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Interactions of theophylline with cyclodextrins in water

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Using calorimetry, ^{1}H NMR and solubility methods, this thermodynamic study of the interactions of theophylline with α-, β- and hydroxypropyl-β-cyclodextrins in water at 298.15 K shows the formation of weak entropically stabilised molecular complexes only with β-cyclodextrin.

Theophylline (1,3-dimethylxanthine, Figure 1), a poorly water soluble purine alkaloid, is widely used in medicine.[1,2] The use of pure theophylline is limited by its very fast absorption and conversion into inactive metabolites. Moreover, theophylline in high doses causes unwanted side effects.[3] To remove these disadvantages, coated controlled-release theophylline tablet formulations have been obtained in recent years. Acrylic and ion-exchange resins, paraffin, ethyl cellulose[4–6] and cyclodextrins (CDs)[7–9] were proposed as coating and encapsulating materials. The use of CDs as solubilising and stabilising agents is based on their ability to form inclusion complexes with organic substrates.[10] The most commonly used α-, β- and γ-cyclodextrins consist of six to eight glucopyranose units, respectively, and possess hydrophilic exterior and hydrophobic internal cavity. Placing inside the CD molecular cavity the substrate can considerably improve physico-chemical and pharmacological properties (solubility, stability, bioactivity, *etc.*).

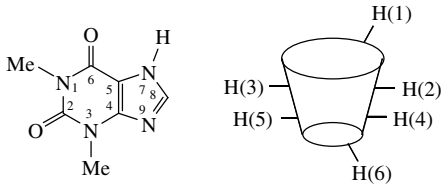

Figure 1 Structures of theophylline and CD.

In particular, the influence of β-CD and its derivatives on the dissolution properties of theophylline was studied by Horiuchi *et al.*[8] The pH-independent theophylline release from pharmaceutical formulations is accelerated by β-CD, while it is decelerated by heptakis(2,6-di-*O*-ethyl)-β-CD. The release of theophylline from carboxymethylethyl-β-CD complex was found pH-dependent and increased with pH. The enhancement of aqueous solubility of theophylline in the presence of β-CD at 293 K observed by Pina *et al.*[11] was attributed to the complex formation process, and the stability constant of β-CD/theophylline complex $K = 1.62$ dm^3 mol^{-1} was reported. The effect of β-CD on the solubility and bioavailability of theophylline was also investigated by Ammar *et al.*[12] A clear difference in the solubility and pharmacokinetic parameters of free and complexed theophylline was revealed. The improvement in the solubilization and bioavailability of theophylline was explained by its 2:1 complexation with β-CD.

Note that the reported stability constants of the β-CD/theophylline complex vary from 1.62[11] to 130[13] dm^3 mol^{-1}. Information on the binding mode and thermodynamic parameters of complex formation (ΔH_c and ΔS_c) of theophylline with CDs is absent. Therefore, the aim of this work was to reveal the ability of different CDs discriminating by the cavity diameter and the availability of substituents to form inclusion complexes with theophylline in water.

The interactions of theophylline with α-CD (Fluka), β-CD (Fluka) and hydroxypropyl-β-CD (HP-β-CD, Aldrich) were studied at 298.15 K by calorimetry and ^{1}H NMR. The solubilization effect of β-CD and HP-β-CD was additionally examined. Forming thermodynamically stable crystallohydrates the amount of water in the crystal lattices has been determined by thermogravimetry and taken into account at calculation of concentration of the solutions. Randomly substituted HP-β-CD has the average substitution degree 0.6 per glucose unit. All solutions were prepared by weight using doubly distilled deionised water.

The thermodynamic parameters of theophylline-CD interactions were determined by calorimetry. The enthalpies of solution of α- and β-CD in water and aqueous solutions of theophylline were measured using an isothermal calorimeter.[14] The experimental error of heat effect measurements was 0.6%. The concentration of CDs corresponded to the constant value [(1.70±0.05)×10^{-3} mol kg^{-1}], whereas the theophylline concentration was changed from 0 to 0.03 mol kg^{-1}. The enthalpies of transfer of CD from water to aqueous solution of theophylline [$\Delta_{tr}H$(w → w + y)] were calculated on the basis of experimental data by the following way:

$$\Delta_{tr}H(\mathrm{w} \rightarrow \mathrm{w} + \mathrm{y}) = \Delta_{sol}H(\mathrm{w} + \mathrm{y}) - \Delta_{sol}H(\mathrm{w}), \quad (1)$$

where $\Delta_{sol}H$(w) and $\Delta_{sol}H$(w + y) are the enthalpies of CD solution in pure water (w) and aqueous solution of theophylline (w + y), respectively. The concentration dependences of $\Delta_{tr}H$(w → w + y) are presented in Figure 2.

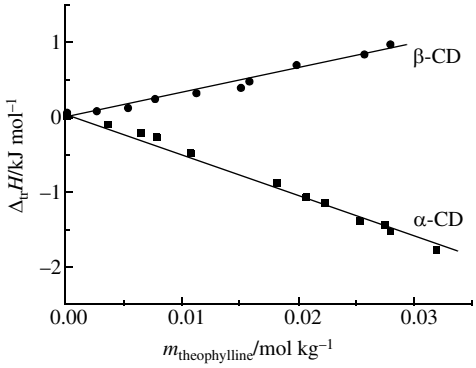

Figure 2 Enthalpy of transfer of α- and β-CD from water to aqueous solutions of theophylline *vs.* theophylline concentration at 298.15 K.

Table 1 Chemical shift changes of theophylline and CD protons (D_2O, 298.15 K).

Theophylline + CD	$\Delta\delta^a$/ppm								
	Theophylline protons			CD protons					
	H(1)	H(3)	H(8)	H(1)	H(2)	H(3)	H(4)	H(5)	H(6)
Theophylline + α-CD	0.00	–0.01	0.00	0.00	0.00	0.00	–0.01	0.00	0.00
Theophylline + β-CD	0.04	0.06	0.03	–0.01	0.00	–0.01	0.00	0.00	0.00
Theophylline + HP-β-CD	0.00	0.01	0.00	—[b]	—	—	—	—	—

[a]–$\Delta\delta = \delta_{\text{theophylline + CD}} - \delta_{\text{free theophylline}}$. [b]The ^{1}H NMR spectrum of HP-β-CD was not considered due to the peak overlapping.

The linear character of the dependences shown in Figure 2 points to the weak interactions of theophylline with α- and β-CD. The weak interactions were characterised by the enthalpic virial coefficients obtained according to the McMillan–Mayer theory:[15,16]

$$\Delta_{tr}H(w \rightarrow w + y) = 2h_{xy}m_y + 3h_{xyy}m_y^2 + 3h_{xxy}m_x m_y + \ldots, \quad (2)$$

where m_x and m_y are the molalities of CD and theophylline, respectively; h_{xy}, h_{xyy} and h_{xxy} are the enthalpic coefficients of pair and triplet interactions. Since the CD concentration was very low, the last term in equation (2) can be neglected. Thus, equation (2) can be easily transformed into equation (3):

$$\Delta_{tr}H(w \rightarrow w + y)/m_y = 2h_{xy} + 3h_{xyy}m_y, \quad (3)$$

from which h_{xy} can be calculated by the linear least squares analysis.

Interactions of theophylline with α-CD are characterised by a negative enthalpic coefficient (h_{xy} = –10695±2411 J kg mol^{-2}). In contrast, a positive enthalpic coefficient (h_{xy} = 12139±722 J kg mol^{-2}) corresponds to interactions of theophylline with β-CD consisting of seven glucose units. Thus, the size of the macrocyclic cavity defines h_{xy}.

The enthalpic coefficients are the sum of enthalpy changes caused by solute–solvent and solute–solute interactions.[17] It is known[18] that the interactions of CDs with guest molecules have a non-covalent nature and include van der Waals, electrostatic and hydrophobic interactions, as well as hydrogen bonding. The calculations of the theophylline molecule geometry performed using the HyperChem v.7.01 program with AM1 force field showed that the theophylline molecule is 7.7 Å in length and 6.0 Å in height. Consequently, the internal diameter of the α-CD cavity (5.7 Å[19]) is too small for inclusion of the theophylline molecule. Probably, prevalence of the exothermal effects and the negative h_{xy} value of α-CD interactions with theophylline are determined by van der Waals interactions and hydrogen bonding. The internal diameter of β-CD cavity (7.8 Å[19]) is suitable for accommodation of the theophylline molecule. However, the formation of stable inclusion complex was not noted in this case. Small endothermic effects ($h_{xy} > 0$) are mainly caused by the dehydration of theophylline and β-CD molecules.

^{1}H NMR measurements were additionally performed at 298.15±0.10 K in D_2O solutions using a Bruker AC-200 spectrometer operating at 200 MHz. Cyclohexane was used as an external reference. The error of the chemical shift determination was not greater than 0.01 ppm.

^{1}H NMR spectra of theophylline (0.004 mol kg^{-1}) alone and in the presence of the excess amounts of CDs (0.12, 0.013 and 0.16 mol kg^{-1} for α-CD, β-CD and HP-β-CD, respectively) were recorded. The ^{1}H NMR spectrum of theophylline in D_2O consists of the signals of H(1), H(3) and H(8) protons (Figure 1), the chemical shift changes of which induced by addition of CDs of the indicated above concentration are summarised in Table 1. No chemical shift changes were observed in the presence of α-CD and HP-β-CD. Thus, the interactions of theophylline with α-CD and HP-β-CD are not accompanied by complex formation. The measurable $\Delta\delta$ values obtained for interaction of theophylline with β-CD indicate the complex formation in this system. The marginal changes (Table 1) in the ^{1}H NMR spectrum of α- and β-CD (0.005 mol kg^{-1}) induced by the addition of theophylline (0.025 mol kg^{-1}) also point out the binding which is too weak to quantitative analysis by ^{1}H NMR.

Finally, the influence of β-CD and HP-β-CD on the water solubility of theophylline was investigated. For this purpose, an excess amount of theophylline was added to aqueous solutions containing β-CD (0–0.014 mol kg^{-1}) and HP-β-CD (0–0.02 mol kg^{-1}). The solutions were continuously stirred at 298.15 K for 48 h until equilibrium was achieved. After equilibration the solutions were centrifuged at 298.15 K, and the solid phase was removed by filtration (Acrodisc CR syringe filter, PTFE, 0.2 μm pore size) in a special temperature-controlled box. The concentration of theophylline was determined spectrophotometrically (Specord SF-46) at 273 nm (ε = 10552 kg mol^{-1} cm^{-1}). Note that the solubility of theophylline in pure water obtained in this work (0.0345 mol kg^{-1}) is in a good agreement with the value reported by Pérez-Tejeda *et al*. (0.035 mol dm^{-3}).[20]

The variation of theophylline solubility *versus* CD concentration is illustrated in Figure 3. The addition of β-CD slightly increases the theophylline solubility. According to Higuchi and Connors,[21] the linear solubility diagram observed for β-CD + theophylline system corresponds to 1:1 complex formation and can be described by the equation:

$$S = S_0 + KS_0C_{CD}, \quad (4)$$

where S and S_0 are the solubility of theophylline in CD solution and pure water, respectively; K is the stability constant of the complex; C_{CD} is the CD concentration. The calculated from equation (4) by the linear least squares analysis the stability constant of theophylline/β-CD complex is 1.8±0.1 kg mol^{-1}.

Note that HP-β-CD has no influence on the theophylline solubility (Figure 3). Probably, the bulky hydroxypropyl groups, which partially substitute the OH groups surrounding the β-CD cavity, raise the steric hindrance and prevent complex formation. It is interesting to compare the K value obtained with

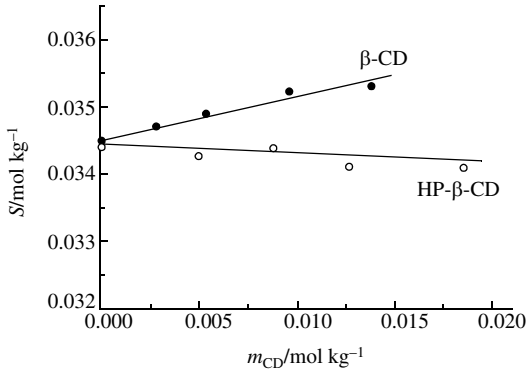

Figure 3 Solubility of theophylline in aqueous solutions of β-CD and HP-β-CD at 298.15 K.

published data.[11,13] As was found by Wei *et al.*,[13] theophylline forms complexes with both β-CD and HP-β-CD in a Britton–Robinson buffer solution at 293 K. The stability constants calculated from the fluorimetric measurements are 130.0 and 233.3 $dm^3\ mol^{-1}$ for β-CD and HP-β-CD, respectively. These values are in disagreement with our results and could be explained by different experimental conditions. Probably, the composition of the Britton–Robinson buffer composed of the equimolar amounts of 0.04 M acetic, phosphoric and boric acids adjusted to the required pH with NaOH has an influence on the binding constants. Similar solvent effects were observed earlier.[22] For instance, the addition of inorganic salts (such as LiCl and NaCl) leads to an increase of the stability constant of the 1:1 complex of theophylline with methyl cinnamate, whereas the enhancement of the organic cosolvent amount (*e.g.*, MeCN, MeOH and $C_4H_8O_2$) leads to decreasing K values. On the other hand, our K value is in an agreement with the value (1.62 $dm^3\ mol^{-1}$) obtained by Pina and Veiga[11] for aqueous medium and $T = 293$ K. The minor enhancement of K values with temperature indicates that the binding of β-CD with theophylline should be accompanied by small endothermic effects. This assumption is confirmed by the calorimetric data, namely, by the positive value of h_{xy}. Thus, the formation of a weak molecular complex between β-CD and theophylline is governed by the entropic term, which should be positive. Consequently, solvent effects play an important role in complexation.

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