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Simultaneous determination of cyclodextrin stability constants as a function of pH and temperature – A tool for drug formulation and process design

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ABSTRACT

The stability constant for complex formation is an important physicochemical property used to guide drug formulation development with cyclodextrins. Complex formation depends on both pH and temperature, factors often altered during pharmaceutical processing and manufacturing. Hence, their influence on the stability constant must be considered during drug formulation to define a robust formulation and manufacturing process. This work demonstrated how a mechanistic model, based upon physical chemical laws, for the apparent stability constant as a simultaneous function of pH and temperature accurately could estimate the apparent stability constant for cyclodextrin complexes. The model required multiple thermodynamic inputs, i.e. the pK_a value of guest and buffer, measured stability constants for the cyclodextrin complex, the change in enthalpies and the change in heat capacities. A comprehensive set of isothermal titration calorimetry data for β-CD:ibuprofen at six different pH values and four temperatures were compared to the model calculations. A good agreement was observed between the experimental data and the modelled data, indicating that the model could be used to predict the stability constant at any pH and temperature. The model can be used as an important tool during drug formulation and process design to optimize formulation work with cyclodextrins.

1. Introduction

Cyclodextrins (CDs) are common excipients used in the pharmaceutical industry, and they are present in numerous marketed drug products [1,2]. Medicinal products often contain excipients to ensure stability, bioavailability and patient acceptability [3]. CDs are not an exception from this general use of excipients, as they are applied to enhance solubility, disguise unpleasant taste and/or odor, and increase stability of active molecules in drug formulations [1,4]. CDs consist of 6–8 glucopyranose units forming a cone-like structure with a hydrophobic cavity and hydrophilic surface [5], making them able to form inclusion complexes with small hydrophobic guest molecules [6]. Through formation of inclusion complexes, CDs modify the apparent physicochemical properties of the guest molecule without affecting the intrinsic properties [7,8].

Though the chemical mechanism of CDs are easy to understand, the practical application of CDs in drug formulations requires a thorough understanding of the interplay between many factors. First, the physicochemical properties of the excipients, as well as any potential interaction between different excipients must be characterized and documented [3]. Second, external factors influencing the interactions between CD and guests must be evaluated, e.g. temperature and pH. A drug formulation must be robust, i.e. the formulation should stay physical and chemical stable during manufacturing, shipping, storage and use at all potential conditions [9]. As part of ensuring a robust formulation, it is important to guarantee that small variations in components or environmental factors, e.g. temperature or pH, do not have major effects on the formulation. The stability of CD complexes depends on temperature, pH and presence of co-solutes [10–16], thus, buffer composition, pH and temperature are some of the most important parameters to optimize during early drug formulation with CDs.

The pH value are considered to address potential issues like aggregation, degradation and solubility enhancement of components [17]. The pH of a solution is usually maintained with a buffer, and the pK_a

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value of the buffer governs the solution pH. However, for CD complexes, the pH also affects the stability constants of CD complexes, when the guest molecule is ionizable [9,15]. The different species of an ionizable guest molecule will have different affinities for the CD cavity, where the highest affinity for the CD cavity is in generally observed for the neutral species [18]. Previous work has demonstrated how the apparent stability constant can be modelled as a function pH [15].

Temperature might change during manufacturing, transportation or storage, hence it is important to consider. Equilibrium constants, such as the stability constant for a CD complex or the pK_a values of the guest molecule or buffer, depend on temperature as described by the van't Hoff equation. The stability constants of CD complexes often decrease with increasing temperature, i.e. the individual species are favored relative to the complex, and pK_a values usually decrease with increasing temperature over larger temperature ranges [19].

CD drug formulations involve the interplay of complexation and ionization equilibria. In this work, a simultaneous evaluation of the effects of buffer, pH, and temperature are considered by making a chemical mechanistic model. The model uses the van't Hoff equation, the Henderson-Hasselbalch equation and the relation between the apparent stability constant and pH. The model was validated by comparing it with experimental data using a model system of β-CD and ibuprofen. The developed model may serve as a tool to optimize formulation work and documentation with CDs.

2. Theoretical background

In this work, both ionization equilibria and complex equilibria are used, and the corresponding equilibrium constant will be referred to as ionization constants, K_a and pK_a, and stability constants for the complex, K_B, $K_{CD:Ibu}$, $K_{CD:Ibu}$, respectively. These notations will be used throughout this work to avoid mix up between the different equilibrium constants.

Equilibrium constants are typically expressed in terms of the concentrations of reacting species and products formed, for a CD interaction the equation is;

$$CD + Guest \rightleftharpoons CD : Guest \tag{1}$$

$$\frac{[CD : Guest]}{[CD][Guest]} \approx K \tag{2}$$

2.1. Temperature-dependency of the equilibrium constant

The equilibrium constant is a thermodynamic parameter, strongly related to the energy that drives reactions, i.e. the change in standard Gibb's free energy (ΔG°) of the reaction.

$$\Delta G^\circ = -RTlnK \tag{3}$$

where R is the gas constant, and T is the temperature at which the reaction takes place. The change of free energy of the reaction is defined by the change in enthalpy (ΔH°) and entropy (ΔS°) at constant temperature and pressure.

$$\Delta G^\circ = \Delta H^\circ - T\Delta S^\circ \tag{4}$$

By combining Eqs. (3) and (4), it is possible to relate the equilibrium constant to the change in enthalpy and entropy of a reaction.

$$lnK = -\frac{\Delta H^\circ}{RT} + \frac{\Delta S^\circ}{R} \tag{5}$$

By differentiating the expression in Eq. (5) with respect to T, the van't Hoff equation is obtained, which describes the dependency of the equilibrium constant as a function of temperature.

$$\frac{\partial lnK}{\partial T} = \frac{\Delta H^\circ}{RT^2} \tag{6}$$

Typically, the van't Hoff equation will be expressed as a specific integral between temperatures T_1 and T_2, allowing for calculations of the equilibrium constant K_2 at temperature T_2.

$$ln\frac{K_2}{K_1} = \frac{-\Delta H^\circ}{R}\left(\frac{1}{T_2} - \frac{1}{T_1}\right) \tag{7}$$

The van't Hoff equation shows the link between the equilibrium constant, enthalpy of the reaction and the temperature based on the assumption that ΔH° is constant. In cases where the enthalpy is numerically large, the equilibrium constant will be strongly temperature-dependent. However, the change in enthalpy is temperature-dependent, which must be accounted for when applying the van't Hoff equation to a larger temperature interval. The dependency of the change in enthalpy on temperature is quantified in terms of the change in heat capacity (ΔC_p).

$$\Delta C_p = \frac{\partial \Delta H}{\partial T} \tag{8}$$

Integrating Eq. (8) with respect to temperature yields ΔH as a function of temperature. This expression combined with Eq. (6), followed by integration with respect to temperature, results in the extended van't Hoff equation as a specific integral between two temperatures.

$$lnK_2 = \frac{\Delta H_1 - T_1\Delta C_p}{R}\left(\frac{1}{T_1} - \frac{1}{T_2}\right) + \frac{\Delta C_p}{R}\ln\left(\frac{T_2}{T_1}\right) + lnK_1 \tag{9}$$

The subscripts refer to the values of enthalpy and equilibrium constants at temperatures T_1 and T_2.

Based on the extended van't Hoff equation, it is possible to calculate the equilibrium constant, e.g. the ionization constant or the stability constant, as a function of temperature, as long as the quantities ΔH and ΔC_p of the reactions are known.

2.2. The stability constant for CD complexes depends on pH

Several studies have demonstrated that pH affects CD complex formation, when the guest is ionizable (e.g. Refs. [10,13,15,20–22]). Different species of an ionizable molecule will have different affinities for the CD cavity [18]. Generally, neutral species will have a higher affinity for the CD cavity, since it is more hydrophobic compared to charged species. Due to the difference in affinity for the various species, the stability constant for the CD complex depends on pH [4]. A theoretical expression describing this dependency has been reported previously by Samuelsen and co-workers [15].

The stability constant for a CD complex with an ionizable guest molecule can be expressed in terms of an overall equilibrium between the CD and the guest.

$$CD + Guest \rightleftharpoons CD : Guest \tag{10}$$

The ionizable guest may exist in different charge states determined by the pK_a of the guest and pH of the solution.

$$C_{Guest} = \Sigma[Guest^x] \tag{11}$$

where x represents the charge state. The number of pK_a values determines the number of potential guest species. The overall equilibrium (Eq. (10)) can be split into individual equilibria for each species of guest molecule.

$$CD + Guest^x \rightleftharpoons CD : Guest^x \tag{12}$$

For each species of guest molecule, a new equilibrium can be written. The apparent stability constant (K_B) for the overall equilibrium (Eq. (10)) can be expressed as the sum of all the stability constants (K_x) times the fraction of guest species (defined in Eq. (14)).

$$K_B = \Sigma(K_x\alpha_x) \tag{13}$$

where α is the fraction of the ionizable guest.

$$\alpha = \frac{[Guest^x]}{C_{Guest}} \tag{14}$$

As an example, α for a monoprotic acid may be expressed in terms of an ionized (G^-) and neutral (HG) species of the guest.

$$\alpha = \frac{[G^-]}{[G^-]+[HG]} = {}^{1}\Big/\frac{[G^-]+[HG]}{[G^-]} = {}^{1}\Big/\left(\frac{[HG]}{[G^-]}+1\right) \tag{15}$$

The pH of the solution and the pK_a value of the guest determines the relation between the neutral and ionized species. This relation is described by the Henderson-Hasselbalch equation (Eq. (16)).

$$pH = pK_a + log\frac{base}{acid} = pK_a + \log\frac{[G^-]}{[HG]} \tag{16}$$

A more thorough presentation of the theoretical relation between the apparent stability constant (K_B) and pH can be found in previous work [15,23].

3. Material and methods

3.1. Reagents

Ibuprofen (CAS: 15687-27-1, ≥98%, M_w = 206.28 g/mol) and β-CD (CAS: 7585-39-9, ≥97%, M_w = 1134.98 g/mol) were purchased from Sigma-Aldrich and used as received. Other chemicals used were of analytical grade.

3.2. Isothermal titration calorimetry

Isothermal titration calorimetry (ITC) was used to determine the stability constant and enthalpy of reactions for β-CD and ibuprofen in 55 mM acetate buffer at six pH values (3.0, 3.5, 4.0, 4.5, 5.0, and 5.5) for four different temperatures: 15, 25, 40, and 55 °C. The experimental procedure and data for the ITC measurements have previously been reported in another study [15]. Shortly, measurements were performed using a MicroCal VP-ITC Microcalorimeter (Malvern Panalytical, Worchestershire, UK) with ibuprofen loaded into the sample cell with a total volume of 1.4257 mL, and the β-CD loaded into a 250 μL injection syringe. Titrations were performed by adding 10 μL aliquots during 20 s with an interval of 200 s between injections until the syringe was empty. Stirring speed was 310 rpm. Heat of dilution was corrected for by subtraction of blank titrations. Some of the data in this work were previously presented [15], however, new additional data were added to this work.

4. Results and discussion

4.1. Determination of stability constant and enthalpy of reaction for β-CD:ibuprofen

Isothermal titration calorimetry (ITC) was used to study the interaction between β-CD and ibuprofen in acetate buffer at six pH values and four temperatures. A representative example of ITC data is shown (Fig. 1). The heat was measured during titration resulting in heat data as a function of the molar ratio between β-CD and ibuprofen, and these data were fitted to a one set of sites model to yield the stoichiometry of the complex (*N*), the stability constant (*K*) and the change in enthalpy of the reaction (Δ*H*). All titrations yielded a stoichiometry close to 1, with low standard errors of fitting, confirming formation of a 1:1 complex between β-CD and ibuprofen.

The apparent stability constant (K_B) and change in enthalpy of the reaction (*ΔH*) for the β-CD:ibuprofen complex depended on pH (Fig. 2). The results demonstrated that at low pH, where ibuprofen is predominantly neutral, the stability constant for the neutral complex ($K_{CD:Ibu}$) was large relative to the stability constant ($K_{CD:Ibu^-}$) at higher pH, where ibuprofen is ionized. Complex formation for CDs are typically associated

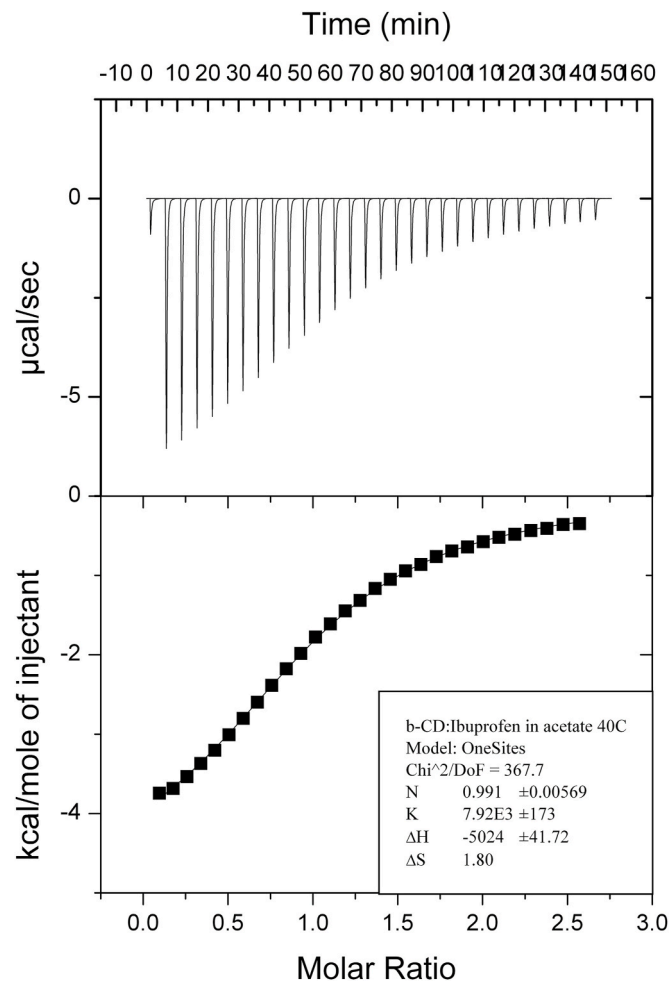

Fig. 1. Representative example of ITC data. The data show a titration of β-CD into in ibuprofen in acetate buffer (pH 5.5) at 40 °C.

with a large, negative *ΔH*, and a *ΔS* value, which can be either negative or positive. However, the thermodynamics of the interaction depends on the specific guest molecule and its properties [24]. Many consider the displacement of water from the CD cavity to be an important driving force for CD complexation [24,25]. The results obtained in this study showed that *ΔH* depended on the pH of the solution, and there was a good agreement between the theoretical predictions and the data. The small discrepancies between the theoretical model and ITC data is likely due to experimental uncertainties. Since *ΔH* is an input in the van't Hoff equation, it is important for the simultaneous determination of temperature and pH effects. The results in Fig. 2 were consistent with the theoretical understanding that complex formation is associated with a large, negative *ΔH*, and that the complex formation depends on pH. Increasing the pH value of a solution containing β-CD:ibuprofen resulted in a decrease of K_B and an increase of *ΔH*, consistent with less complex formation.

4.2. Extrapolation of the apparent stability constant

It may be useful to identify possible pH or temperature ranges, which influence the robustness of a CD formulation prior to testing a solution of CD, guest and buffer or during processing of the drug formulation, e.g. due to sterilization or storage conditions. By combining the van't Hoff equation with the pH-dependency of K_B in a single model, it was possible to extrapolate K_B to any temperature and/or pH value. Python scripts are available in SI.

The starting point for the following section will be two outputs

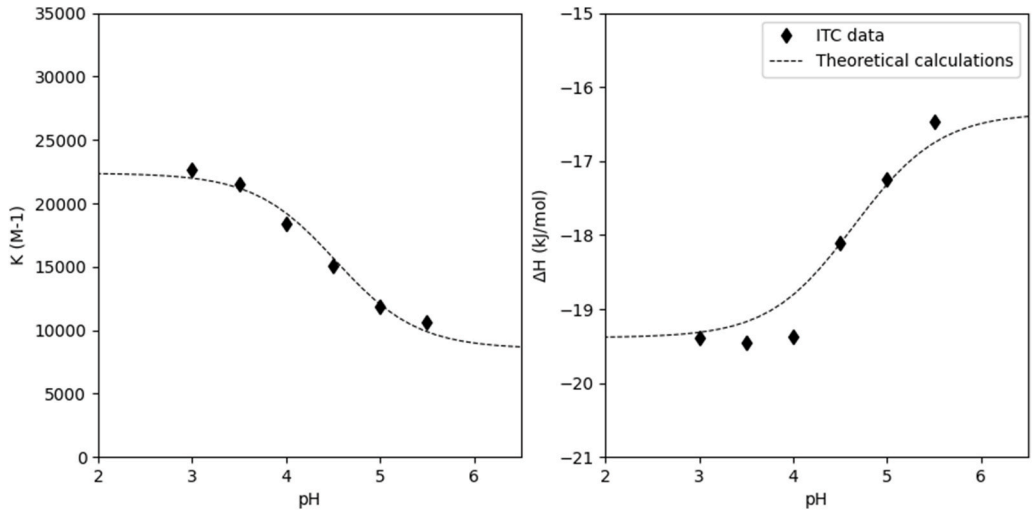

Fig. 2. K (M^{-1}) and ΔH (kJ/mol) determined by ITC for β-CD and ibuprofen at 25 °C in the pH range 3.0–5.5. Figure modified from Ref. [15]. The theoretical calculations for ΔH as a function of pH is based on the theoretical expression: $\Delta H = (1-\alpha_{CD})\Delta H_{CD:Guest,\ neu} + \alpha_{CD}\Delta H_{CD:Guest,\ ion} + (\alpha-\alpha_{CD})\Delta H_{ion}$ (see SI for derivation of the theoretical expression).

relevant in the formulation process; 1) a three dimensional surface plot showing K_B as a function of both temperature and pH, and 2) a graph of K_B as a function of temperature at a specific solution pH determined by the buffer. The main difference between scenario 1) and 2) is whether the buffer is considered. In scenario 1), the buffer is excluded from the calculations as the entire pH interval is examined, making it possible to choose an appropriate pH value for the formulation and from there define a buffer suiting this pH. In scenario 2), the buffer is a very important part of the considerations, as the results are pH specific, and the $pK_{a,\text{Buffer}}$ controls the solution pH, so the two models could be considered as a step-wise approach in a formulation selection process.

4.2.1. Scenario 1

The first scenario is the most simple of the two from a modelling perspective. In this scenario, large pH and temperature ranges may be evaluated, and it may be used as a tool to identify the regions of interest, where either changes in pH or temperature will significantly affect the stability of a CD-drug interaction. It can aid researchers in choosing a suitable pH value for a specific CD solution. Scenario 1) relies on the following assumptions: a) the $pK_{a,\text{guest}}$, $K_{CD:Ibu}$ and $K_{\overline{CD}:Ibu}$ depend on temperature (Eq. (9)), b) α for the neutral and ionized guest depends on pH (Eqs. (15) and (16)) and c) K_B depends on pH (Eq. (13)). It is important to first consider the variation in $pK_{a,\text{guest}}$ with temperature, because $pK_{a,\text{guest}}$ is a required input when estimating α. The approach of scenario 1) can be split into three steps (I-III), see flowchart in Fig. 3. The inputs needed for the calculations are presented in Table 1 for ibuprofen – together with the parameters used in scenario 2).

The resulting surface plot showed that K_B depends on both pH and temperature (Fig. 4). Changing the temperature will significantly affect the stability at low pH, whereas changing the pH will significantly affect the stability at low temperatures. The results showed that K_B at 100 °C would be in the range $2.6*10^2$–$6.9*10^2$ M^{-1} depending on the pH. Such a small difference would be insignificant for practical application of CDs. However, the decrease in the stability as a function of temperature from the range of $8.5*10^3$–$2.2*10^4$ M^{-1} at 25 °C to $2.6*10^2$–$6.9*10^2$ M^{-1} at 100 °C must be considered a significant variation. Hence, the difference in temperature will have an effect on a formulation with β-CD:ibuprofen. During drug formulation, a temperature range of 0–140 °C is relevant to consider, depending on the specific dosage form. Low temperatures are relevant due to storage conditions, where temperatures can be as low as 5 °C, though it may vary from country to country due to climate conditions [19]. High temperatures arise during autoclaving or high pressure homogenization, where temperatures increase to 130–140 °C. For a β-CD:ibuprofen formulation, which must be able to endure temperature changes due to variation in storage temperature or during the manufacturing process, a high pH value would ensure small variations in the stability constant. In Scenario 1), a large temperature and pH range can be evaluated, which may be used to guide the formulation work ensuring optimal conditions for a specific formulation.

Considering the change in pH of the solution for the β-CD:ibuprofen complex, K_B decreased by a factor two in the pH range from 3 to 5. The effect of pH on the stability constant for a CD complex is relative and depends on the position of the ionizable group of the guest relative to the CD cavity. For other CD complexes, differences between the stability constant for the neutral and ionized complex has been reported to be a factor of 11–36 [29]. Another study has even reported an unusual high differences of a factor 150 and 6000 for two β-CD complexes [30]. Depending on the specific system, it may be paramount to maintain a constant pH to ensure the stability of the complexes. The surface plot gives no information on how the pH of the solution changes with temperature, as this parameters is excluded from scenario 1).

4.2.2. Scenario 2

In scenario 2), the model factors in that both pK_a values of guest and buffer depend on temperature. The pH of the solution depends on the buffer and the variation in $pK_{a,\text{buffer}}$ as a function of temperature. The assumptions for scenario 2) were: a) the $pK_{a,\text{buffer}}$ depends on temperature (Eq. (9)), b) the pH of the solution depends on the $pK_{a,\text{buffer}}$ as described by the Henderson-Hasselbalch equation (Eq. (16)), c) the $pK_{a,\text{guest}}$, $K_{CD:Ibu}$ and $K_{\overline{CD}:Ibu}$ depend on temperature (Eq. (9)), d) α for the neutral and ionized guest depends on solution pH (Eqs. (15) and (16)) and e) K_B depends on pH of the solution (Eq. (13)). In scenario 2), the first calculation step is the calculation of $pK_{a,\text{buffer}}$ as a function of temperature and the calculation of the solution pH. The step is important, as it is needed for the calculation of K_B as a function of solution pH. Scenario 2) can be split into four steps (I-IV) following each assumption, see flowchart in Fig. 3. Again, the inputs needed for the calculations are listed in Table 1. The resulting graph showed that K_B decreased with increasing temperature at pH 4.5 for the ibuprofen system (Fig. 5). The results showed that a large variation in K_B may be expected as a function of temperature for a solution in acetate buffer with the initial pH of 4.5. The pK_a value of acetate does not depend strongly on temperature [19], so the pH of the solution is close to constant as a function of temperature (Fig. 5, dashed line). Instead, the effect of temperature is caused by the temperature-dependency of K_B.

In general, carboxylic acid buffers, like acetate, are least affected by

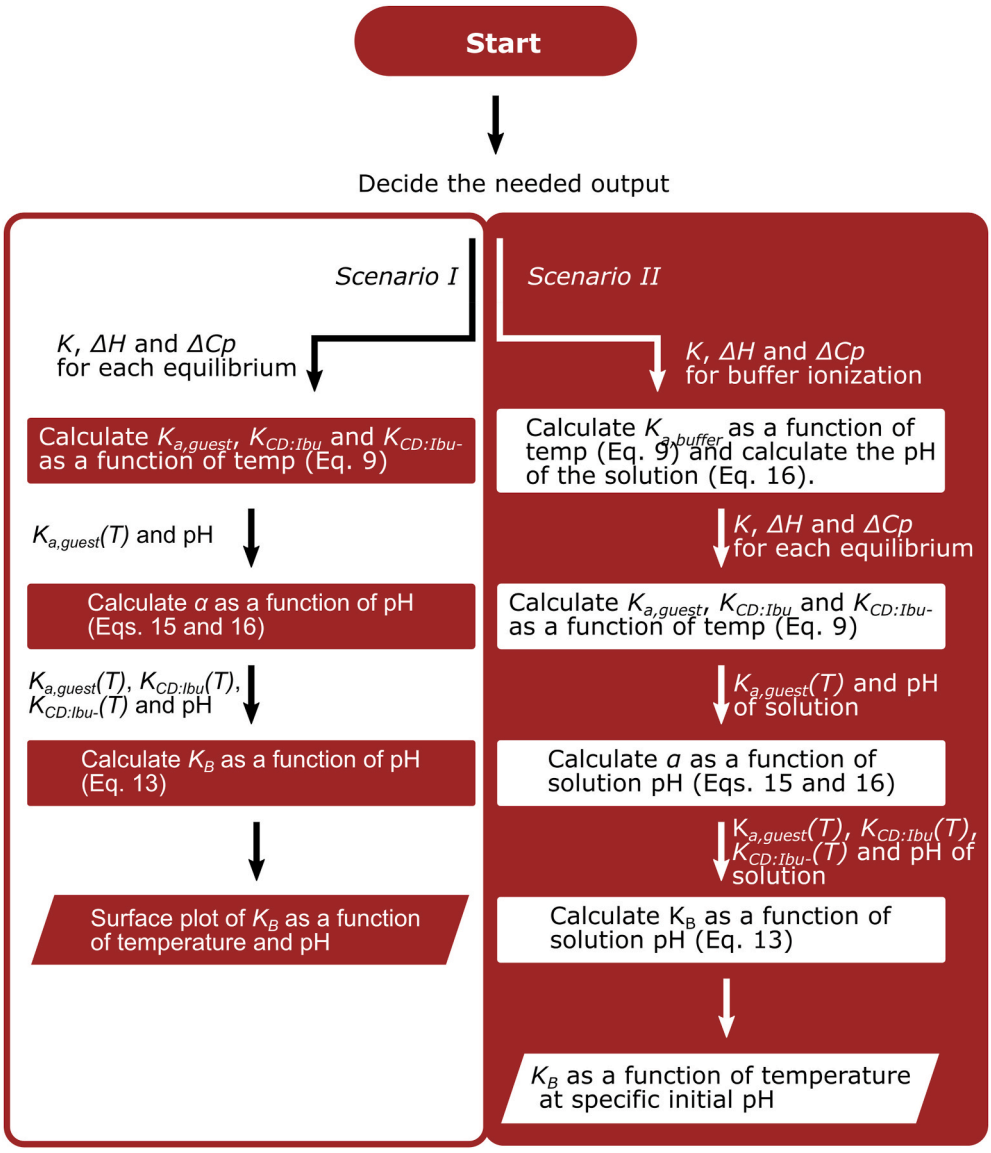

Fig. 3. Flowchart of models used to calculate K_B as a function of temperature and pH showing the inputs needed and the outputs generated.

Table 1
List of inputs needed for the model to predict K_B as a function of pH and temperature, and specific inputs at reference temperature 25 °C for the example of the complex formation between β-CD and ibuprofen.[a] [26],[b] [27],[c] [28],[d] [15], [e]ITC data from this work.

Inputs	β-CD:Ibuprofen
$pK_{a,\mathrm{buffer}}^{a}$	4.76
$\Delta H_{\mathrm{buffer}}^{a}$	−410 J/mol
$\Delta Cp_{\mathrm{buffer}}^{a}$	−142 J/(mol*K)
$pK_{a,guest}^{b}$	4.53
ΔH_{guest}^{b}	1733 J/mol
ΔCp_{guest}^{c}	383 J/(mol*K)
$K_{CD:Ibu}^{d}$	22,380 M^{-1}
$\Delta H_{CD:Ibu}^{e}$	−20,447 J/mol
$\Delta Cp_{CD:Ibu}^{e}$	−278 J/(mol*K)
$K_{CD:Ibu}^{d}$	8,538 M^{-1}
$\Delta H_{CD:Ibu}^{e}$	−16,464 J/mol
$\Delta Cp_{CD:Ibu}^{e}$	−389 J/(mol*K)

changes in temperature [26,31], whereas Tris buffer is very sensitive to temperature changes [26,32]. According to the van't Hoff equation, the pK_a value of Tris changes from 8.06 at 25 °C to 6.07 at 130 °C [19]. By changing the inputs in the model, it is possible to simulate the effect of temperature and pH for another CD complex and/or buffer.

Multiple inputs are required based on thermodynamic data. For many buffers, the thermodynamic quantities are well-established and can easily be found in the literature, e.g. a table of thermodynamic values of many buffers have been published [26]. Besides, physico-chemical properties, e.g. pK_a values of the guest molecules, are often determined early during drug development. This means that even though the model appears to require many inputs, most of the inputs should be available for formulation scientists, and it would require limited experimental efforts to collect missing information.

4.3. Model validation with data for β-CD:ibuprofen complex

Based on the model approach presented above, it was possible to estimate K_B in the pH range 3.5–5.5 at any given temperature by using the thermodynamic quantities K, ΔH and ΔCp for the neutral and ionized species obtained by ITC data. The results showed good agreement

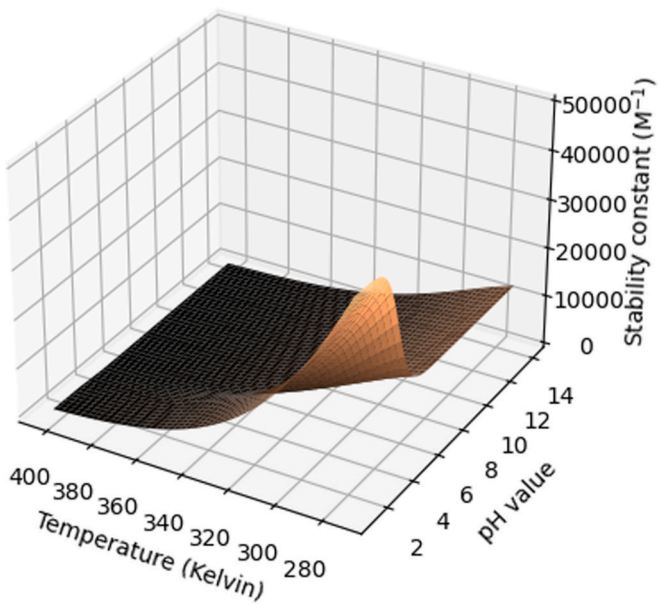

Fig. 4. Surface plot of K_B (M^{-1}) as a function of temperature (kelvin) and pH for the β-CD:ibuprofen complex.

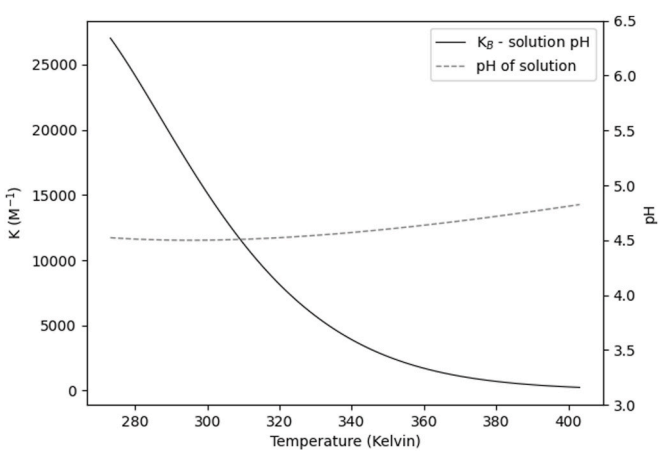

Fig. 5. Simulated stability constant (K_B, black line) as a function of temperature for β-CD:ibuprofen in acetate buffer with an initial pH value of 4.5 at 25 °C, considering that the pH of the solution (grey dashed line) depends on $pK_{a,Buffer}$.

between the values calculated by the model and the ITC data obtained at 15, 25, 40 and 55 °C at six pH values (Fig. 6). ITC data can be expected to have a precision of approximately 3% [33]. Also, binding enthalpies from ITC are shown to agree with the temperature dependency of the binding free energy as described by van't Hoff [34]. Thus, using ITC data as inputs yield very accurate predictions, and should be used if very accurate data is needed. Small, systematic discrepancies with a maximum magnitude of 7*10^2 M^{-1}, which corresponds to approximately 5% deviation, were seen between model calculations and ITC data at pH 4.0 and 5.5. These may have occurred due to slight errors in the initial pH of the solution or the $pK_{a,\text{guest}}$ used for the calculations. Uncertainty in the $pK_{a,\text{guest}}$ value or the pH value of the solution will affect the certainty of the stability constants calculated by the model. It is worth mentioning that obtaining exact pK_a values from the literature can be difficult, e.g. for ibuprofen the pK_a value has been reported in the range from 4.27 to 5.20 [35,36]. In this study, the pK_a value of ibuprofen was set at 4.53 based on an ITC determination [27]. Also, exact determinations of $K_{CD:Ibu}$ and $K_{CD:Ibu}$ are paramount for the calculation of the stability constant as a function of pH.

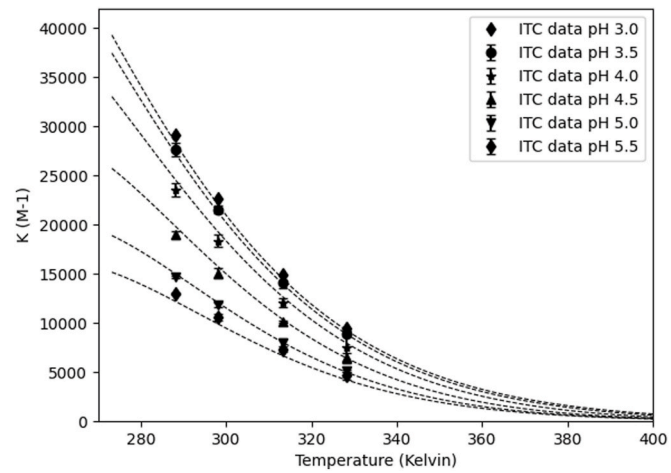

Fig. 6. Stability constants K (M^{-1}) as a function of temperature (kelvin) for β-CD:ibuprofen complex determined by ITC in the pH range 3.0–5.5 and the temperature range 15–55 °C (data points) and calculated stability constants based on the model with inputs from Table 1 (dashed line).

5. Conclusions

A model for prediction of the stability constant for CD complexes as a function of pH and temperature was presented. The model was used to predict the stability constant for β-CD:ibuprofen complex. The model was based on; 1) the van't Hoff equation, 2) the Henderson-Hasselbalch relation and 3) the stability constant as a function of pH. Multiple inputs were required, many of which are typically determined during early drug development, and thus readily available for the formulation scientists. The agreement between model and ITC data was excellent, confirming the accuracy of the model. The model presented in this work may be a useful tool for formulation scientists, as it enhances the understanding of the physicochemical properties over a range of pH values and temperatures through graphical outputs. Based on the predictions made by the model, the formulation scientists can experimentally test the formulation under relevant conditions.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jddst.2021.102675.

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