**Introduction**

The calcium-channel blockers nifedipine (NIF) and nicardipine (NIC) hydrochloride (Scheme 1) are ester derivatives of 4-aryl-1,4-dihydropyridine-3,5-dicarboxylate, and they are widely used for the treatment of moderate hypertension and cerebral disease\(^1,2\). Because NIF and neutral NIC have low solubility in aqueous solutions and high permeability across biomembranes, they are categorized as class-II drugs on the Biopharmaceutics Classification System (BCS) catalog\(^3\). The poor solubility of class-II drugs decreases both their absorption and distribution; therefore, an improvement in their solubility is required to enhance the bioavailability and transportability toward their cellular targets. Cyclodextrin (CD) is a cyclic (α-1,4)-linked oligosaccharide of α-D-glucopyranose. It is widely used to increase the aqueous solubility, stability, and bioavailability of drugs; in addition, it is used to convert crystalline drugs into microcrystalline powders, prevent drug-drug or drug-additive interactions, decrease gastrointestinal irritation, and eliminate unpleasant taste\(^4\). These applications exploit the ability of CD and its derivatives to capture insoluble drugs, either by inclusion in the hydrophobic central cavity or by adsorption at the hydrophilic outer surface\(^5\). Hydroxypropyl-β-cyclodextrin (HP-β-CD) is a CD alternative, and shows improved aqueous solubility of drugs and resistance to chemical and photodegradation\(^6\)–\(^8\). Moreover, HP-β-CD is utilized in medicines approved for clinical use in oral and intravenous products and suppositories in the United States, Belgium, and Switzerland\(^9\). In a previous study, we investigated the physicochemical properties of NIF/HP-β-CD and NIC/HP-β-CD complexes by differential scanning calorim-

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**Phase Solution and Solution Recrystallization Equilibrium Constants of Hydroxypropyl-β-cyclodextrin Complexes with Nifedipine and Nicardipine Hydrochloride**

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**Summary**: The structure of a cyclodextrin (CD) complex depends on the factors such as the guest hydrophobic molecule, steric hindrance, and charge. Apart from thermal analysis, crystal analysis, and nuclear magnetic resonance (NMR), the phase solution graph can be used to analyze and insure this structure. In this study, solubility and dissolution rate of nifedipine (NIF) [or nicardipine (NIC) hydrochloride]/hydroxypropyl-β-cyclodextrin (HP-β-CD) complexes were investigated to surmise the structures of the complexes. Solubility improvements of NIF and NIC in HP-β-CD solution revealed the possible interaction between NIF/HP-β-CD and NIC/HP-β-CD complexes. The values of the solubility equilibrium constant and the recrystallization equilibrium constant indicated that NIF interacts with HP-β-CD in an equimolar fashion because of its hydrophobicity. In contrast, NIC interacts with HP-β-CD through multiple drug links, probably because of its ionization and hydrophilicity. The study on phase solution and dissolution rate of CD complex could be a novel aspect to distinguish the complex structure when there is neither UV/vis spectrum (Job’s plot of spectroscopy) nor NMR data could quantify the distinction of the complexes, such as NIF or NIC/HP-β-CD complexes.

**Keywords**: hydroxypropyl-β-cyclodextrin; nifedipine; nicardipine hydrochloride; interaction

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etry, X-ray powder diffraction, Fourier-transform infrared spectroscopy, and molecular dynamics simulation\textsuperscript{10}. The complex formed between NIF and HP-\(\beta\)-CD showed equimolar stoichiometry, whereas multiple contact groups were found for the NIC/HP-\(\beta\)-CD complex. In the present study, we concentrate on the intermolecular interaction mechanism of HP-\(\beta\)-CD and NIF/NIC complexes using phase solubility analysis and supersaturation curve analysis.

**Materials and Methods**

1. **Materials**
   HP-\(\beta\)-CD, NIF (PubChem CID: 4485), NIC hydrochloride (NIC salt, PubChem CID: 41114) and all other chemicals and solvents were purchased from Wako Pure Chemicals (Kyoto, Japan). Because NIF and NIC salt are light sensitive, the samples were protected from light by wrapping the containers in aluminum foil during the analyses. The degree of substitution (DS) of HP-\(\beta\)-CD was confirmed by electrospray ionization mass spectrometry (910, Varian, Palo Alto, CA). The DS of HP-\(\beta\)-CD was calculated at 6.32 ± 0.74 from the mass spectrum peak heights.

2. **Phase solution study**
   The solubility of NIF and cationic NIC was measured in various concentrations of HP-\(\beta\)-CD. The concentrations of NIF and cationic NIC were determined using high-performance liquid chromatography (HPLC), in which solution samples were analyzed using a mobile phase of acetonitrile-methanol-deionized water-acetic acid (30:30:45:1) with a flow rate of 1 mL min\(^{-1}\) in a C18 reversed phase column (Capcell Pak C18; 5 \(\mu\)m, size 4.6 mm\(\Phi\) x 250 mm, Shiseido) at 313 K. NIF and cationic NIC elution was monitored at 340-nm and 360-nm wavelengths, respectively.

3. **Dissolution rate study**
   The dissolution rates of a NIF crystal, a solution-treated sample of NIF prepared as described below, and a solution-treated complex of NIF and HP-\(\beta\)-CD at molar ratios of 1:1 were analyzed. The solution-treated samples, which appeared in 3.2 part of this paper, were prepared by evaporation of the samples dissolved in acetone and ethanol at 313 K, after which they were dried in vacuo at room temperature for 3 days. Seventy milligrams of each sample, i.e., NIF crystal, solution-treated NIF, and solution-treated NIF/HP-\(\beta\)-CD complex, was added into 8 mL of hydrochloric acid solution at pH 1.2. The mixtures were shaken in a bath at 310 K for 1, 2, 3, 5, 7, 14, and 33 days. Afterward, the aqueous supernatant was filtered using a 0.45-\(\mu\)m porous filter (Minisart RC 4, 0.45 \(\mu\)m, Sartorius), and the NIF concentration was evaluated by HPLC. We used the molecular ratio of 1:1 in the NIF/HP-\(\beta\)-CD solution, because NIF is quantitatively complexed with HP-\(\beta\)-CD, according to the report of Yáñez et al\textsuperscript{11}.

   The dissolution rates of the NIC salt and its complex were evaluated following the same method as NIF, but using a different sample quantity. Given that the NIC salt and its mixtures appeared more soluble in our preliminary experiments, a 1,000 mg sample of either crystalline NIC salt, solution-treated NIC salt, or solution-treated NIC/HP-\(\beta\)-CD complex was added into 8 mL of HCl solution at pH 1.2 to ensure the complete saturation of the NIC solution.

**Results and Discussion**

1. **Phase solubility of NIF and cationic NIC**
   We measured the solubility of NIF and cationic NIC in various concentrations of HP-\(\beta\)-CD. The solubility of both NIF and cationic NIC is linearly correlated to HP-\(\beta\)-CD concentrations (Figs. 1 and 2). The trend slope in Fig. 1 remains almost unchanged after 1, 3, 5, 7, and 12 days (inset, Fig. 1). This indicates that NIF is stable at all analyzed concentrations of HP-\(\beta\)-CD. Similar stability is obtained for cationic NIC (inset, Fig. 2). The trend slopes of the phase-solubility diagrams of NIF and cationic NIC are 1.5 \(\times\) 10\(^{-3}\) and 6.1 \(\times\) 10\(^{-2}\), respectively, which indicates that solubility in both cases increases linearly with HP-\(\beta\)-CD concentrations. The \(y\)-intercepts of NIF and cationic NIC are 2.7 \(\times\) 10\(^{-5}\) mol L\(^{-1}\) and 1.5 \(\times\) 10\(^{-3}\) mol L\(^{-1}\). We classify both Figs. 1 and 2 as A\(_L\)-type Higuchi phase-solubility diagrams\textsuperscript{12,13}. Higuchi presented solubility measurements that can be used to classify the molecular interaction between the host molecule (CD) and the guest molecule.
Hence, the association constant $\beta$ for the association of a substrate $S$, i.e., NIF or NIC, and the ligand $L$, i.e., HP-$\beta$-CD, at the 1:1 ratio using Eq 14,15:

$$[S \cdot L] = K_1[S][L]$$  \hspace{1cm} (1)

Then, the total concentration $[L]_t$ of the ligand is equivalent to the sum of the concentrations of the free and bound ligands:

$$[L]_t = [L] + [S \cdot L] = [L](1 + K_1[S])$$  \hspace{1cm} (2)

In contrast, the total concentration $[S]_t$ of the drug is expressed by the linear combination of the $[L]_t$:

$$[S]_t = [S] + [S \cdot L] = [S] + K_1[S][L]$$  \hspace{1cm} (3)

Accordingly, a phase-solvability diagram is produced, which fits the linear profile usually describing type $A_1$\textsuperscript{13}. The apparent stability constant $K_1$, is calculated from the phase-solvability diagram, assuming a 1:1 stoichiometry, according to Eq 4:

$$slope = \frac{K_1[S]}{1 + K_1[S]}$$  \hspace{1cm} (4)

Hence, the association constant $K_1$ is given by Eq 5:

$$K_1 = \frac{slope}{[S](1 - slope)}$$  \hspace{1cm} (5)

where $[S]$ is the solubility of $S$ in the absence of HP-$\beta$-CD, i.e., the y-intercepts in Figs. 1 and 2\textsuperscript{41}. Thus, $K_1$ (NIF) and $K_1$ (cationic NIC) are 5.6 $\times$ 10 L mol\textsuperscript{-1} and 4.3 $\times$ 10 L mol\textsuperscript{-1} according to Eq 5.

Although Eq 3 illustrates our results, we confirm whether the phase-solvability diagram corresponds to type $A_1$ or to another profile, if a ligand $L$ is located on double or multiple sites bound to the substrate. Here the inductions of Langmuir's adsorption isotherm\textsuperscript{40} and Michaelis--Menten's enzyme kinetic equation\textsuperscript{47} are favorable. If the binding affinity of each site does not affect the constants, the successive equilibrium constants of the association between substrates $S$ and the ligand $L$ are given by Eqs 6 and 7:

$$[S_2L] = K_2[S][L]$$

$$[S_nL] = K_n[S][S_{n-1}L] = K_1K_2...K_n[S]^n[L]$$  \hspace{1cm} (6)

Here, $n$ is the total number of sites on the multiple ligands. $K_j$ is an equilibrium constant of the $j$-th substrate $S$ and of a multiple ligand $S_{j,L}$ to the complex $S_jL$. Then, the total concentration $[L]_t$ of the ligand equals the sum of the concentration of various states, as described in Eqs 8 and 9:

$$[L]_t = [L] + [S \cdot L] + [S_2 \cdot L] + ... + [S_n \cdot L]$$  \hspace{1cm} (8)

$$[L]_t = [L] + K_1[S][L] + K_2[S]^2[L] + ... + \prod_{j=1}^{n} [K_j[S]^n[L]$$

$$\hspace{1cm} = \left[ [L] + \sum_{i=1}^{n} \prod_{j=1}^{i} [K_j] [S]^i \right]$$  \hspace{1cm} (9)

In this case, the total concentration $[S]_t$ of the drug is also expressed by the linear combination of the $[L]_t$ as shown in Eqs 10, 11, and 12.

$$[S]_t = [S] + [S \cdot L] + 2[S_2 \cdot L] + ... + n[S_n \cdot L]$$  \hspace{1cm} (10)

$$[S]_t = [S] + K_1[S][L] + 2K_2[S]^2[L] + ... + \prod_{j=1}^{n} [K_j[S]^n[L]$$

$$\hspace{1cm} = [S] + \sum_{i=1}^{n} \left[ \prod_{j=1}^{i} [K_j] [S]^i \right]$$  \hspace{1cm} (11)

$$[S]_t = [S] + \frac{\sum_{i=1}^{n} \left[ \prod_{j=1}^{i} [K_j] [S]^i \right]} {1 + \sum_{i=1}^{n} \left[ \prod_{j=1}^{i} [K_j] [S]^i \right] [L]_t}$$  \hspace{1cm} (12)
For a ligand with multiple sites, the number of individual forms of the binding ligand depends on the number of occupied sites in the number of all sites. Because the drug may have several binding sites with a hydrogen or ionic bond, the number of individual forms is equivalent to the number of sites. If the intrinsic equilibrium constant of the corresponding site is homogeneous, we can define the intrinsic binding constant \( k \) of the individual site. As a result, \( K_1, K_2, \) and \( K_i \) correspond to \( nk, (n-1)k/1, nk, (n-1)k/2, \) and \( (n-i+1)k/i, \) respectively. Therefore, Eq. 12 is transformed to Eq. 13:

\[
[S]_i = [S] + \frac{\sum_{i=1}^{n} i \left( \prod_{j=1}^{i} \frac{n-j+1}{j} \right) (k[S])^i}{1 + \sum_{i=1}^{n} \frac{n!}{(n-i)!i!} (k[S])^i} [L]_i \tag{13}
\]

The product of the sequence \( \prod_{j=1}^{i} \frac{n-j+1}{j} \) is transformed to Eq. 14 using factorials:

\[
\prod_{j=1}^{i} \frac{n-j+1}{j} = \frac{n!}{(n-i)!} \tag{14}
\]

Hence, the total concentration \( [S]_i \) is given by Eq. 15:

\[
[S]_i = [S] + \frac{\sum_{i=1}^{n} \frac{n!}{(n-i)!} (k[S])^i}{1 + \sum_{i=1}^{n} \frac{n!}{(n-i)!i!} (k[S])^i} [L]_i \tag{15}
\]

According to the binomial theorem, formulae efficiently reflecting the equations are conducted as follows:

\[
(1+x)^n = 1 + \sum_{i=1}^{n} \frac{n!}{(n-i)!i!} x^i \tag{16}
\]

\[
n(1+x)^{n-1} = \sum_{i=1}^{n} \frac{n!}{(n-i)!(i-1)!} x^{i-1} \tag{17}
\]

Therefore, we obtain Eq. 18 as a relationship similar to Eq. 3:

\[
[S]_i = [S] + \frac{n(1+k[S])^{n-1} k[S]}{(1+k[S])^n} [L]_i
\]

\[
= [S] + \frac{nk[S]}{1+k[S]} [L]_i \tag{18}
\]

This series of calculations reveals that the type \( A_L \) phase-solubility diagram indicates the molar ratio of \( n:1 \) forms a complex between single or multiple sites and \( L (n = 1, 2, ..., n) \). Application of this algebraic interpretation requires three inherent assumptions of the Langmuir's adsorption isotherm. To begin, the number of sites is finite. Next, all sites are equivalent and equimolar to the binding drugs. Finally, a new interaction between the drug and the site is independent, regardless of whether the adjacent sites are free or occupied. According to these assumptions, it is expected that stepwise associations or dissociations take place consecutively, without hysteresis, even if there are multiple binding sites of HP-\( \beta \)-CD.

According to the formula derivation above, an \( A_L \) type phase-solubility diagram indicates a complex with the molar ratio of 1:1 or \( n:1 \), i.e., if all complexes formed are of the first order in ligand, the complex would be formed between single or multiple substrate (S: NIF or NIC), and a ligand (L: HP-\( \beta \)-CD). Saturation would occur in the equimolar interaction \( SL \) and in the multiple-substrate-linked \( S_L \). The presented type-\( A_L \) profiles indicate that NIF/HP-\( \beta \)-CD and NIC/HP-\( \beta \)-CD belong to the single or the multiple-drug-linked complexes.

For the other type diagrams developed by Higuchi, \( A_S \) profiles suggest the formation of higher order complexes with respect to the CD at higher CD concentrations. In addition, \( A_S \) profiles suggest the possibility of self-association of the solubilizer at high concentrations.

2. Solution/recrystallization equilibrium constant of NIF/HP-\( \beta \)-CD and NIC salt/HP-\( \beta \)-CD complex

Figure 3 shows the course of the NIF concentration in solution of the NIF crystal, the solution-treated NIF and the solution-treated NIF/HP-\( \beta \)-CD complex. The dissolution curve of the NIF crystal and the solution-treated NIF shows little difference, equilibrating at a concentration of 28 \( \mu \)mol L\(^{-1} \) after 1 day. If the solubilization process consists of solute release from solid into solution and, then, solvation of the solute by the solvent, the rate-determining step for the solubilization of both the NIF crystal and the solution-treated NIF corresponds to the solvation (hydration) step. In contrast,
NIF concentration in the solution of the NIF/HP-β-CD complex maximizes on the third day, and then gradually decreases to approximately 34% higher than that in the solution of the NIF crystal. NIF concentration in the NIF/HP-β-CD solution does not decrease, however, beyond the concentration level of the NIF crystal solution. The initial dissolution rate of the mixture of equimolar NIF and HP-β-CD is higher than that of crystalline NIF. Complex formation with HP-β-CD would accelerate this rate-determining step, as the CD derivative hides the hydrophobic nature of the NIF molecule and carries it into the aqueous environment.

In our previous study, there was no difference between guest, i.e., NIF or NIC, and complex, i.e., NIF or NIC/HP-β-CD, indicated by the UV/vis spectrum and nuclear magnetic resonance (NMR) because of the weak interactions of the NIF/HP-β-CD and NIC salt/HP-β-CD complexes in solution. We used solution/recrystallization equilibrium constant here to analysis the complex structures. The dissolution processes of the NIF/HP-β-CD complex correspond to a series of consecutive reactions. The NIF/HP-β-CD solid complex (X) is dissolved into solution, with the dissolution and precipitation rate constants $k_1$ and $k_2$, respectively. Then, the NIF/HP-β-CD complex in solution (Y) is equilibrated with the free NIF and the free HP-β-CD (Y'), where the dissociation and association rate constants are $k_a$ and $k_b$, respectively. Finally, the free NIF is equilibrated with the stable crystal (Z), where the precipitation and dissolution rate constants are $k_3$ and $k_4$, respectively. The stability of the NIF and the NIC salt in HP-β-CD solution (insets in Figs. 1 and 2) guarantees the feasibility of this experiment.

\[
\begin{align*}
X \text{ (solid)} & \xrightarrow{k_1} Y \text{ (solute)} \xrightarrow{k_a} Y' \text{ (solute)} \xrightarrow{k_3} Z \text{ (solid)} \\
k_2 & \xrightarrow{k_b} k_4
\end{align*}
\]

Because the concentrations of Y and Y' are difficult to measure, we considered the dissociations of Y to Y' as rapid balance reactions. Thus, this “immeasurable process” (Y to Y') could be conjectured by the reaction of X to Y, and the reaction of Y' to Z, at both ends of the whole reaction. According to the rate theory of reversible consecutive reactions, the relationship between the reactant concentration and the reaction time $(t)$ is as follows. Here $x, y, z$ represent the concentrations of X, Y, and Z.

\[
\begin{align*}
\frac{dx}{dt} &= k_{2y} - k_{1x} \\
\frac{dy}{dt} &= k_{1x} + k_{2z} - (k_2 + k_3)y \\
\frac{dz}{dt} &= k_{3y} - k_4z
\end{align*}
\]

We use the two variables $\alpha$ and $\beta$ (Eq 20) to simplify the results.

\[\alpha + \beta = k_1 + k_2 + k_3 + k_4\]

\[\alpha \beta = k_{3k} + k_{k4} + k_{k3}\]

Therefore, the concentrations of X, Y and Z are given by the rate constants $k_1, k_2, k_3, k_4$, and the variables $\alpha$ and $\beta$. (Eq 21)

\[
x = \frac{k_{2k} + k_{2k} - k_{1} \alpha + k_{3} \beta}{(\beta - \alpha) \alpha} \exp(-\alpha t) - \frac{k_{2k} - k_{1} \beta + k_{3} \beta}{(\beta - \alpha) \beta} \exp(-\beta t)
\]

\[
y = \frac{k_{3k} - k_{1} \beta k_{3}}{(\beta - \alpha) \alpha} \exp(-\alpha t) + \frac{k_{1} k_{3}}{(\beta - \alpha) \beta} \exp(-\beta t)
\]

\[
y = 1 - x - z
\]

The concentration profiles of X, Y, and Z changing with reaction time appear in Fig. 3. The reaction rate constants $k_1, k_2, k_3, k_4$ are calculated by fitting the reaction rate formula of successive reactions to the dissolution curve. The rate constants were calculated through kinetic analysis for the dissolution processes of NIF/HP-β-CD (Table I).

Figure 4 presents the concentrations of NIC in solutions of the crystalline NIC salt, the solution-treated NIC salt, and the solution-treated NIC salt/HP-β-CD complex, as a function of time. The concentration of the crystalline NIC salt is stable around 1,865 μmol L$^{-1}$ after 1 day. The highest concentration of the solution-treated NIC salt is 9,027 μmol L$^{-1}$, after 1 day. The concentration gradually decreases to 1,794 μmol L$^{-1}$, which is not significantly different from the solubility of the crystalline NIC salt. In this case, the crystalline NIC salt transforms to the amorphous state by preparation of a solution-treated sample. Consequently, the solvation step is faster when NIC is in amorphous rather than crystalline state. Therefore, the initial solution becomes supersaturated. In contrast with NIC, the solution-treated NIF does not exhibit any change in the solvation rate, because solution treatment cannot affect the NIF crystallinity. Recrystallization of NIC decreases the subsequent solubility to the same concentration as that of the crystalline NIC salt$^{10,19}$. The concentration curve of the solution-treated NIC/HP-β-CD complex peaks at 48,647 μmol L$^{-1}$ after 1 day and immediately decreases, finally stabilizing after 12 days. The final concentration is approximately 5,794 μmol L$^{-1}$, nearly three times the concentration observed for the crystalline NIC salt solution and the solution-treated NIC salt solution after 30 days. The dissociation and association rate constants are calculated using the kinetic analysis described above for NIC/HP-β-CD (Table I). Furthermore, the solubility equilibrium constant ($K_s$), which is calculated as $k_1/k_3$, and the recrystallization equilibrium constant ($K_r$), which is calcu-
The calculated values of the calculated values of $k_2$ and $k_3$ of NIF/HP-β-CD and NIC/HP-β-CD complexes are determined (Table II). By comparing the calculated values of $K_r$ for the NIF/HP-β-CD and NIC/HP-β-CD complexes, we conclude that the $K_r$ of NIC is nearly twice that of NIF, whereas the $K_r$ of NIC is only 0.05 times that of NIF.

The calculated rate constants confirm that the dissolution rate of the NIC/HP-β-CD complex is higher than that of the NIF/HP-β-CD complex. Moreover, NIC in HP-β-CD solution is quite stable, whereas NIF in HP-β-CD solution recrystallizes rapidly. The equimolar interaction provides a reasonable explanation for the instability of NIF in HP-β-CD solution. Similarly, multiple interactions between substrate and ligand would explain the greater observed stability of NIC in HP-β-CD solution. Finally, this conclusion is consistent with the interactions of NIF/HP-β-CD and NIC/HP-β-CD complexes, which are proven by thermodynamics analysis.

**Conclusion**

The affinity of NIF for HP-β-CD is nearly 1.3 times that of the NIC salt, according to the association constant of their phase-solubility diagrams (NIF-$K_r$ was $5.6 \times 10^4$ and NIC-$K_r$ was $4.3 \times 10^4$), when the host-guest interaction is assumed at a 1:1 stoichiometry. Whereas with HP-β-CD present, the rate constant of the NIC salt is nearly double that of NIF for the dissolution process, and only 0.05 times that of NIF for the recrystallization process. Because of the significant differences in stability between NIF/HP-β-CD and the NIC salt/HP-β-CD complexes, we suspect there are different interactions in these two kinds of complexes. The solubility curves of NIF and cationic NIC in HP-β-CD solution are classified as showing type-A, Higuchi phase-solubility profiles. In such linearly correlated curves, either equimolar or multiple-substrate-linked host-guest molecule interactions are implicated. Because of its high dissolution rate and stability in HP-β-CD solution, NIC is proposed to interact with HP-β-CD by multiple-drug-links, probably because of its ionization and hydrophilicity. On the other hand, NIF is proposed to interact with HP-β-CD in an equimolar fashion, because of its hydrophobicity. Furthermore, the solution/recrystallization equilibrium constant provides information on the complex interaction and stability, when there are neither a UV/vis spectrum (Job’s plot of spectroscopy) nor NMR data available that could quantify the distinction of the complex, such as NIF or NIC salt/HP-β-CD complexes.

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**References**


| Table I. Reaction rate constants $k_1$, $k_2$, $k_3$, and $k_4$ of NIF/HP-β-CD and NIC/HP-β-CD complexes |
|---------------------------------|------------|------------|------------|
| Rate Constants (s$^{-1}$) | $k_1$ | $k_2$ | $k_3$ | $k_4$ |
| NIF/HP-β-CD | $1.0 \times 10^{-3}$ | $3.2 \times 10^{-6}$ | $9.3 \times 10^{-2}$ | $2.9 \times 10^{-4}$ |
| NIC/HP-β-CD | $6.7 \times 10^{-2}$ | $1.1 \times 10^{-4}$ | $1.2 \times 10^{-2}$ | $7.1 \times 10^{-4}$ |

| Table II. Equilibrium constants $K_s$ and $K_r$ of NIF/HP-β-CD and NIC/HP-β-CD complexes |
|---------------------------------|----------|----------|
| Equilibrium constant | $K_s$ | $K_r$ |
| NIF/HP-β-CD | 316.9 | 319.0 |
| NIC/HP-β-CD | 632.0 | 17.3 |