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Influence of lipophilicity on drug–cyclodextrin interactions: A calorimetric study

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ABSTRACT

This study presents a systematic investigation of the interaction of three functionally related drugs, ibuprofen, ketoprofen and flurbiprofen, with two distinct forms of cyclodextrin at three specific temperatures, 298, 303 and 310 K using isothermal titration calorimetry (ITC). Although all three pharmaceutical compounds have similar p*K*a values, they exhibit widely differing lipophilicities. While previous authors have presented data regarding the binding of flurbiprofen and ibuprofen with β-cyclodextrin, this is the first report of the interaction of all three drug substances with β-cyclodextrin and 2-(hydroxypropyl)-β-cyclodextrin at controlled pH and temperature. For all scenarios, the associated changes in Gibbs free energy, enthalpy and entropy are presented alongside the stoichiometry and binding constants concerned. In all cases the binding was found to occur at a 1:1 ratio with an associated negative enthalpy and Gibbs free energy with the formation of the complex enthalpically, rather than entropically driven. The data further demonstrates a clear relationship between the thermodynamic behaviour and log *P* of the drug molecules. This work confirms the suitability of ITC to determine thermodynamic data for drug–cyclodextrin complex formations and provides an insight into the selection of appropriate cyclodextrins for bespoke pharmaceutical formulations.

1. Introduction

A significant proportion of pharmaceutical compounds have limited aqueous solubility which, in turn, restricts the variety of potential formulations that can be developed. Several solutions to this problem exist including surfactant enhanced solubilisation and, in the last 20 years, the introduction of cyclodextrin-based compounds. Cyclodextrins are enzymatically modified starches consisting of glucopyranose units arranged in a ring. The combination of a cyclodextrin and drug molecule gives rise to a guest–host inclusion complex which in many cases produces an increase in the aqueous drug solubility. It has been found that a pre-formed drug–cyclodextrin complex when placed in aqueous solution will release the drug molecule through a three-stage process of dissolution, dissociation and recrystallisation [1]. Dissolution involves many changes in the intermolecular forces experienced by the complex and requires a negative net change in Gibbs free energy for the process to occur spontaneously. The process of dissolution is often well characterised, yet for this complex system it is the subsequent drug dissociation stage that is of thermodynamic significance. Many pharmaceutical compounds have previously been successfully complexed with a variety of cyclodextrin-based structures [2–4] including several commercial products. In addition, many modifications have been made to the naturally occurring α,β and γ-cyclodextrins to enhance their complexation characteristics [5,6]. One factor often investigated is the size of the cavity in the cyclodextrin structure which directly correlates with the size of the guest molecule [7]. In the majority of cases the host (drug)–guest (cyclodextrin) ratio is 1:1, although exceptions have been documented [8]. This work focuses on investigating two cyclodextrin-based structures, namely β-cyclodextrin and 2-(hydroxypropyl)-β-cyclodextrin. The latter has a hydroxypropyl group located at the C6 position on each sugar residue. To date, only very limited research has focused on probing the thermodynamics of drug–cyclodextrin complexes [9,10] despite the importance this plays in formulation potential, product stability and ultimately drug dissociation *in vivo*. For example, previous work has confirmed the driving force for the thermodynamics of the binding of benzene to β-cyclodextrin to be the hydrophobic effect [11], yet the same approach is not routinely applied for drug complexes. Extensive research has been undertaken to investigate the thermodynamics of non-pharmaceutical, chemical-cyclodextrin complex formations. These include complexes with hexanol [12], cyclohexanol [13], butanediol [14], adamantane [15], benzoic acid [16,17], amino acids [18,19], glucose [20], aspartame [21] and many others [22–25].

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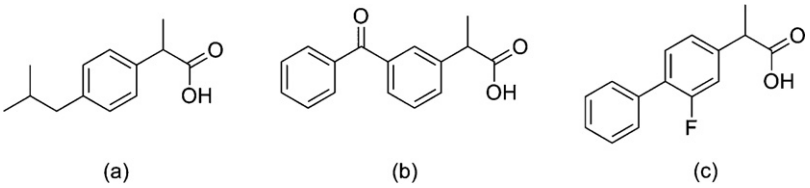

Fig. 1. Chemical structures of ibuprofen (a), ketoprofen (b) and flurbiprofen (c). All compounds were racemic mixtures.

In investigating the complexation process it is important to appreciate the binding mechanism, specifically that the more lipophilic part of the molecule will enter the cavity whereas the more hydrophilic part will remain exposed to bulk solvent. The complex formation process in aqueous solutions is a series of thermodynamic processes involving direct guest–host interactions alongside rearrangement, removal and addition of water for both the guest and host molecules [26–28]. Bonding is usually attributed to van der Waals and hydrophobic interactions [29,30] and in some cases, hydrogen bonding and steric effects [31,32]. Previous research has utilised a variety of techniques to investigate the thermodynamic processes involved in complex formation [33]. Spectroscopic techniques such as electronic absorption [34], circular dichroism [35], fluorescence and nuclear magnetic resonance [36] have been shown to provide thermodynamic data for such complexes. Chromatography has also assisted in the determination of thermodynamic parameters including liquid chromatography [37] and capillary electrophoresis [38] along with potentiometry [39] and solubility based determinations [40]. However, each of these techniques has their own disadvantages which can hinder establishing an accurate and precise thermodynamic profile for the complexation process. For example, some guest molecules lack a suitable chromophore, thus requiring the addition of a 'marker' for UV spectroscopic analysis. In addition, it can be hard to acquire sufficient quantities of data on cyclodextrin-based complexes using chromatography, as these interactions are comparatively weak in nature [37].

Calorimetry provides many advantages over alternative methods to fully characterise the thermodynamic processes involved in the complexation event. Uniquely, the change in enthalpy (ΔH) associated with the formation of the complex can be measured directly. This, combined with the equilibrium constant, can provide thermodynamic information including changes in the Gibbs free energy, entropy and heat capacity for any guest–macrocyclic ligand interaction [41]. In particular, microcalorimetry introduces significant advantages when attempting to characterise comparatively weak interactions, such as those encountered in this work. Isothermal titration calorimetry (ITC) is a differential technique incorporating direct enthalpic measurement as two solutions are mixed and they subsequently interact [42]. Despite the significant benefits offered by ITC in determining thermodynamic information for drug–cyclodextrin complexes, little has been reported in this area [10]. This is particularly surprising considering the importance of understanding the complexation process as this is undoubtedly linked with the subsequent drug release *in vivo*. It is envisaged that by investigating and characterising the thermodynamics of the initial complex formation event *in vitro* it will be possible to tailor the final drug dissolution profile, and thus maximising the efficacy of the pharmaceutical formulation.

The work presented here is an investigation into the potential application of ITC to thermodynamically differentiate the complex formation for three guest molecules of pharmaceutical interest with two distinct forms of cyclodextrin over a range of temperatures. The complex formation event for the initial binding process *in vitro* is considered in the knowledge that the cyclodextrin will subsequently release the drug *in vivo*, thus justifying the inclusion of studies at the relevant physiological temperature (310 K).

2. Materials and methods

2.1. Materials

β-Cyclodextrin, 2-(hydroxypropyl)-β-cyclodextrin, ibuprofen (Fig. 1a), ketoprofen (Fig. 1b), sodium dihydrogen phosphate and disodium hydrogen phosphate were purchased from Sigma (Dorset, UK). Flurbirpofen (Fig. 1c) was purchased from TCI Europe (Zwijndrecht, Belgium). All reagents were of 99+% purity, racemic and used as received.

2.2. Method

All ITC experiments were conducted using a MicroCal VP-ITC MicroCalorimeter. The sample and reference cells were enclosed in an adiabatic outer shield jacket and were, during all experiments, completely filled. It should be noted that the sample cell fill volume was 1.8 mL with a 1.4 mL working cell volume. Experiments initially involved a primary temperature equilibration period for the sample in the cell, followed by a secondary equilibration with the syringe in place. Periodic calibration was conducted to confirm the validity of the data produced in this work with all calibration results in an acceptable range. Chemical calibration utilised the complex formation between barium and 1,4,7,10,13,26-hexaoxacycloöctadecane (18-crown-6). For all experiments the reference cell was filled with degassed pH 8 phosphate buffer with no significant difference in mass recorded before and after degassing. Stirring speed was maintained at 300 rpm to ensure thorough mixing throughout the experiment. Twenty-nine consecutive injections were then injected into the sample cell, each of 10 μL volume with sufficient time allowed between injections. Drug concentrations in the syringe varied in the range 0.01–0.03 M with cyclodextrin concentrations in the sample cell in the range 0.0005–0.001 M. Software provided with the VP-ITC (Origin) was used to analyse the data using standard fitting models to calculate reaction stoichiometry (n), binding constant (K_b) and enthalpy (ΔH). The change in Gibbs free energy was calculated using the derived K_b value and the van't Hoff isotherm with the change in entropy subsequently calculated using the established equation (Eq. (1)).

$$\Delta G = \Delta H - T\Delta S \quad (1)$$

All six possible drug–cyclodextrin complexes were each studied at three temperatures, namely 298, 303 and 310 K to determine the significance of temperature on the complex formation. All experiments were repeated in a minimum of triplicate for statistical validation with the contributions from heats of dilution subtracted from all isotherms.

3. Results and discussion

ITC was used to determine the stoichiometry (n), binding constant (K_b) and change in enthalpy (ΔH) for a total of 18 complexation events. From these values it was possible to calculate

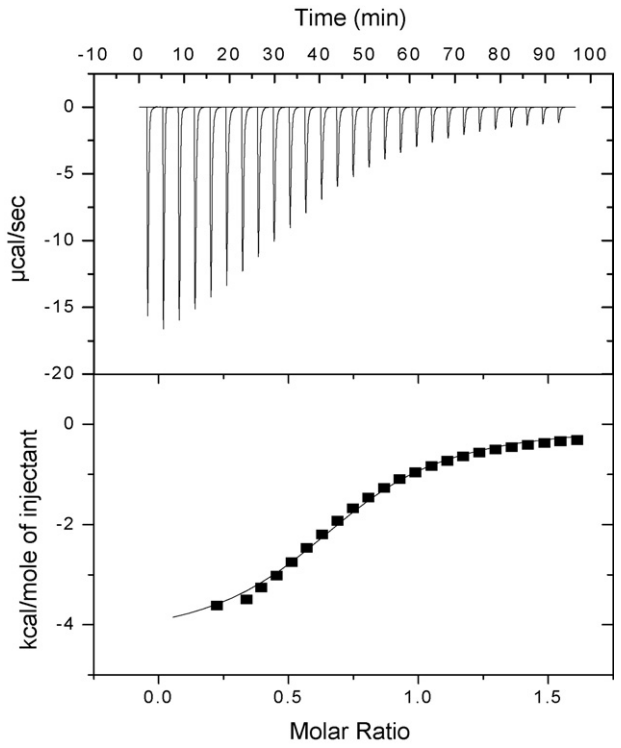

Fig. 2. An example of experimental data acquired using ITC for the binding of ibuprofen with β-cyclodextrin at 310 K in pH 8 phosphate buffer together with the corresponding binding isotherm.

associated thermodynamic properties, i.e. changes in Gibbs free energy (ΔG) and entropy (ΔS) for each complex formation. Experimental data for a typical ITC result can be seen in Fig. 2 alongside the corresponding binding isotherm.

The titration curve displayed in Fig. 2 is for the binding of ibuprofen with β-cyclodextrin at 310 K and can be seen to reach saturation, at which point the cell signal can be solely ascribed to the enthalpy of dilution. Fig. 2 also includes the binding isotherm from which the stoichiometry, binding constant and change in enthalpy were determined. Using these data, the van't Hoff isotherm and Eq. (1) facilitated the elucidation of the full thermodynamic profile for this particular scenario. A similar approach was then adopted for other permutations considered in this work.

Previously, only the interaction of flurbiprofen and β-cyclodextrin at 298 K in pH 8 buffer has been published with an enthalpy of $-17\,\mathrm{kJ\,mol^{-1}}$ [10]. For this particular process we obtained values of $-15\,\mathrm{kJ\,mol^{-1}}$ across the range of temperatures studied which correlates well with the published enthalpy and suggests an unchanged binding mechanism. The trend for the binding constant of this system to decrease with an increase in experimental temperature is also in agreement with published values. In addition, experimental data has recently been published for ibuprofen and β-cyclodextrin at 298 K [43] which again provided similar values to those presented in this work with the small discrepancy between enthalpic and binding constant values, a consequence of the difference in aqueous buffer composition and pH. In this work several variables have been systematically considered: the choice of drug, the choice of cyclodextrin and the experimental temperature. A summary of the calorimetrically measured and subsequently calculated values is presented in Table 1.

In all scenarios investigated it can be clearly seen that the stoichiometry remains constant as a 1:1 ratio despite differences in the sizes of the drug molecules (from comparatively small ibuprofen to the larger ketoprofen) and the degree of steric hindrance of the two cyclodextrins.

The derived binding constant (K_b) can be represented by the following equation for a drug binding with cyclodextrin (CD) (Eq. (2)):

$$\mathrm{DRUG} + \mathrm{CD} \rightleftharpoons \mathrm{DRUG} \times \mathrm{CD} \quad (2)$$

$$K_b = \frac{[\mathrm{DRUG} \times \mathrm{CD}]}{[\mathrm{DRUG}][\mathrm{CD}]} \quad (3)$$

For ketoprofen ($\log P = 0.97$ [44]) at 298 K, the binding constant is $1.09 \times 10^3\,\mathrm{dm^3\,mol^{-1}}$. For ibuprofen ($\log P = 3.6$ [44]) at 298 K, the binding constant is $8.34 \times 10^3\,\mathrm{dm^3\,mol^{-1}}$, while for flurbiprofen ($\log P = 4.2$ [45]) at 298 K, the binding constant is $14.93 \times 10^3\,\mathrm{dm^3\,mol^{-1}}$. Based on these data, there is a clear correlation between the lipophilicity of the drug molecule and the experimentally determined binding constant. Moreover, for the ketoprofen and ibuprofen variations of the experimental temperature from 298 to 303 to 310 K result in only a small change in the binding constant, whereas for flurbiprofen a more pronounced trend of decreasing binding constant with increasing temperature

Table 1
Data for the three drugs complexed with the two forms of β-cyclodextrin at three temperatures using ITC including apparent thermodynamic properties. All data presented is an average of a minimum of three repeat experiments.

Drug	Cyclodextrin	Temperature (K)	Drug:CD ratio	$10^3 K_b$ ($\mathrm{dm^3\,mol^{-1}}$)	ΔH ($\mathrm{kJ\,mol^{-1}}$)	ΔG ($\mathrm{kJ\,mol^{-1}}$)	ΔS ($\mathrm{kJ\,K^{-1}\,mol^{-1}}$)
Ibuprofen	β-CD	298	1:1	8.34 (±0.6)	−10.6 (±0.4)	−22.4 (±0.2)	0.04 (±0.002)
		303	1:1	6.72 (±0.3)	−12.2 (±0.6)	−22.2 (±0.1)	0.03 (±0.002)
		310	1:1	9.51 (±0.5)	−12.8 (±0.2)	−23.6 (±0.3)	0.03 (±0.002)
	2-(Hydroxypropyl)-β-CD	298	1:1	1.58 (±0.1)	−7.2 (±0.3)	−18.2 (±0.1)	0.04 (±0.002)
		303	1:1	2.10 (±0.8)	−8.9 (±1.0)	−19.3 (±0.8)	0.03 (±0.002)
		310	1:1	2.52 (±0.7)	−11.1 (±1.1)	−20.2 (±0.9)	0.03 (±0.002)
Ketoprofen	β-CD	298	1:1	1.09 (±0.1)	−14.2 (±1.1)	−17.3 (±0.1)	0.01 (±0.001)
		303	1:1	1.14 (±0.1)	−16.0 (±0.5)	−17.7 (±0.2)	0.01 (±0.002)
		310	1:1	1.14 (±0.1)	−17.4 (±0.1)	−18.1 (±0.1)	0.01 (±0.001)
	2-(Hydroxypropyl)-β-CD	298	1:1	0.48 (±0.1)	−10.2 (±0.1)	−15.3 (±0.5)	0.02 (±0.001)
		303	1:1	0.72 (±0.1)	−10.8 (±0.9)	−16.7 (±0.1)	0.02 (±0.002)
		310	1:1	0.82 (±0.1)	−12.9 (±0.2)	−17.3 (±0.1)	0.01 (±0.001)
Flurbiprofen	β-CD	298	1:1	14.93 (±0.6)	−15.1 (±1.4)	−23.8 (±0.1)	0.03 (±0.002)
		303	1:1	8.83 (±0.8)	−15.0 (±1.9)	−22.9 (±0.6)	0.03 (±0.002)
		310	1:1	5.44 (±0.4)	−15.0 (±0.6)	−22.2 (±0.1)	0.02 (±0.002)
	2-(Hydroxypropyl)-β-CD	298	1:1	5.29 (±0.1)	−15.8 (±0.1)	−21.2 (±0.1)	0.02 (±0.002)
		303	1:1	6.46 (±0.1)	−16.8 (±0.1)	−22.1 (±0.1)	0.02 (±0.001)
		310	1:1	6.53 (±0.1)	−18.5 (±0.2)	−22.6 (±0.1)	0.01 (±0.001)

is observed. The aforementioned positive correlation between the log *P* of drug substance and binding constant may well be a reflection of the greater affinity of the lipophilic compounds towards the less polar internal cavity of cyclodextrin as compared with water. For ketoprofen the binding constant appears to remain static over the temperature range studied. For ibuprofen, the trend in binding constants with temperature is also largely unchanged within experimental error. Therefore, in both cases temperature has a minimal effect on the equilibria for the formation of the drug–cyclodextrin complex. At all temperatures, there is significantly more complexed flurbiprofen than free drug. However, at elevated temperatures this trend implies that more drug exists uncomplexed in the aqueous environment.

As expected, the same trends are observed for the apparent changes in Gibbs free energy for the β-cyclodextrins, based on their determination from the van't Hoff isotherm. Overall, all changes in Gibbs free energies are negative and thus favour complex formation.

Overall, the binding constants appear smaller for 2-(hydoxypropyl)-β-cyclodextrin compared with β-cyclodextrin. Again, binding constants increase with increasing lipophilicity of the drug substance. No similar trend in decreasing binding constant with increasing temperature was observed for flurbiprofen with 2-(hydroxypropyl)-β-cyclodextrin. With respect to the changes in Gibbs free energies for the 2-(hydroxypropyl)-β-cyclodextrins, they are all negative, yet less so than the values observed for the β-cyclodextrins.

With respect to changes in enthalpy it can be seen that for all complexation events a significantly negative value is observed and it can therefore be said that the process is exothermic and enthalpically driven. The magnitude of the values is as expected for such complexation phenomena [10]. The exception is once again flurbiprofen, where there is no variation in enthalpy change for the β-cyclodextrin over the temperature range and for 2-(hydroxypropyl)-β-cyclodextrin, the enthalpy for the process is slightly larger and increases with temperature. In addition to lipophilic differences, alternative explanations for the unique behaviour of flurbiprofen can be hypothesised. For example, the presence of fluorine within the compound may have a subsequent impact on hydrogen bonding potential both with water and the host cyclodextrin. For all scenarios it can be seen that the change in entropy is comparatively small.

4. Conclusions

In summary, this work presents data concerning the thermodynamic processes associated with the complexation of three drugs of differing lipophilicity with two forms of cyclodextrin over a range of temperatures. Analysis of the data confirms that all complexes are formed in a 1:1 stoichiometric ratio and furthermore, suggests that there is a positive correlation between drug lipophilicity and the measured binding constant. In general, all complexes formed were thermodynamically favourable, i.e. all displayed a negative change in Gibbs free energy. Overall, the most favourable complexation process was that for flurbiprofen and β-cyclodextrin at 298 K ($\Delta G = -23.8$ (± 0.1) kJ mol^{-1}). In addition, it is an enthalpic rather than an entropically driven complex formation process.

In conclusion, ITC offers the potential for an informed excipient choice based on an understanding of the relationship between thermodynamic parameters and their relationship with drug lipophilicity, i.e. ITC may help in the selection of specific drugs with natural or derivatised cyclodextrins from a range of possibilities based on the acquisition of thermodynamic data. This tailored selection process could ultimately help in the development of superior pharmaceutical formulations with optimal drug release.

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