alpha$ -CD was the most efficient in retarding iodine desorption. Later, various concentrations of  $\alpha$ -CD were used in the desorption experiment to observe its volatile suppression effect and determine the stability constant of iodine/ $\alpha$ -CD complexation. At  $\alpha$ -CD concentration of 10.3 mM, no loss of iodine from the solution was detected. A model was developed for desorption of iodine from the solution based on mass transfer theory. The stability constant  $K$  given by this model was  $3.28 \times 10^4 \text{ M}^{-1}$  which was in the same order as the value estimated in this study by solubility method and as well those reported by other authors. In release experiments of solid state inclusion complexes, stability of inclusion complex powders decreased in the order of  $\alpha$ -CD >  $\beta$ -CD > randomly methylated  $\beta$ -CD (RM- $\beta$ -CD).

### Introduction

The white root rot caused by the fungus *Rosellinia necatrix* Prillieux is destructive to many fruit tree species including almond, peach, plum, apple, pear, olive, cherry and avocado. Usually, symptoms of the disease consist of collar and root rot which result in different degrees of canopy decline, followed by leaf drop, wilting and death of the tree [1]. In Japan, this fungal disease, which spreads rapidly and is very difficult to prevent, has done great damage to commercially grown grapevines, apple and pear trees, and other crops [2]. The only measure to prevent infection of this parasitic disease is through repetitive application of agrichemicals. The problem of high chemical residue and laborious effort has therefore emerged. The chemical residual problem is not merely the consumer problem but also an environmental problem.

Iodine is a bluish-black, lustrous solid that sublimates at ambient temperatures into a blue-violet gas with an irritating odor. In terms of application, iodine has been utilized in a wide range of products namely photosensitizing agent, catalyst, stabilizer, polarizing film of liquid crystal display panel, etc. Owing to high reactivity, iodine compounds have also been used as reaction intermediates. Iodine is an element with

antimicrobial activity that has low water solubility which has been used as bactericidal agent since long ago. In recent years, the worsening infection problem by the methicillin-resistant *Staphylococcus aureus* (MRSA) has again shed light on iodine as an important bactericidal drug [3]. At present, there is a wide variety of iodine containing products in the market such as radiocontrast agents, bactericidal agents, pharmaceutical compounds, catalytic organic compounds, herbicides, etc.

Iodine/ $\beta$ -CD complex was patented of its usages in products like bactericide aerosols, deodorants for human body [4], preservative in fish paste [5] and frozen marine products [6].  $\beta$ -CD solution can also be used to separate bromine and iodine from gaseous chlorine in gas mixture produced from electrolysis of NaCl [7]. However, all of these patented usages are based only on complexation with  $\beta$ -CD.

This research was done based on the objective to produce inclusion complexes between iodine and CDs aiming for fighting the white root rot problem. In this study, two estimation methods of the stability constant of iodine/ $\alpha$ -CD complex in solution were compared: one based on solubility and the other on mass transfer theory, in order to study the applicability of the latter model. The release characteristics of various iodine/CD complexes were also studied at high storage humidity (75% RH).

\* Author for Correspondence. E-mail: yoshii@bio.tottori-u.ac.jp

## Experimental

### Materials

$\alpha$ -,  $\beta$ - and  $\gamma$ -CD were obtained from Ensuiko Sugar Refining Co., Ltd. (Yokohama, Japan). Standard grade randomly methylated  $\beta$ -CD (RM- $\beta$ -CD) with degree of substitution (DS) of 1.6–1.9 per anhydrous glucose unit and 2-hydroxypropyl- $\beta$ -CD (HP- $\beta$ -CD) with DS of 0.6–0.9 per anhydrous glucose unit from Wacker-Chemie GmbH (Munich, Germany) were purchased from Cyclochem Co., Ltd. (Kobe, Japan). All CDs were subjected to vacuum drying at 90 °C for 24 h prior to use. The MCDI-6 solution (methyl- $\beta$ -cyclodextrin iodine complex containing 6% iodine) was a gift from Nippon Chemicals Co., Ltd. (Tokyo, Japan). Iodine was obtained from Nacalai Tesque, Inc. (Kyoto, Japan). Sodium thiosulfate solution (0.1N) and sodium chloride were purchased from Wako Pure Chemical Industries, Ltd. (Osaka, Japan). Distilled water was used throughout the entire study. Unless otherwise noted, all the chemicals used were of analytical reagent grade.

### Solubility of iodine in various CD solutions

Powders of CDs ( $\alpha$ -,  $\beta$ -,  $\gamma$ -, RM- $\beta$ - and HP- $\beta$ -CD) were weighed and added with distilled water to obtain concentration of  $1 \times 10^{-2}$  M for  $\alpha$ -,  $\beta$ - and  $\gamma$ -CD; and  $5.0 \times 10^{-1}$  M for RM- $\beta$ - and HP- $\beta$ -CD. Thereafter, dilution was performed to obtain  $\alpha$ -,  $\beta$ - and  $\gamma$ -CD with concentrations within the range of 0.1–7.5 mM, whereas, RM- $\beta$ - and HP- $\beta$ -CD solutions were diluted to concentrations within a higher range of 0.01–0.1 M.

Solubility studies were performed as described by Higuchi and Connors [8]. Ten milliliters each of the prepared CD solution and distilled water were transferred into vials (24 mm in diameter  $\times$  50 mm in height) by using micropipette. Subsequently, 150 mg of iodine was added. These vials were later placed in the bioshaker (BR-15LF, Taitec Corp., Saitama, Japan) with constant temperature of 25 °C and shaken at 150 rpm for 10 days. This length of time was considered sufficient to reach equilibrium. Within this period of time, these vials were steeped once a day in the Bransonic Ultrasonic Cleaner (1510J-MT, Branson Ultrasonic Corp., Connecticut, U.S.A.) for promoting equilibrium. After 10 days, the saturated solutions of iodine were filtered using syringe filter through a 0.4  $\mu$ m glass fiber filter paper (Advantec GB-140, Toyo Roshi Kaisha, Ltd., Tokyo, Japan) and the filtrates were taken as the saturated solutions of iodine with different CD concentrations. Concentration of iodine dissolved in the saturated solutions was determined by the below iodometric titration. The phase solubility diagrams of iodine in CD solutions were prepared based on the iodometric titration data.

By using micropipette, 1.0 ml of saturated iodine solution was filled into a vial and then titrated with sodium thiosulfate solution (0.01N) using a 2-ml

micrometer syringe (S-1200, Gilmont Instruments Inc., Illinois, U.S.A.). Titration was continued until the solution turned colorless. Triplicate was done for every saturated solution. Iodine concentration is given by:

$$\text{Iodine concentration (M)} = \frac{N_{\text{ST}} \times V_{\text{ST}}}{2V_{\text{SS}}} \quad (1)$$

where  $N_{\text{ST}}$  denotes the normality of sodium thiosulfate solution (0.01N) and  $V_{\text{ST}}$  the volume of sodium thiosulfate added during titration (ml). As for denominator,  $V_{\text{SS}}$  denotes the volume of saturated iodine solution titrated (ml).

### Iodine desorption experiment

Iodine solution with concentration of 100 ppm was prepared by weighing 50 mg of iodine and 500 ml of distilled water into a 500-ml screw-capped laboratory bottle. The bottle was shaken in the bioshaker (BR-15LF, Taitec Corp., Saitama, Japan) equipped with an air bath that was set at 25 °C for thorough dissolution of iodine. About 200 ml of the iodine solution was measured into a 500-ml tall form beaker. It was then placed inside a 25 °C water bath to hold the temperature throughout the experiment.

For examination of the effect of CDs on desorption of solubilized iodine, CDs were added, in the amount with which 200 ppm of CD concentration was achieved, into the 200 ml iodine solution and dissolved completely. During the desorption experiment, the air was bubbled at a controlled flow rate of 0.5 l min<sup>-1</sup> into the solutions. At predetermined intervals, samplings were made for measurement of iodine retention by spectrophotometer. Iodine concentration and CD concentration of sample solutions analyzed are summarized in Table 1. Changes in iodine concentration of solutions throughout the desorption experiment were monitored by using the spectrophotometer.

### Spectroscopy

Spectroscopy analysis of solutions of iodine and/or CD was conducted using the UV-vis spectrophotometer (V-560ST, Jasco Corp., Tokyo, Japan) operating on the Spectra Manager software. During desorption experiment, solution of about 1.3 ml was sampled into the

Table 1. Concentration of iodine and CD in the solutions analyzed by spectrophotometer

Sample	Iodine concentration (mM)/(ppm)	Type of CD	CD concentration (mM)/(ppm)
1	0.38/100	–	0
2	0.38/100	$\alpha$ -CD	0.21/200
3	0.38/100	$\beta$ -CD	0.18/200
4	0.38/100	RM- $\beta$ -CD	0.15/200
5	0.38/100	HP- $\beta$ -CD	0.14/200
6	0.38/100	$\gamma$ -CD	0.15/200

sample cuvette and analyzed using distilled water as reference. All spectra were taken at room temperature. Since the absorption peak of free iodine was shown around 460 nm, changes in intensity of absorption with CD concentration at this wavelength were recorded. Conversion of spectral data to iodine concentration was carried out with a calibration curve prepared beforehand.

#### Determination of stability constants

##### Determination of apparent 1:1 stability constant by solubility method

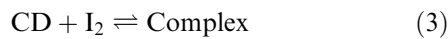
The apparent 1:1 stability constant  $K'$  ( $M^{-1}$ ) of iodine/ $\alpha$ -CD system was calculated using the below equation as reported by several authors [3, 9, 10],

$$K' = \frac{\text{slope}}{[\text{intercept} \times (1 - \text{slope})]} \quad (2)$$

where  $K'$  denotes the apparent stability constant. The slope and intercept values of the initial linear portion from the phase solubility diagram were used.

##### Determination of the stability constant $K$ based on mass transfer theory

In developing the model for estimation of the apparent stability constant  $K$ , a few assumptions were made. The encapsulation reaction between iodine and  $\alpha$ -CD was assumed to have occurred at the molar ratio of 1:1 and thus giving rise to the following equilibrium equation:



And hence, at equilibrium, the apparent stability constant  $K$  could be deduced as

$$K = \frac{[\text{Complex}]}{[\text{CD}][I_2]} \quad (4)$$

where [Complex] is the concentration of inclusion complex formed between the iodine and the CD, [CD] the concentration of dissolved, guest-free CD and  $[I_2]$  the concentration of free dissolved iodine. Also, the total concentration of iodine [Total  $I_2$ ] could be represented as below:

$$[\text{Total } I_2] = [I_2] + [\text{Complex}] \quad (5)$$

Substitution of (4) into (5) and rearrangement enable expression of  $[I_2]$  in terms of [Total  $I_2$ ] as shown below:

$$\begin{aligned} *20c[\text{Total } I_2] &= [I_2] + K[\text{CD}][I_2] \\ [I_2] &= \frac{[\text{Total } I_2]}{(1 + K[\text{CD}])} \end{aligned} \quad (6)$$

Secondly, we assumed that the volatilized iodine were those free dissolved iodine which were not included within the CD cavity. Therefore the mass balance of iodine at the gas-liquid surface during desorption is given by

$$-\frac{d[\text{Total } I_2]}{dt} = (k_L a)[I_2] \quad (7)$$

where  $(k_L a)$  is the volumetric mass transfer coefficient and  $a$  the specific gas-liquid surface area. This model also includes the assumption that the flavor transport across the gas-liquid interface can be described by the film theory of the interfacial mass transfer.

Substitution of (6) into (7) with subsequent integration over time gives a first-order release equation as shown by (9):

$$-\frac{d[\text{Total } I_2]}{dt} = \frac{(k_L a)}{(1 + K[\text{CD}])} [\text{Total } I_2] \quad (8)$$

$$-\ln \frac{[\text{Total } I_2, t=t]}{[\text{Total } I_2, t=0]} = -\ln R_s = \frac{(k_L a)}{(1 + K[\text{CD}])} t = (k_L a)_{\text{app}} t \quad (9)$$

$(k_L a)_{\text{app}}$  in Equation (9) represents the apparent volumetric mass transfer coefficient and  $R_s$  is the retention of [Total  $I_2$ ] at time  $t$  with respect to the initial value.  $(k_L a)_{\text{app}}$  can be rewritten as:

$$(k_L a)_{\text{app}} = \frac{(k_L a)}{(1 + K[\text{CD}])} \quad (10)$$

The reciprocal function of the  $(k_L a)_{\text{app}}$  can then be presented as:

$$\frac{1}{(k_L a)_{\text{app}}} = \frac{K}{(k_L a)} [\text{CD}] + \frac{1}{(k_L a)} \quad (11)$$

Therefore, the linear plot of the inverse number of  $(k_L a)_{\text{app}}$  versus CD concentration may have the intercept at  $[\text{CD}] = 0$  as the inverse number of  $(k_L a)$  and the slope as the division of  $K$  by  $(k_L a)$ . This estimation model of apparent stability constant  $K$  was applied to the desorption of iodine from solutions.

#### Preparation of iodine/CD complexes

##### Iodine/ $\alpha$ -CD complex

First, 100 g of MCDI-6 solution was added into a beaker followed by 23 g of  $\alpha$ -CD. The mixture was stirred using magnetic stirrer for 1 h at ambient temperature. Vacuum filtration of solution was performed to recover the precipitate. Rinsing of beaker with distilled water was done to make sure of complete precipitate recovery. The precipitate was then washed again in distilled water and subjected to freeze drying for 24 h. The inclusion complex was kept in hermetic condition until subsequent analysis.

##### Iodine/ $\beta$ -CD complex

$\beta$ -CD solution with 5 wt% concentration at 50 °C was prepared by adding 52.6 g of  $\beta$ -CD into 1000 ml of distilled water inside a 1000-ml laboratory bottle with

screw-cap. The bottle was placed in a bioshaker (BR-15LF, Taitec Corp., Saitama, Japan) set at 60 °C for iodine dissolution. Overnight storage of the bottle in the cooled incubator (MIR-253, Sanyo Electric Biomedical Co., Ltd., Tokyo, Japan) of constant temperature of 50 °C was performed to stabilize the temperature of the solution. Subsequently, iodine of equal mole to  $\beta$ -CD (11.57 g) was added and the mixture was shaken in the bioshaker (BR-15LF, Taitec Corp., Saitama, Japan) at 50 °C to dissolve iodine. After complete dissolution, the solution was cooled slowly down to 4 °C to allow complex crystallization. Centrifugation of the cooled solution was done at 8000 rpm, 4 °C for 60 min. The supernatant was further vacuum filtered and washed with 100 ml of distilled water. The complex collected from filtration and the residue were freeze dried for 24 h and then kept in hermetic condition before analysis.

#### *Iodine/RM- $\beta$ -CD complex*

RM- $\beta$ -CD (10.0 g) and iodine (2.32 g) were mixed and inserted into a round bottom flask. The weight of iodine added was calculated based on 1.2 mol times of RM- $\beta$ -CD. The round bottom flask was then attached to a rotary vacuum evaporator (EYELA N-NK, Tokyo Rikakikai Co., Ltd., Tokyo, Japan) and steeped in 50 °C water bath (EYELA NE-1, Tokyo Rikakikai Co., Ltd., Tokyo, Japan). Mixing of iodine and RM- $\beta$ -CD was done for 2 h. Inclusion complexation was expected to have occurred first through the sublimation of iodine at high temperature and followed by the inclusion of gaseous iodine into RM- $\beta$ -CD cavity. The inclusion complex was collected and kept in hermetic condition before analysis.

#### *Release characteristic of inclusion complexes at constant temperature and relative humidity*

Inclusion complex of ca. 0.1 g was inserted into each vial and spread evenly over the bottom of the vials. They were then put into storage in desiccators with constant relative humidity of 75% RH and constant storage temperature of 25 °C. The relative humidity was controlled within the range of  $\pm 5\%$  RH using saturated sodium chloride solution [11]. The desiccators were placed in the oven (Masuda SA460, Masuda Corp., Osaka, Japan) adjusted at 25 °C for at least 24 h before use. A thermo recorder (TR-72U, T&D Corp., Nagano, Japan) was placed inside the desiccator to monitor the relative humidity and temperature. At every prescribed time interval within the storage period, three vials were withdrawn from the desiccator for measurement of iodine retained. The iodine retention  $R(-)$  was defined as follows:

$$R = \frac{\text{Amount of } I_2 \text{ remained after prescribed time}}{\text{Initial amount of } I_2} \quad (12)$$

#### *Quantification of iodine in the complex powder*

Iodine content of inclusion complexes was also determined by iodometric titration. Three vials were withdrawn from the desiccator and measured to produce triplicate. First, 4 ml distilled water was added to completely dissolve the inclusion complex. The solution was titrated with sodium thiosulfate solution (0.01N) using a 2-ml micrometer syringe (S-1200, Gilmont Instruments Inc., Illinois, U.S.A.). Titration was continued until the solution turned colorless. Iodine concentration was calculated using Equation (1) and the inclusion ratio was determined thereafter.

## Results and discussion

#### *Water solubility enhancement of iodine by various CDs*

Figure 1 shows the phase solubility diagrams of iodine at 25 °C in various CD solutions. As for natural CDs, increase in concentrations of CDs had comparatively trivial effect on water solubility of iodine, whereas modified CDs have shown far greater effect.

$\beta$ -CD was, among the natural CDs, the most effective in solubilizing iodine. Nonetheless, the enhancement effect on iodine solubility was somewhat restricted when comparison was made with its modified counterparts – RM- $\beta$ - and HP- $\beta$ -CD – which showed far greater impact. It is plausible to infer from the significant difference in their solubility that the low water solubility of  $\beta$ -CD might have limited its efficacy in promoting iodine solubility unlike its modified counterparts. While investigating the solubility of iodine in  $\alpha$ -CD solution, a fairly unique phenomenon was noticed. A plateau was resulted in at  $\alpha$ -CD concentration above 2 mM which was inferred to as the effect of the limitation of iodine/ $\alpha$ -CD complex solubility as explained by Szejtli [9]. Owing to low complex solubility, the inclusion complex precipitated during equilibration in the mixing procedure giving a constant value of iodine solubility. Effect of  $\gamma$ -CD on solubility enhancement of iodine was the most insignificant among all CDs. This phenomenon might probably be due to the large size cavity of  $\gamma$ -CD.

According to Szejtli [9], the isotherm shown by RM- $\beta$ -CD could be classified as ‘A<sub>P</sub>’ type whereby the solubility curve deviated upwards showing the iodine solubility increased faster than the CD concentration. Whereas the isotherm of HP- $\beta$ -CD was of ‘A<sub>L</sub>’ type in which the correlation was strictly linear indicating complex of constant composition was formed.

#### *Influence of CD on desorption of iodine*

Figure 2 shows the effects of various CDs on desorption of iodine. It is observable that the desorption of iodine was apparently inhibited with the addition of  $\alpha$ -CD. The retention time-courses of iodine with the rest of the CDs showed no divergence from the control sample. In other

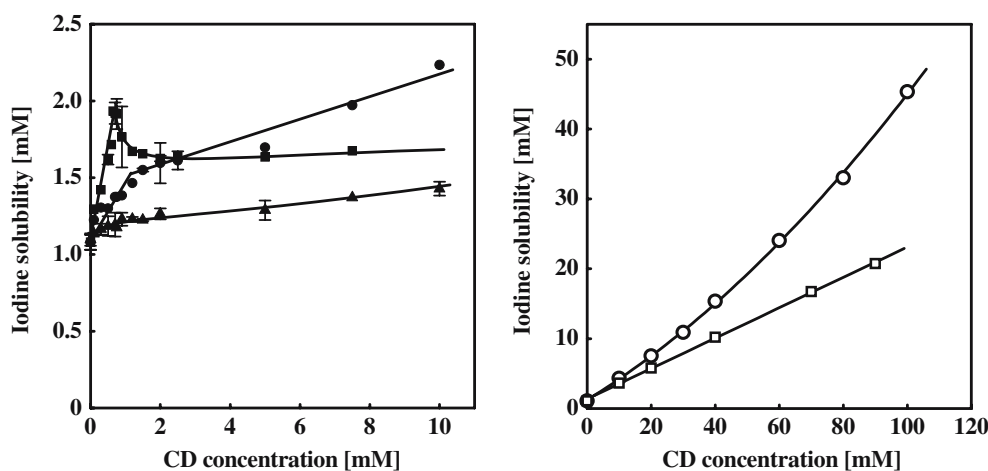


Figure 1. Phase solubility diagrams of iodine/CD systems in water at 25 °C.  $\alpha$ -CD (■);  $\beta$ -CD (●);  $\gamma$ -CD (▲); RM- $\beta$ -CD (○) and HP- $\beta$ -CD (□).

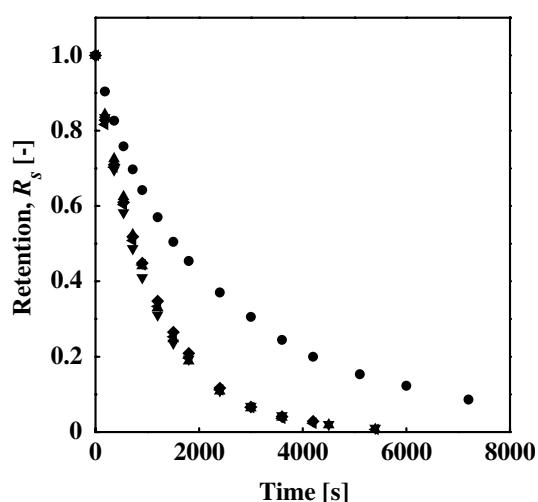


Figure 2. Depression effect of various CDs on desorption of iodine at 25 °C. No CD/control (○);  $\alpha$ -CD (●);  $\beta$ -CD (▲);  $\gamma$ -CD (▼); RM- $\beta$ -CD (◆) and HP- $\beta$ -CD (◄).

words, inclusion complexation of iodine with  $\alpha$ -CD might have occurred more readily and hence substantially increased the iodine stability in aqueous phase.

From the above result acquired, effect of  $\alpha$ -CD on inhibition of desorption of iodine in solution was further examined. In this experiment,  $\alpha$ -CD was added into iodine solution to make up concentration from 0 to 10.3 mM, and then the similar experimental procedure was executed. The results obtained are described in Figure 3. The desorption rate of iodine was found decreasing with the increase of  $\alpha$ -CD concentration. At the highest  $\alpha$ -CD concentration of 10.3 mM, no desorption was perceived.

#### Stability constants

The first linear section in the phase solubility diagram was used for determination of the apparent stability constant. Table 2 compares the stability constant  $K'$  of iodine/natural CD systems estimated by solubility method to the values reported by various authors. The  $K'$  value of iodine/ $\alpha$ -CD complex was computed as  $5.81 \times 10^4 \text{ M}^{-1}$  with the assumption that complexation of

$\alpha$ -CD and  $\text{I}_2$  molecule occurs at 1:1 molar ratio. Comparing to the stability constant values reported by Tomono *et al.* [3] and Terada *et al.* [12], our result was higher though in the same order. Tomono *et al.* [3] attributed the difference of their results from others' to experimental error caused by the high volatility of iodine. It is also possible that this difference may be caused by the difference in experimental conditions such as temperature. The  $K'$  values for complexes from  $\beta$ - and  $\gamma$ -CD were 302 and  $117 \text{ M}^{-1}$ , respectively, comparing  $1.50 \times 10^3$  and  $350 \text{ M}^{-1}$  given by Terada *et al.* [12]. On the other hand, by spectroscopic measurement at 23 °C, Chachisvilis *et al.* [13] estimated the equilibrium constant of iodine/ $\beta$ -CD complex as  $530 \text{ M}^{-1}$ .

The retention data for  $\alpha$ -CD concentration of 0–2.06 mM within the first 30 min of desorption experiment was utilized for determination of the apparent volumetric mass transfer coefficient  $(k_L a)_{\text{app}}$ . Figure 4 is the plot of  $\ln R_s$  versus time produced in accordance to (9) and the slopes of the straight lines plotted gave the apparent volumetric mass transfer coefficients as de-

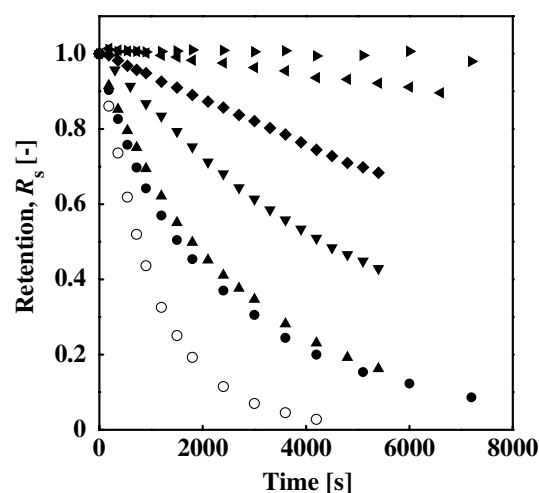


Figure 3. Depression effect of  $\alpha$ -CD of various concentrations on iodine volatility in desorption experiment at 25 °C.  $\alpha$ -CD concentration: 0 mM (○); 0.21 mM (●); 0.41 mM (▲); 1.03 mM (▼); 2.06 mM (◆) 5.04 mM (◄) and 10.3 mM (►).

Table 2. Comparison of stability constant  $K'$  in iodine/natural CD systems estimated by solubility method to the values reported by various authors

System	$K'$ ( $M^{-1}$ )			
	Solubility method <sup>a</sup>	Tomono <i>et al.</i> [3] <sup>b</sup>	Tereda <i>et al.</i> [12] <sup>a</sup>	Chachisvilis <i>et al.</i> [13] <sup>c</sup>
iodine/ $\alpha$ -CD	$5.81 \times 10^4$	$1.36 \times 10^4$	$2.00 \times 10^4$	–
iodine/ $\beta$ -CD	302	$1.08 \times 10^3$	$1.50 \times 10^3$	530
iodine/ $\gamma$ -CD	117	–	350	–

<sup>a</sup>25 °C.

<sup>b</sup>5 °C.

<sup>c</sup>23 °C.

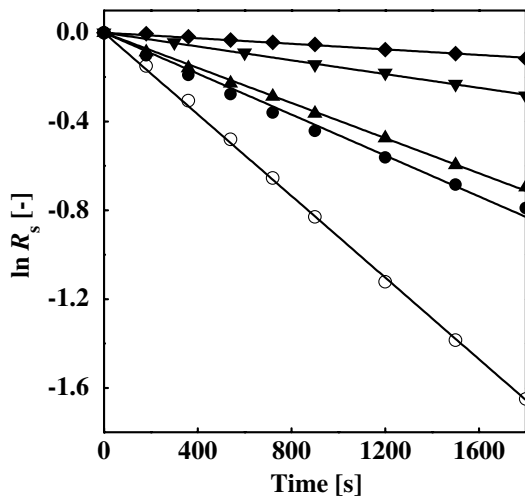


Figure 4. Plot of  $\ln R_s$  versus desorption time for determination of  $(k_{L,a})_{app}$  for each  $\alpha$ -CD concentration.  $\alpha$ -CD concentration: 0 mM ( $\circ$ ); 0.21 mM ( $\bullet$ ); 0.41 mM ( $\blacktriangle$ ); 1.03 mM ( $\blacktriangledown$ ) and 2.06 mM ( $\blacklozenge$ ).

Table 3. The  $(k_{L,a})_{app}$  value calculated from the plot of  $\ln R_s$  versus desorption time

$\alpha$ -CD concentration (mM)	$(k_{L,a})_{app} \times 10^4$ ( $s^{-1}$ )
0	9.19
0.21	4.61
0.41	3.96
1.03	1.55
2.06	0.63

scribed by (10). The apparent volumetric mass transfer coefficients are listed in Table 3. Figure 5 represents the plot of the reciprocal number of these apparent volumetric mass transfer coefficients versus the concentration of  $\alpha$ -CD. This plot could satisfactorily be linearly correlated. As shown in (11), the stability constant  $K$  can be computed by dividing the slope by the intercept on the  $1/(k_{L,a})_{app}$  axis. The  $K$  value obtained was  $3.28 \times 10^4 M^{-1}$ . This value is a little lower in comparison to the one estimated from solubility method. This may imply that there might be some other factors that were responsible for the desorption of iodine from  $\alpha$ -CD solution, as this model was developed based merely on

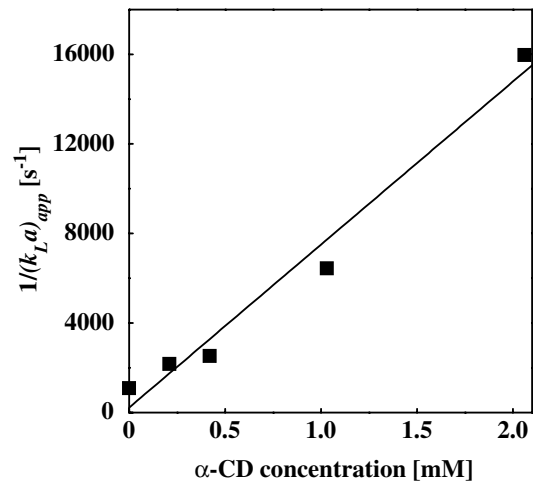


Figure 5. Determination of apparent stability constant  $K$  by linear correlation of inverse number of  $(k_{L,a})_{app}$  versus  $\alpha$ -CD concentration.

mass transfer theory. Nonetheless, since the order of the  $K$  value was the same to that from solubility method and as well those reported by other authors, the model may be considered applicable.

#### Release of iodine from the complex powder

Figure 6 shows the retention of iodine complexes with  $\alpha$ -,  $\beta$ - and RM- $\beta$ -CD stored in accelerated storage condition of 75% RH, 25 °C. The iodine retention data was correlated with the following Avrami's Equation (13) as presented by the solid lines in Figure 6 which described the release characteristics:

$$R = \exp(-[kt]^n) \quad (13)$$

In Equation (13),  $R$  (–) represents the retention of iodine in the complex with various CDs at time  $t$  (s),  $k$  ( $s^{-1}$ ) the release rate constant and  $n$  (–) the release mechanism parameter. The Avrami's equation, though was originally developed to express the crystal growth of polymers [14], has successfully been applied to correlate the

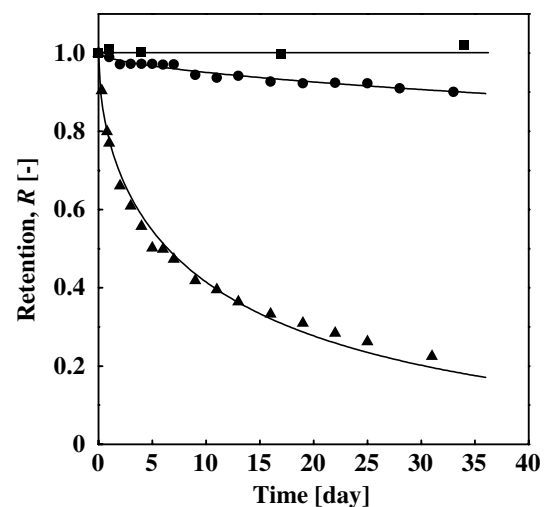


Figure 6. Release time-courses of iodine complexes with various CDs at 75% RH and 25 °C. Inclusion complex of iodine with  $\alpha$ -CD ( $\blacksquare$ );  $\beta$ -CD ( $\bullet$ ) and RM- $\beta$ -CD ( $\blacktriangle$ ).

Table 4. Parameters of release time-courses of various iodine/CD complexes at 75% RH and 25 °C

Inclusion complex	$N$	$k$ (s <sup>-1</sup> )
iodine/ $\alpha$ -CD	–	0
iodine/ $\beta$ -CD	0.599	$7.95 \times 10^{-9}$
iodine/ $\gamma$ -CD	0.544	$9.15 \times 10^{-7}$

release time-courses of spray dried flavor emulsions [15], allyl isothiocyanate/CD complex [16] and *d*-limonene/modified  $\beta$ -CD complex [17]. It is observable in Figure 6 that the correlations were well done with this equation. By a linear plot of  $\ln(-\ln R)$  versus  $\ln t$  from Equation (13), we obtained the  $n$  value from the inclination and the release rate constant  $k$  from the interception at  $\ln t=0$  as summarized in Table 4. Theoretically, the parameter  $n=0.54$  corresponds to diffusive release. Thus,  $n$  values around this figure may approximate to diffusion limited release. The complex powder from RM- $\beta$ -CD released iodine at the highest rate whereas iodine encapsulated in  $\alpha$ -CD was not observed of being released. As prevention of iodine desorption by  $\alpha$ -CD was also observed previously, presumably iodine fits tightly in the  $\alpha$ -CD cavity and thus resistant to release. When comparing three natural CDs in complexation with iodine, Munaf *et al.* concluded that  $\alpha$ -CD formed more stable complex than  $\beta$ - and  $\gamma$ -CD [18].

## Conclusion

In aqueous phase,  $K'$  values of complexes of iodine with natural CDs decreased in the order of  $\alpha$ -CD >  $\beta$ -CD >  $\gamma$ -CD. In desorption experiment,  $\alpha$ -CD prevented volatilization of iodine the most. Although the stability constants of iodine/ $\alpha$ -CD complex estimated by solubility method and mass transfer theory were different, the model developed based on mass transfer theory could still be considered applicable since the  $K$  value was in the same order as the estimated  $K'$  value and also the other reported values. The applicability of this model on other types of CD, however, should be studied individually.

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