Journal of Pharmaceutical & Biomedical Analysis
Vol. 4, No. 1, pp. 107–110, 1986
Printed in Great Britain

0731–7085/86 $3.00 + 0.00
Pergamon Press Ltd.

Short Communication

A microcalorimetric investigation of the binding of flurbiprofen to cyclodextrins

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Keywords: *Microcalorimetry; flurbiprofen; cyclodextrins; thermodynamics; binding constants.*

Introduction

Earlier investigations have shown that cyclodextrins complex with the poorly soluble anti-inflammatory drug, flurbiprofen-[2(2-fluoror-4-biphenyl) propionic acid] [1]. Complexation of the drug with the cycloamyloses increases the bioavailability, increases the peak plasma levels and shortens the time taken for the drug to reach this peak, when compared to that for the drug alone following oral administration to rabbits [2]. It is of interest to investigate the thermodynamics of the interaction between the drug and the cyclodextrins in aqueous solution.

Materials

The flurbiprofen was a gift of Boots Pharmaceuticals, Inc. (Shreveport, LA) and was used without further purification. The α-, β-, γ-cyclodextrins, manufacturered by Nihon Shokuhin Kako Co., Ltd (Tokyo, Japan) were a gift of Professor K. Uekama (Kumamoto, Japan) and were used as supplied. All buffer materials were of reagent grade and deionized water was used throughout the study.

Method

All measurements were made in an LKB Flow Microcalorimeter Model 2107-121 (LKB Bromma, Sweden). Full details of the experimental method and methods of calculation of the thermodynamic parameters are given in an earlier paper [3]. The titrations were performed with constant drug concentration. An accurately known total

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flow rate of approximately 26 ml h^{-1} of the 0.1 M pH 7.0 phosphate buffer at 25°C was used.

Results and Discussion

Figures 1 and 2 show the titration curves of heat flux as a function of cyclodextrin concentration. It is clear that plateau values of the heat flux can be estimated with considerable reliability to aid in the computation of the equilibrium constant (K) and the heat of reaction per mole of complex (ΔH), assuming a 1:1 interaction. The good fit of the theoretical lines with the experimental data indicate the formation of only the 1:1 complex under these experimental conditions. Although the literature reports a 1:2 complex for α-cyclodextrin with an equilibrium constant of 6.7 M^{-1} as well as the 1:1 complex, this was not confirmed in the present investigation. This is not surprising since the equilibrium constant is very low and probably the heat of reaction is also small. Table 1 shows the binding constants from the literature and the current investigations. It should be noted that the literature values were obtained in pure water, whereas the current measurements were made at pH 7.0, when the drug is fully ionized (pK_a = 4.13). The derived thermodynamic parameters are also shown in the table; Gibbs free energy is represented by $\Delta G = -RT\ln K$, where K in M^{-1} is corrected to a unitless mole fraction scale by use of the approximation (1000 d_w/18.02) or 55.34 where d_w is the density of water at 25°C. Entropy is then obtained from $\Delta G = \Delta H - T\Delta S$. The data suggest that the small cavity of the α-cyclodextrin allows little penetration of the flurbiprofen molecule, whereas the large β and γ-cycloamyloses allow significant penetration of the drug. The value of the equilibrium constant obtained by calorimetry for the interaction of β-cyclodextrin and flurbiprofen in water is in excellent agreement with that obtained by the solubility method [1]. Interactions with α and γ-cyclodextrin in water gave small exothermic reactions but the fluxes were too small for quantitative interpretation. For the interaction with β-cyclodextrin the binding constant with the drug in the ionized form is significantly reduced in a similar manner to that reported for the barbiturates [4, 5]; the reaction is accomplished, however, by a large evolution of heat. This is probably due to changes of interaction of water with the carboxylate ion following complexation, and to ion-dipole interactions with the cyclic amylose. The earlier work, in water, had suggested that the cavity size of the β-cyclodextrin was ideal for the interaction with flurbiprofen, as both the 6- and 8-membered ring moieties gave lower binding constants than the 7-membered, β-form. In all instances, NMR data suggested that the predominant reaction was of the fluorobenzene ring with the cyclodextrins [1].

The interaction of the ionized drug with γ-cyclodextrin is stronger by almost an order of magnitude than that of the unionized drug, suggesting that the carboxylate ion is necessary to impart rigidity to the complex. With β-cyclodextrin the binding constants of 10^{-3} M^{-1} are found with both the ionized and unionized moieties; apparently the fit of the drug within the cavity of the β-cyclodextrin produces a rigid complex whether or not the drug is ionized. In contrast, the smaller cavity of α-cyclodextrin does not appear to allow sufficient penetration by the drug to form a strong complex.

In all the reactions investigated there is an evolution of heat on complex formation and a substantial gain in entropy suggesting a large involvement of water molecules in the interaction. Complexation of flurbiprofen with β-cyclodextrin has been shown previously to enhance the bioavailability of the drug [2]; it is possible that complexation can be used to advantage in the analysis of the drug in biological samples.

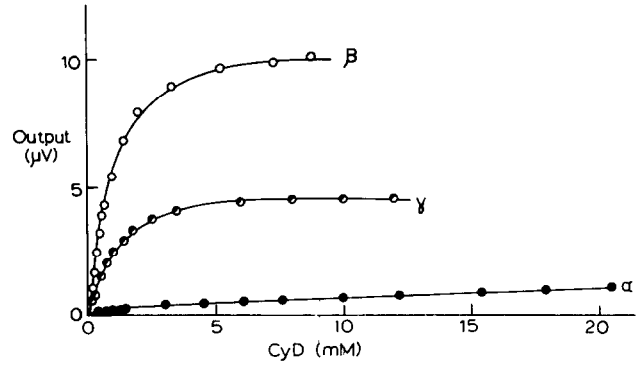

Figure 1
Voltage output of the calorimeter for the reaction between flurbiprofen and cyclodextrins as a function of cyclodextrin (CyD) concentration at pH 7.0 and 25°C. Voltage output × calibration constant^{-1} × flow rate = observed ΔH (Joules) [3].

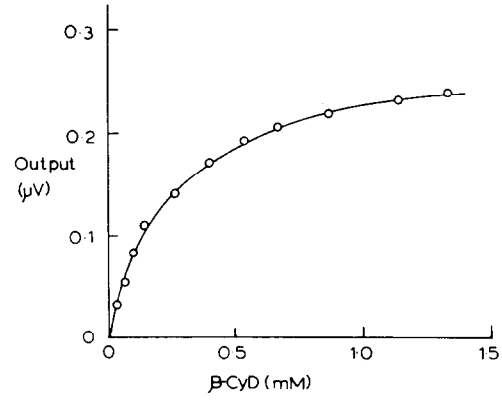

Figure 2
Voltage output of the calorimeter for the reaction between flurbiprofen and β-cyclodextrin in water at 25°C.

Table 1
Equilibrium constants and derived thermodynamic parameters for the interaction between flurbiprofen and cyclodextrins at 25°C.

Cyclodextrin	K_{Lit}* (mol l^{-1})	K_{Exptl} (mol l^{-1})	ΔH (J mol^{-1})	ΔG (J mol^{-1})	ΔS (J mol^{-1} K^{-1})
α-(pH 7.0)	29 (water)	69.7	−3681	−20,459	+56.3
β-(pH 7.0)		1966	−23,267	−28,733	+18.3
β-(water)	5100	4460	−14,884	−30,763	+53.3
γ-(pH 7.)	460 (water)	3054	−10,073	−29,824	±66.3

* All literature values were obtained in water.

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[*First received for review 6 July 1984; revised manuscript received 10 October 1984*]