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Thermodynamics of prednisone complexation in β-cyclodextrin

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Abstract

The binding constant and stoichiometry for the complexation of prednisone with β-cyclodextrin in aqueous solution, and the Gibbs energy for the transfer of β-cyclodextrin and prednisone from water to chloroform are reported. These data are used to evaluate, from the thermodynamic point of view, the influence of β-cyclodextrin on the transfer of prednisone from aqueous to non-aqueous phase.

INTRODUCTION

The ability of cyclodextrins to form inclusion complexes with a large variety of substances has promoted research to find applications for them in the design of drug formulations [1]. It has been found that cyclodextrin complexation improves stability [2] and bioavailability [3–7] of many drugs that are poorly soluble in water.

The bioavailability of an orally administered drug is controlled by its solubility and dissolution rate in the gastrointestinal fluid, and by the transfer rate of the dissolved drug through the absorption barrier into the blood.

Cyclodextrin complexation represents a true molecular micro-encapsulation that transforms the drug into a more hydrophilic compound, where the drug molecules are isolated from one another and dispersed, on the molecular level, in an oligosaccharide matrix; therefore, the solubility and dissolution rate of the cyclodextrin-complexed drug are higher than those of the non-complexed drug.

β-Cyclodextrin (βCD) is an appropriate cyclodextrin for oral drug formulations, and it has no toxic effects [8, 9]. βCD is resistent to

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saliva-amylase and acidic hydrolysis; it is metabolized by the bacterial flora in the colon [10, 11]. Therefore, a drug complexed in βCD is protected before absorption; it reaches the small intestine in complexed form, and it is released there from the βCD cavity by dissociation of the complex.

This paper is concerned with the determination of the thermodynamic parameters that control the bioavailability of prednisone orally administered in the form of βCD complex, in order to study the influence of βCD complexation on the bioavailability of this drug.

Prednisone (1,4-pregnadiene-17α,21-diol-3,11,20-trione) is a synthetic corticosteroid, five and three times more active than cortisone and hydrocortisone respectively, and less toxic. However, its low water solubility limits its bioavailability.

MATERIALS AND METHODS

β-Cyclodextrin was used as supplied by Merck, without further purification. The molecular weight was considered as 1326 g mol^{-1}, after determining that solid samples contain 14.4% of hydration water. Prednisone was from Fluka. Reagent-grade chloroform was used as a membrane-like solvent.

Calorimetric measurements were performed in the flow-mixing vessel of a thermal activity monitor (ThermoMetric AB, Sweden). The microcalorimetric vessel was calibrated electrically. Two peristaltic pumps (Masterflex, Cole Parmer) were used for the flow of the reactant solutions. The flow rate was 0.445 ml min^{-1} for βCD solutions, and 0.483 ml min^{-1} for prednisone solutions. The solubility of prednisone in water and in chloroform was determined spectrophotometrically (Hitachi U-200 spectrophotometer) at 240 and 250 nm.

All measurements were made at 298.15 K.

RESULTS AND DISCUSSION

The apparent binding constant and enthalpy change for formation of the βCD–prednisone complex in aqueous solution were calculated from calorimetric data, minimizing $\sum (P_{exp} - P_{calc})^2$ through the Levenverg–Marquardt procedure. Several stoichiometric models were used for minimization, but calorimetric data were only consistent with the model assuming 1:1 stoichiometry for the complex.

Values for the apparent binding constant, Gibbs energy, enthalpy and entropy are shown in Table 1.

The uncertainties assigned to the values for $\Delta H^{\ominus\prime}$ and K' are twice the standard deviation given by the minimization program (which is calculated

TABLE 1

Thermodynamic parameters for complexation of prednisone with β-cyclodextrin in aqueous solution at 298.15 K

K'	$\Delta G^{\ominus\prime}$	$\Delta H^{\ominus\prime}$	$\Delta S^{\ominus\prime}$
3944 ± 210	−20.52 ± 0.13	−28.46 ± 0.28	−26.6 ± 1.4

K' in l mol^{-1}; $\Delta G^{\ominus\prime}$ in kJ mol^{-1}; $\Delta H^{\ominus\prime}$ in kJ mol^{-1}; $\Delta S^{\ominus\prime}$ in J mol^{-1} K^{-1}.

as the square root of the diagonal elements of the covariance matrix). The uncertainty for $\Delta G^{\ominus\prime}$ was estimated by an error propagation equation, from the uncertainty in the apparent equilibrium constant. For the error assignment to the apparent entropy change, the maximum and minimum $\Delta S^{\ominus\prime}$ values that can be obtained by combination of the $\Delta G^{\ominus\prime}$ and $\Delta H^{\ominus\prime}$ values and their respective error limits, were calculated, and half this interval was considered as the uncertainty in $\Delta S^{\ominus\prime}$.

No heat production was detected when chloroform solutions of βCD and prednisone were mixed in the microcalorimeter; this suggests that there is no complexation in chloroform. This lack of complexation was confirmed

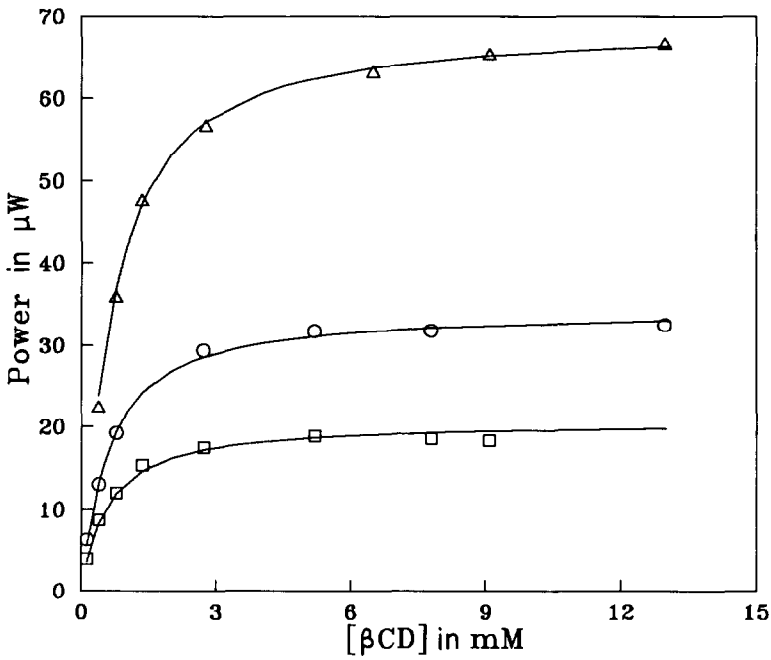

Fig. 1. Thermal power for prednisone complexation with β-cyclodextrin in aqueous solution. Comparison between experimental values (points) and calculated values (solid line) for 1:1 stoichiometry. Prednisone concentration: △, 0.3 mM; ○, 0.15 mM; □, 0.09 mM.

spectrophotometrically: no change in absorbance was observed when adding excess of βCD to chloroform solutions of prednisone at different concentration.

The apparent Gibbs energies of transfer of free βCD and free prednisone from water to chloroform, determined from solubility data in these solvents are $\Delta G_t^{\ominus\prime}(\beta\text{CD}) = 16.28\ \text{kJ mol}^{-1}$ and $\Delta G_t^{\ominus\prime}(\text{P}) = -9.37\ \text{kJ mol}^{-1}$.

The transfer of free βCD from water to non-aqueous phase is not thermodynamically favourable. This is in agreement with studies in which the blood level of βCD after oral administration was found to be almost negligible [12].

The Gibbs energy for transfer of the complex can be calculated by considering the cycle

$$\begin{array}{ccc} \text{P}_{(\text{aq})} + \beta\text{CD}_{(\text{aq})} & \xrightleftharpoons{\Delta G_c(\text{aq})} & \text{P}\text{–}\beta\text{CD}_{(\text{aq})} \\ \uparrow\downarrow \Delta G_t(\text{P}) \quad \uparrow\downarrow \Delta G_t(\beta\text{CD}) & & \uparrow\downarrow \Delta G_t(\text{P}\text{–}\beta\text{CD}) \\ \text{P}_{(\text{org})} + \beta\text{CD}_{(\text{org})} & \xrightleftharpoons{\Delta G_c(\text{org})} & \text{P}\text{–}\beta\text{CD}_{(\text{org})} \end{array}$$

$$\Delta G_t(\text{P}\text{–}\beta\text{CD}) = \Delta G_t(\text{P}) + \Delta G_t(\beta\text{CD}) + \Delta G_c(\text{org}) - \Delta G_c(\text{aq})$$

Because there is no complexation in chloroform, we could not determine $\Delta G_c^{\ominus\prime}(\text{org})$, but this indicates that the transfer of the drug in complexed form is not thermodynamically favourable, which from the therapeutic point of view is favourable, because only the free drug is biologically active.

The Gibbs energy value for transfer of prednisone from the complex

$$\text{P}\text{–}\beta\text{CD}_{(\text{aq})} \xrightleftharpoons{\Delta G_t^{\ominus\prime}(\text{P}_{\text{compl}})} \beta\text{CD}_{(\text{aq})} + \text{P}_{(\text{org})}$$

$$\Delta G_t^{\ominus\prime}(\text{P}_{\text{compl}}) = \Delta G_t^{\ominus\prime}(\text{P}) - \Delta G_c^{\ominus\prime}(\text{aq}) = 11.15\ \text{kJ mol}^{-1}$$

indicates that the drug is not transferred directly from the complex; the transfer of free prednisone, after dissociation of the complex in aqueous phase, is thermodynamically more favourable. Therefore, from the thermodynamic point of view, β-cyclodextrin complexation does not improve absoption directly, it could even retard it, because as concentration of free drug decreases by absorption, the complex dissociation equilibrium will shift toward complex formation, as βCD absorption is negligible; then the free drug concentration will further decrease due to the increasing βCD excess in the gastrointestinal fluid. The excess of free βCD might decrease if it can form complexes with substances from the gastrointestinal fluid or substances administered together with the complex, which could act as competing agents [13, 14].

The knowledge of the binding constant and stoichiometry of the β-cyclodextrin complex in aqueous solution allows further studies to

control the transfer of the drug by manipulating appropriately the complex dissociation equilibrium [15].

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