Cyclodextrin/Weak-Electrolyte Complexation: Interpretation and Estimation of Association Constants from Phase Solubility Diagrams

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INTRODUCTION

The acid and base conjugate forms of a weak electrolyte (weak acid or base) differ in their ability to form inclusion complexes with cyclodextrin (CD) (1–3). Upon oral administration the CD inclusion complexes are subjected to a pH change in the gastrointestinal fluid. Therefore, the substrate ionization effect on the stability of complexes is important. The potentiometric method capable of studying complexes of ionizable substrates (3) is based on the assumption that a change in the apparent dissociation constant (pK_a') prior to and after complexation can be observed if the acid and conjugate base forms of a substrate form cyclodextrin complexes of different strengths. In the potentiometric method, the pK_a's of the weak electrolyte in the presence of cyclodextrin were determined by potentiometric titration. The equilibrium constants for the acid and base conjugate forms were estimated with the magnitudes and variability of pK_a' shifts. While this method is able to identify the differences among the acid and conjugate base forms of a weak electrolyte in forming the inclusion complexes with CD, it requires a complicated titration procedure and mathematical calculation.

The present communication describes a phase solubility approach capable of providing estimates of equilibrium constants for both the acid and the conjugate base forms. The apparent slopes of the ascending linear phase solubility diagrams of CD/weak electrolyte complexation vary with pH's (4), a phenomenon which can be described by a mathematical model.

THEORETICAL

We considered a weak acid capable of forming 1:1 complex with CD. Other weak electrolytes can be treated in a similar manner. The association equilibria of the conjugate acid and base forms of a weak electrolyte and CD can be described as shown in Scheme I. The terms AH and A^- represent the acid and conjugate base forms of a weak electrolyte, respectively. The solubility of A^- in an aqueous medium is assumed to be significantly higher. L and H^+ denote CD molecules and protons; and AH-L and A^--L refer to the CD inclusion complexes of the acid and conjugate base species, respectively. In the presence of an excess amount of solid drug, the mass balance of drug and CD in an aqueous solution may be represented by Eqs. (1) and (2):

$$[A]_t = [AH]_0 + [A^-] + [AH\text{-}L] + [A^-\text{-}L] \quad (1)$$

$$[L]_t = [L] + [AH\text{-}L] + [A^-\text{-}L] \quad (2)$$

where $[A]_t$ is the total drug concentration; $[AH]_0$, the intrinsic solubility of the free acid; $[A^-]$, the concentration of the free conjugate base; [AH-L], the concentration of the acid/CD complex; $[A^-$-L], the concentration of the conjugate base/CD complex; $[L]_t$, the total concentration of CD; [L], the concentration of free CD; and K_a, K_a', K_{eq}, and K_{eq}' are the equilibrium constants, which are defined as follows:

$$K_a = [H^+][A^-]/[AH]_0 \quad (3)$$

$$K_a' = [H^+][A^-\text{-}L]/[AH\text{-}L] \quad (4)$$

$$K_{eq} = [AH\text{-}L]/[L][AH]_0 \quad (5)$$

$$K_{eq}' = [A^-\text{-}L]/[L][A^-] \quad (6)$$

From Eqs. (1)–(6), Eqs. (7) and (8) can be obtained.

$$[A]_t = [AH]_0(1 + K_a/[H^+]) + (K_{eq} + K_{eq}' \cdot K_a/[H^+])[AH]_0[L] \quad (7)$$

$$[L] = [L]_t/(1 + K_{eq}[AH]_0 + K_{eq}'K_a[AH]_0/[H^+]) \quad (8)$$

Combining Eqs. (7) and (8) yields Eq. (9):

$$[A]_t = [AH]_0(1 + K_a/[H^+]) + \frac{(K_{eq} + K_{eq}' \cdot K_a/[H^+])[AH]_0}{(K_{eq} + K_{eq}' \cdot K_a/[H^+])[AH]_0 + 1}[L]_t \quad (9)$$

Therefore, the apparent slope of Eq. (9), where $[A]_t$ is plotted against $[L]_t$, can be defined as Eq. (10):

$$\text{Slope} = \frac{(K_{eq} + K_{eq}' \cdot K_a/[H^+])[AH]_0}{(K_{eq} + K_{eq}' \cdot K_a/[H^+])[AH]_0 + 1} \quad (10)$$

The apparent slope of the linear ascending phase solubility diagrams of CD/weak acid complexation is a function of proton concentration. Rearrangement of Eq. (10) gives Eq. (11),

$$K_{eq}' = \frac{[H^+]}{K_a}\left(\frac{\text{Slope}}{(1 - \text{Slope})[AH]_0} - K_{eq}\right) \quad (11)$$

K_{eq} can be estimated by constructing the phase solubility diagram at a pH value where the acid form is the dominant species. Similarly, K_{eq}' may also be calculated by solving a group of equations derived from Eq. (10) using different proton concentrations.

RESULTS AND DISCUSSION

The theory of the phase solubility approach is similar to that of the potentiometric method (1–3), except that the phase solubility diagram is constructed from equilibrium solubility measurements in the presence of an excess amount of solid drug. Therefore, there is less variability in the phase solubility method than in the potentiometric method. In a

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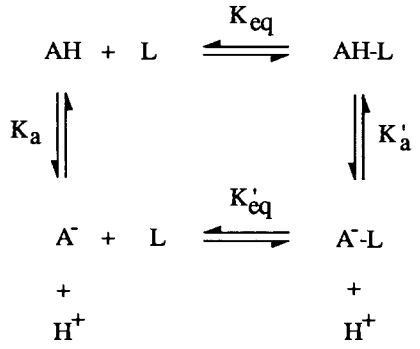

Scheme I. Association equilibria of a weak acid and cyclodextrin.

recent report, Backensfeld and co-workers (4) observed the effect of pH on the apparent slopes of the phase solubility diagrams of indomethacin/hydroxypropyl-β-CD (HPCD) complexation. The results showed an increase in the apparent slopes as a function of increasing pH values. Their data (Table I) can be best described by our proposed method.

The pK_a of indomethacin of 4.5 was used to calculate the intrinsic solubilities of indomethacin at various pH's (Table I). As expected, the values of the intrinsic solubilities are similar. According to theory (3), both acid and conjugate base forms can interact with CD. In this case, the concentration of the acid is a constant which is equal to the intrinsic solubility, whereas the concentration of the conjugate base is a variable quantity which increases with pH. Knowing the intrinsic solubility, apparent slope, and proton concentration, a series of equations concerning equilibrium constants can be obtained using Eq. (10). A group of equations containing any two of these equations (two equations and two unknowns) is enough to solve for K_{eq} and K_{eq}'. The values for K_{eq} and K_{eq}' calculated with the data obtained from the phase solubility diagrams at various pH's were 3780 ± 645.9 and 528.3 ± 28.1 M^{-1} (± SE; n = 3), as shown in Table II.

According to previous definitions, the relationship between the equilibrium constants of complexation and the dissociation constants of indomethacin can be written as Eq. (12),

$$K_a' \cdot K_{eq} = K_a \cdot K_{eq}' \quad (12)$$

The dissociation constant for the complex form of indomethacin can be estimated with Eq. (12), which turns out to be 4.42×10^{-6}, approximately seven times lower than that of free indomethacin. The rise in pH after complexation reported by the authors may be attributable to the increase in pK_a of the indomethacin/HPCD complex, which led to a decrease in acidity of the aqueous solution.

The numerical difference of equilibrium constants for the conjugate acid and base forms of indomethacin indicates that the ionization of indomethacin can significantly change the complex stability. The complex formed by nonionized indomethacin and HPCD is more stable than that with ionized species. Therefore, under physiological conditions (pH 7.4), indomethacin is not able to form an inclusion complex efficiently.

Table I. Data of the Phase Solubility Diagrams of Indomethacin with HPCD at Different pH Values (Reproduced from Ref. 4)

No.	pH	$[A]_t$ (mM)	$[AH]_0$ (mM)	Slope
1	4.9	0.0123	0.0035	0.019
2	5.5	0.0587	0.0053	0.046
3	6.1	0.240	0.0058	0.131
4	6.7	0.950	0.0059	0.285
5	7.3	2.93	0.0046	0.358
6	7.8	4.64	0.0023	0.441

Table II. Equilibrium Constants for the Conjugate Acid and Base Forms of Indomethacin

Data source	K_{eq} (M^{-1})	K_{eq}' (M^{-1})
pH 4.9 and 5.5	4362	466
pH 4.9 and 6.1	2491	585
pH 5.5 and 6.1	4489	534

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