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Calorimetric studies of diclofenac sodium in aqueous solution of cyclodextrin and water–ethanol mixtures

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Abstract

The technique of solution calorimetry has been employed to study the interaction between diclofenac sodium and β-cyclodextrin by determining the enthalpies of solution of the drug in water and in aqueous β-cyclodextrin solution. Thermodynamic parameters characterizing the binding process such as enthalpy ΔH^0, equilibrium constant K, free energy ΔG^0 and entropy ΔS^0 have been calculated to be -12.00 kJ mol^{-1}, 1670 dm^3 mol^{-1}, -19.03 kJ mol^{-1} and 22.98 J K^{-1} mol^{-1}, respectively. Enthalpies of solution of diclofenac sodium have also been determined in water–ethanol mixtures.

Introduction

Diclofenac sodium, a non-steroidal anti-inflammatory drug, has been evaluated as an alternative to topical steroids for treating ocular inflammation (Kraff et al 1990; Herbort et al 1992). Many studies have demonstrated its effi ciency in reducing post-surgical ocular inflammation (Hayashi et al 1984; Quentin et al 1989; Kraff et al 1991; Othenin-Girard et al 1992), intraocular pressure following cataract extraction (Strelow et al 1992) and preventing surgically induced miosis (Bonomi et al 1987). Unfortunately the drug has low solubility in water due to its hydrophobicity and is also susceptible to photodegradation in aqueous solution. The stability of a drug is of utmost importance as its products of decomposition may give rise to undesirable effects. Methods have been developed to stabilize drugs by adding cyclodextrins and their derivatives to form inclusion complexes in solution (Backensfeld et al 1991; Arancibia & Escandar 1999) and in solid state (Cwiertnia et al 1999). Determination of the association constants of drug–cyclodextrin inclusion complexes in dilute aqueous solution is very important because, from a practical standpoint, the main interest is to enhance the solubility of drug precisely in water. Moreover, it reflects the magnitude of interaction between host and guest molecules. Calorimetry is an important method for direct measurement of the change in enthalpy associated with the inclusion process and evaluation of the binding constant. This study was undertaken to calculate the thermodynamic parameters of binding of diclofenac sodium to β-cyclodextrin by determining the enthalpies of solution of drug in water as well as in aqueous solution of β-cyclodextrin by direct calorimetric measurement. We have also determined the binding enthalpy (ΔH^0), and hence free energy (ΔG^0) and enthalpy (ΔS^0), for the binding process. As far as we are aware no such study using this technique has been reported in literature.

Enthalpies of solution of the drug were also measured in water–ethanol mixtures as diclofenac sodium has also been reported to be absorbed from the skin

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(Nishihata et al 1988; Obata et al 1990) which can further be enhanced by addition of ethanol to the formulation (Berner et al 1989).

Materials and Methods

Materials

Diclofenac sodium (99.9% pure), a gift sample from Ind Swift Ltd, India, and β-cyclodextrin (>98.0%), supplied by E. Merck, Germany, were used without any further purification. Ethanol–water mixtures of known dielectric constants (Mashimo & Kuwabara 1989; Mashimo & Umehara 1991) were prepared by volume starting with ethanol of BP grade dried over molecular sieves (Bengal Chemical & Pharmaceuticals Ltd, India) and with triple-distilled water over the whole concentration range (0–100% of ethanol). Both the solvents were maintained at 37°C before mixing them. The aqueous solutions of β-cyclodextrin were prepared by weight (± 0.01 mg) before each run in triple-distilled water.

Calorimeter

The system used to determine the enthalpies of solution was a heat-flux calorimeter model-C-80 (Setaram, France). In accordance with the Calvet principle, two experimental vessels (reference and sample) were placed in a calorimetric block. Both the vessels had two compartments which were separated by a displaceable lid. The temperature control was ±0.003 K.

The enthalpies of solution of diclofenac sodium in pure solvents, aqueous β-cyclodextrin solution and ethanol–water mixtures were determined by loading the reference cell of the calorimeter with 5 mL of the desired solution. The sample cell was filled with 5 mL of the desired solution and accurately weighed drug, which was separated from the solution by a displaceable lid. After stabilization, the calorimetric block containing the vessels was rotated by 180° several times to displace the lid between the drug and solution, leading to their mixing (Jain et al 2000), and the signal was automatically recorded on the strip chart recorder. The performance of the calorimeter was tested by measuring the enthalpy of solution of KCl (Balk & Benson 1959) in triple-distilled water. The accuracy of any individual measurement was better than 0.5 J mol^{-1} for three consecutive experiments. The samples were weighed in the lower container of the calorimetric vessel itself using a single-pan Mettler balance with an accuracy of 0.01 mg. The system shifted from endothermic to exothermic effect as the ethanol–water system approached the ethanol-rich region.

Results and Discussion

The heat of solution of diclofenac sodium in aqueous β-cyclodextrin solution was determined at various concentrations (Table 1). We also determined the molar heat of solution of diclofenac sodium in water at various concentrations (Table 2). It can be seen that the enthalpy of solution of the drug in water was endothermic in nature and nearly independent of concentration. However, the molar heat of solution of the drug in aqueous β-cyclodextrin solution was dependent upon the final concentration of the drug as well as β-cyclodextrin and also exhibited a decrease of endothermic effect.

To ascertain the enthalpy of complex formation we determined the enthalpy of interaction between diclofenac sodium and β-cyclodextrin (β-CD) by equation 1:

$$\Delta H_{Int}\,(m) = \Delta H_{sol}\,(\beta\text{-CD}) - \Delta H_{Sol}\,(W) \qquad (1)$$

where ΔH_{Int} (m) is the observed enthalpy of interaction per mole of drug associated with a particular concentration of β-cyclodextrin, ΔH_{Sol} (β-CD) is the molar enthalpy of the solution of drug in aqueous β-cyclodextrin solution of known concentration and ΔH_{Sol} (W) is the molar enthalpy of solution of drug in water.

We also defined the enthalpy of interaction per litre of solution associated with a particular concentration ΔH_{Int} (l) by equation 2:

$$\Delta H_{Int}\,(l) = [\Delta H_{Int}\,(m)]\,m \qquad (2)$$

where m is the molarity of drug in aqueous solution of β-cyclodextrin.

In this system it is assumed that the following reaction takes place: β-CD + DS ⇔ β-CD:DS, where DS is diclofenac sodium.

Thus the equilibrium constant, K, for complex formation between drug and cyclodextrin is given by equation 3, assuming that the activity is equal to the molarity:

$$K = (m_{\beta\text{-CD:DS}})/(m_{\beta\text{-CD}} - m_{\beta\text{-CD:DS}})\,(m_{DS} - m_{\beta\text{-CD:DS}}) \qquad (3)$$

where $m_{\beta\text{-CD}}$ and m_{DS} are molarities of β-cyclodextrin and diclofenac sodium in solution, respectively. In the presence of a large excess of β-cyclodextrin, equation 3 becomes:

$$K\,m_{\beta\text{-CD}}\,m_{DS} = m_{\beta\text{-CD:DS}} + K\,m_{\beta\text{-CD}}\,m_{\beta\text{-CD:DS}} \qquad (4)$$

Table 1 Thermodynamic parameters for inclusion complexes of diclofenac sodium with β-cyclodextrin.

$10^3 \times$ Diclofenac sodium concn (M)	$10^3 \times \beta$-Cyclodextrin concn (M)	x_1	x_2	ΔH_{Sol} (β-CD) (kJ mol^{-1})	ΔH_{Int}(m) (kJ mol^{-1})	$10^2 \times \Delta H_{Int}$(l) (kJ mol^{-1})	ΔH_{Int} (kJ mol^{-1})
1.886	17.62	0.0967	0.9033	43.89	−11.290	−2.129	−1.091
1.886	8.810	0.1763	0.8237	43.90	−11.270	−2.126	−1.988
1.886	6.289	0.2327	0.7683	44.61	−11.170	−2.106	−2.582
3.144	6.289	0.3329	0.6671	44.00	−11.180	−3.514	−3.726
5.031	6.289	0.4444	0.5556	45.45	−9.731	−4.895	−4.324
6.286	6.289	0.5000	0.5000	46.38	−8.802	−5.532	−4.401
6.286	5.029	0.5551	0.4443	47.42	−7.761	−4.878	−4.312
6.286	3.144	0.6667	0.3333	49.77	−5.411	−3.401	−3.607
6.286	1.885	0.7693	0.2307	51.82	−3.355	−2.108	−2.582
1.250	1.885	0.8696	0.1304	53.44	−1.606	−2.087	−1.397
3.144	3.524	0.4715	0.5285	45.62	−9.285	−2.919	−4.378
5.031	3.524	0.5881	0.4119	48.03	−7.313	−3.679	−4.301
6.286	3.524	0.6408	0.3592	50.00	−5.608	−3.525	−3.594
5.031	5.029	0.5000	0.5000	46.00	−8.798	−4.426	−4.399
3.144	3.143	0.5000	0.5000	46.00	−8.822	−2.773	−4.410
1.886	1.886	0.5000	0.5000	46.00	−8.820	−1.663	−4.411

Table 2 Molar heats of solution of diclofenac sodium in water–ethanol mixtures.

Ethanol (% v/v)	1/∈	ΔH (kJ mol^{-1})						
		Diclofenac sodium concn						
		$10^3 \times 3.14$ (M)	$10^3 \times 5.03$ (M)	$10^3 \times 6.28$ (M)	$10^3 \times 9.43$ (M)	$10^3 \times 12.57$ (M)	Average values	Calculated values
0	0.0135	55.18	55.18	55.18	55.18		55.18	55.20
20	0.0146	52.54	52.54	52.54	52.55		52.54	52.10
30	0.0160	47.50	47.51	47.50	47.49		47.50	48.17
40	0.0174	43.12	43.12	43.12	43.13		43.12	44.23
50	0.0190	39.54	39.55	39.54	39.55		39.54	39.73
60	0.0215		34.12	34.12	34.12	34.13	34.12	32.70
70	0.0250		23.56	23.57	23.57	23.57	23.57	22.86
80	0.0278		14.50	14.51	14.51	14.50	14.51	14.98
90	0.0351		−05.57	−05.58	−05.58	−05.56	−05.57	−05.54
95	0.0400			−18.55	−18.55	−18.56	−18.56	−19.32
98	0.0435			−28.22	−28.23	−28.23	−28.23	−29.16
100	0.0440			−32.32	−32.34	−32.33	−32.33	−30.57

Dielectric constant (∈) values were calculated from literature (Mashimo & Kuwabara 1989; Mashimo & Umehara 1991). ΔH_{Sol} values were calculated from equation 10.

If ΔH^0 (β-CD:DS) is the enthalpy of reaction for the formation of one mole of the complex and ΔH_{Int} (l) is the enthalpy of interaction leading to the formation of m moles of the complex $m_{\beta\text{-CD:DS}}$, then its concentration is given by ΔH_{Int} (l)/ΔH^0 (β-CD:DS). Here, in the presence of a large excess of β-cyclodextrin the equation becomes:

$$\Delta H^0 (\beta\text{-CD:DS})\, K\, m_{\beta\text{-CD}}\, m_{DS} = \Delta H^0 (\beta CD:DS)\, [m_{\beta\text{-CD:DS}} + K\, m_{\beta\text{-CD}}\, m_{\beta\text{-CD:DS}}] \quad (5)$$

$$\Delta H^0 (\beta CD:DS)\, K\, m_{\beta\text{-CD}}\, m_{DS} = \Delta H^0 (\beta CD:DS)\, m_{\beta\text{-CD:DS}}\, [1 + K\, m_{\beta CD}] \quad (6)$$

$$1/\Delta H^0 (\beta\text{-CD:DS})\, K + m_{\beta\text{-CD}}/\Delta H^0 (\beta\text{-CD:DS}) = m_{\beta\text{-CD}}\, m_{DS}/\Delta H_{Int} (l) \quad (7)$$

Similarly, in the presence of large excess of diclofenac sodium the equation becomes:

$$1/\Delta H^0 (\beta\text{-CD:DS})\, K + m_{DS}/\Delta H^0 (\beta\text{-CD:DS}) = m_{\beta\text{-CD}}\, m_{DS}/\Delta H_{Int} (l) \quad (8)$$

The data were fitted to equations 7 and 8 and values of ΔH^0 (β-CD:DS) and equilibrium constant K were calculated by the least-squares analysis.

Equation 7 gave ΔH^0 (β-CD:DS) = -12.04 kJ mol^{-1} and K = 1660 dm^3 mol^{-1} while equation 8 gave ΔH^0 (β-CD:DS) = -11.97 kJ mol^{-1} and K = 1680 dm^3 mol^{-1}, with regression coefficient = 0.99, and showed excellent agreement with average value of ΔH^0 (β-CD:DS.) = -12.00 ± 0.03 kJ mol^{-1} and K = 1670 ± 10 dm^3 mol^{-1}. The values of ΔG^0 and ΔS^0 have been calculated to be -19.13 ± 0.03 kJ mol^{-1} and 22.98 ± 0.16 J K^{-1} mol^{-1}.

A literature survey showed that preliminary studies made by Reer et al (1994) reported values of 2236 M^{-2} and 2811 M^{-2} for the equilibrium constant of diclofenac sodium with hydroxypropyl β-cyclodextrin and methyl β-cyclodextrin, respectively. They calculated equilibrium constants from the slope of the phase solubility diagram assuming formation of a 2:1 complex, not withstanding the fact that pure 2:1 diclofenac–cyclodextrin stoichiometry is not to be expected. This is because the cavity diameter of β-cyclodextrin (6–6.5 Å) cannot accommodate more than one molecule of diclofenac sodium. Moreover, 1:1 stoichiometry has also been reported by Arancibia & Escandar (1999).

However, our calorimetrically determined value for the equilibrium constant (log K = 3.22) for complex formation between diclofenac sodium and aqueous β-cyclodextrin solution compares well with the log K values of 3.0 and 3.15 (Arancibia & Escandar 1999), determined using the technique of potentiometry and spectrofluorimetry.

The reasonable value of 1670 dm^3 mol^{-1} for the equilibrium constant of the inclusion complex indicates that it can be used to improve the bioavailability of the drug. It has been observed that inclusion complexes with stability constant values in the range 200–5000 M^{-1} can be used to improve the bioavailability of hydrophilic drugs (Szejtli 1988). Very high stability constants may lead to very poor release of drug and very low stability constants (>200 M^{-1}) reduce the effect that complexation has on the bioavailability of the drug.

The results can also be treated in an alternative manner whereby the heat of interaction per mole of complex may be considered due to non-ideality of their binary mixtures in terms of their pseudo mole fractions (Figure 1). Thus the enthalpy of interaction per mole of complex (ΔH_{Int}) is found to follow equation 9.

$$\Delta H_{Int} = x_1 x_2 [A + B (x_2 - x_1) + C (x_2 - x_1)^2] \quad (9)$$

where $\Delta H_{Int} = \Delta H_{Int}(m)/[1 + (m_{\beta\text{-CD}}/m_{DS})]$, x_1 is the mole fraction of diclofenac sodium and x_2 is the mole fraction of β-cyclodextrin.

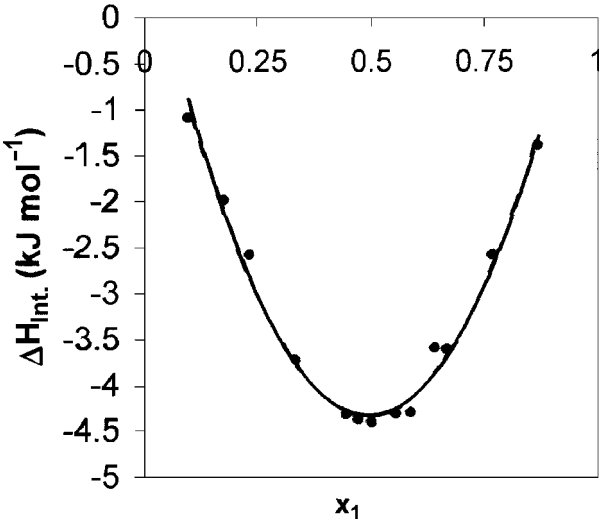

Figure 1 Plot of ΔH_{Int} (kJ mol^{-1}) vs x_1, where x_1 is the mole fraction of diclofenac sodium and ΔH_{Int} is the enthalpy of interaction per mole of complex with β-cyclodextrin.

While calculating mole fractions we ignored the presence of solvent and treated it as a two-component system consisting of diclofenac sodium and β-cyclodextrin. The parameters A, B and C from the least-square fit were found to be -17.59, -28.25 and $+9.74$ respectively with standard deviation equal to ± 0.06 kJ mol^{-1} for the enthalpy of interaction per mole of complex (ΔH_{Int}). This means if we take equal concentrations of the drug and β-cyclodextrin then ΔH_{Int} for one mole of drug and one mole of β-cyclodextrin is equal to -8.79 kJ mol^{-1}, which is consistent with ΔH^0 (β-CD:DS) = -12.00 kJ mol^{-1}, as the equilibrium concentration of the adduct will be less than one mole. This should, however, depend on the initial concentration of diclofenac sodium and β-cyclodextrin in the solution. It may be noted that the concentration of adduct formed can be calculated from the equilibrium constant and known molarities of the components. We found that for the four points when the molarities of the two components are equal, the percentage conversion ranged from 57.6 to 74.6 which is in reasonable agreement with $(8.793/11.97) \times 100 = 73.4$.

Molar heats of solution of diclofenac sodium in water–ethanol mixtures

As mentioned above, the addition of ethanol enhances the percutaneous absorption of diclofenac sodium from the skin. To understand this phenomenon, it was decided to determine heat of solution of diclofenac sodium in

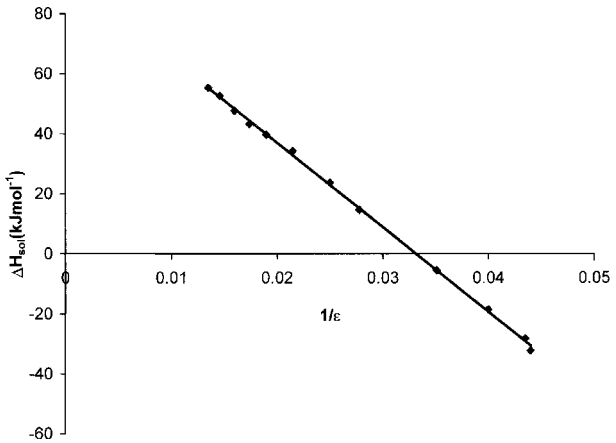

Figure 2 Plot of ΔH_{Sol} (kJ mol^{-1}) vs $1/\in$ for diclofenac sodium in water–ethanol mixture, where ΔH_{Sol} is molar heat of solution and $\in$ is the dielectric constant.

water–ethanol mixtures. It can be seen from Table 2 that the heat of solution decreases as the mole fraction of ethanol increases (55.18 kJ mol^{-1} in pure water; −32.34 kJ mol^{-1} in pure ethanol). The plot of ΔH_{Sol} (mixture) vs $1/\in$ was linear (Figure 2), where $\in$ is the dielectric constant of the ethanol–water mixtures. The dielectric constant values of various ethanol–water mixtures have been calculated from literature (Mashimo & Kuwabara 1989; Mashimo & Umehara 1991) and are given in Table 2. It has been found that ΔH_{Sol} (mixture) as a function of $\in$ is represented fairly accurately by equation 10.

$$\Delta H_{Sol}\,(\text{mixture}) = 93.166 - 2812.2/\in \qquad (10)$$

The values of ΔH_{Sol} (mixture) calculated from equation 10 are given in Table 2 for comparison. Ethanol is known to enhance percutaneous absorption by increasing the solubility of a drug and alters the skin's barrier properties (Good et al 1985; Berner et al 1989). It is known that diclofenac acid has higher pK_a in ethanol–water mixture (Maitani et al 1991) and that due to enhanced hydrolysis of the diclofenac ion the overall process tends to become exothermic as the concentration of alcohol is increased. Thus, the higher pK_a in ethanol–water mixture leads to grater conversion of the ionized form into the unionized acid molecule which is capable of easy diffusion through skin.

Conclusion

This study has been undertaken to determine the enthalpic effect connected with the interaction between diclofenac sodium and β-cyclodextrin using the technique of solution calorimetry. The study indicates that the molar enthalpy of solution of the drug in water is endothermic and is independent of the concentration of the drug. However, a decrease in enthalpy of solution was noted upon the addition of β-cyclodextrin to the solution and the molar enthalpy of solution, ΔH^0, is dependent on the concentration of drug as well as cyclodextrin. Thus the cyclodextrin–drug binding process is exothermic and exhibits a large negative enthalpy, due to the expulsion of enthalpy-rich water from the hydrophobic cavity of β-cyclodextrin. Moreover, this study also supports 1:1 stoichiometry and the equilibrium constant for complex formation has been evaluated to be 1670 dm^3 mol^{-1}. This equilibrium constant value is encouraging from a manufacturing point of view and also compares well with the earlier value determined using potentiometry and spectrofluorimetry techniques.

The study carried out in ethanol–water mixtures is helpful in understanding the behaviour of diclofenac sodium in ethanol-containing formulations applied topically for various ailments. In the ethanol-rich region, the drug shows exothermic enthalpy change leading to more unionized drug and thus to better percutaneous absorption.

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