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Microcalorimetric studies to determine the enthalpy of solution of diclofenac sodium, paracetamol and their binary mixtures at 310.15 K

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Abstract

A sensitive and selective microcalorimetric technique has been used to determine the enthalpy of solution of diclofenac sodium (DS), paracetamol (PC) and their binary mixtures over a wide range of composition in the pH range 4–12. The systems showed endothermic behavior. The molar enthalpies of solutions of DS vary between 42.26 ± 0.16 and 50.48 ± 0.03 kJ mol^{-1} at pH 4–9 and for PC from 24.28 ± 0.05 to 36.03 ± 0.01 kJ mol^{-1} at pH 5–12. The excess molar enthalpy of their mixtures has also been determined. The values of excess molar enthalpy of solutions are negative and very low in magnitude indicating no specific interaction between DS and PC in solution.

Keywords: Binary mixture; Diclofenac sodium; Enthalpy of solution; Excess molar enthalpy; Paracetamol; Isothermal solution microcalorimetry

1. Introduction

Enthalpy of solution of pharmaceuticals is an important thermodynamic property and can be utilized for their characterization [1,2]. The property has been successfully used to determine the extent of crystallinity in drugs and excipients [3] as well as to clarify the role of interactions between the drugs and the carriers in conjunction with solubility and dissolution rate studies [4,5]. It has been used to measure the heat of precipitation of drugs [6]. Enthalpy of solution obtained from solubility data using van't Hoff plot of log solubility against the reciprocal of temperature suffers from the drawback that these plots are not linear in solution over a wide temperature range [7]. This problem is overcome by directly determining the heat of solution calorimetrically [5,8]. The present work reporting the enthalpy of solution of diclofenac sodium (DS), paracetamol (PC) and their binary mixtures is a part of our ongoing studies on the thermodynamic properties of drugs using technique of solution calorimetry which has proved to be an invaluable tool in the realm of pharmaceutical sciences.

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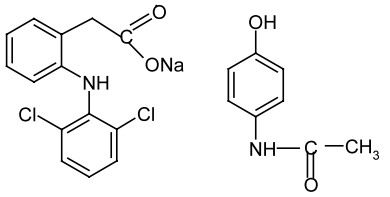

Diclofenac sodium Paracetamol

DS, an anti-inflammatory and analgesic drug exhibits activity by inhibiting the synthesis and release of prostaglandin and leukotrienes in the tissues, which are usually associated with inflammatory processes [9]. The drug is often formulated in tablet dosages form (DICLOWIN PLUS® DICLONAC-P®, 50 mg DS + 500 mg PC) with PC which is analgesic and antipyretic and provides basic relief before the effects of DS set in. These drugs are prescribed in indications such as symptomatic treatment of acute and chronic inflammatory conditions like orchitis, osteoarthritis, myositis, bursitis, fibrositis, tenosynovitis etc. acute painful conditions like renal, intestinal and other visceral colic and soft tissue injuries like sprain, in traumatic and surgical pain, high fever, pyrexia of unknown origin (PPUO), [10] an adjuvant with antibiotic and other antimicrobial therapies.

In order to find any specific interaction between these drugs in the solution state, which may occur without any visible change, the heats of solution of their binary mixtures have been determined. The present communication reveals a simple method to study drug-drug interaction during the dissolution of their mixtures. As far as we know no direct calorimetric data have been reported for above mentioned drugs except those of Lloyd et al. (1999), who have determined the heat of solution of PC in pure water at 310.15 K.

2. Methods and materials

2.1. Chemicals

DS (99.9% pure) and monoclinic PC (99.8% pure, polymorph I) with prismatic and plate like crystals were procured as gift samples from Indswift ltd, India and were used without further purification. Both the drugs were sieved and fractions with particle size 300–350 μm were used throughout the study. Phosphate buffers were prepared using AR grade chemicals.

2.2. Buffers

In the present studies phosphate buffers were prepared by mixing solutions of appropriate sodium salts of phosphoric acid in appropriate ratio according to the given procedures [11]. The ionic strength of all phosphate buffers were 0.2 M. The pH values of various phosphate buffers were measured using pH meter (Elico, India) standardized with pH 4.0, 7.0 and 9.2 solutions.

2.3. Solution microcalorimeter

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 have two compartments which are separated by a displaceable lid. The temperature control was ± 0.003 K. The enthalpies of solution of DS, PC and their binary mixtures in triply distilled water and phosphate buffers of different pH were determined by loading the reference cell of calorimeter with 5.00 ml of desired liquid. The sample cell was filled with 5.00 ml of desired buffer and accurately weighed amount (5.00–10.00 mg) of drug, which was separated from the liquid by a displaceable lid. After thermal stabilization the calorimetric block containing the vessels was rotated by 180° several times, which displaces the lid between the drug and solution leading to their mixing. 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 [12] in triple-distilled water. The precision of any individual measurement was better than 0.02 kJ mol^{-1} for three consecutive experiments and agreed with the standard value within ± 0.03 kJ mol^{-1}.

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. During the experiments 5.00–10.00 mg of each drug was dissolved in 5.00 cm^3 of solution giving $1.57–3.14 \times 10^{-5}$ mol of DS and $3.30–6.61 \times 10^{-5}$ mol of PC. The molarity of DS ranges from 3.14 to 6.28×10^{-3} and for PC it ranges from 6.60 to 13.22×10^{-3} M (Table 1). The minimum weight of the drug sample in our experiments is 5.00 mg with a accuracy of 0.01 mg and the volume of solution used is 5.00 cm^3 with a accuracy of 0.01 cm^3. Therefore, the maximum error in concentration due to their experimental uncertainties is ± 0.003 M. The mixtures of the drugs have been prepared by mechanical mixing drugs. Minimum weight of any one of the drugs in the mixture was 3.00 mg and maximum weight was18.00 mg. For example mole fraction $x = 0.2496$ was prepared by mixing 7.00 mg of DS and 10.00 mg of PC (Table 5). The

Table 1
Molar enthalpies of solution of DS and PC at various pH at 310.15 K

pH	DS			pH	PC		
	$10^2 \times$ mmol of DS/5 ml of solution	$10^3 \times$ [DS] M	ΔH (kJ mol^{-1})		$10^2 \times$ mmol of PC/5 ml of solution	$10^3 \times$ [PC] M	ΔH (kJ mol^{-1})
4	1.57	3.14	42.24	5	3.30	6.60	24.25
	2.51	5.02	42.16		5.29	10.58	24.29
	3.14	6.28	42.39		6.61	13.22	24.32
			42.26 ± 0.16				24.28 ± 0.05
5	1.57	3.14	48.45	6	3.30	6.60	24.69
	2.51	5.02	48.35		5.29	10.58	24.61
	3.14	6.28	48.54		6.61	13.22	24.68
			48.44 ± 0.09				24.66 ± 0.04
6	1.57	3.14	50.02	7	3.30	6.60	24.73
	2.51	5.02	50.01		5.29	10.58	24.81
	3.14	6.28	50.01		6.61	13.22	24.75
			50.01 ± 0.01				24.76 ± 0.04
7	1.57	3.14	50.24	8	3.30	6.60	25.05
	2.51	5.02	50.20		5.29	10.58	25.08
	3.14	6.28	50.28		6.61	13.22	25.04
			50.24 ± 0.04				25.05 ± 0.02
8	1.57	3.14	50.31	9	3.30	6.60	27.37
	2.51	5.02	50.30		50.29	10.58	27.45
	3.14	6.28	50.29		6.61	13.22	27.44
			50.30 ± 0.01				27.42 ± 0.04
9	1.57	3.14	50.45	10	3.30	6.60	33.81
	2.51	5.02	50.51		5.29	10.58	33.83
	3.14	6.28	50.49		6.61	13.22	33.81
			50.48 ± 0.03				33.81 ± 0.01
2			36.3[a]	11	3.30	6.60	35.99
					5.29	10.58	35.99
					6.61	13.22	36.00
							35.99 ± 0.01
3			36.62[a]	12	3.30	6.60	36.03
					5.29	10.58	36.03
					6.61	13.22	36.04
							36.03 ± 0.01
Water							24.18[b]

[a] Calculated values from Eq. (2).
[b] Enthalpy of solution determined by Lloyd et al. (1999).

maximum uncertainty is ± 0.005 due to uncertainties in weight. All experiments were repeated three times.

3. Results and discussion

3.1. Heat of solutions of diclofenac sodium and paracetamol

Our calorimetrically determined values of the enthalpies of solution of DS and PC as a function of pH and concentrations are given in Table 1. An endothermic behavior has been observed and the heat of solution for both the drugs is nearly independent of concentration. However, the values change from 42.26 ± 0.16 to 50.48 ± 0.03 kJ mol^{-1} for DS as pH changes from 4 to 9 and from 24.28 ± 0.05 to 36.03 ± 0.01 kJ mol^{-1} for PC as pH changes from 5 to 12. It can be seen that enthalpy of solution remains constant at lower pH (<8 for PC) and higher pH (>6 for DS) when only one of the species of the drug predominates. As expected the maximum change is near the pH equal to pKa of the drug.

DS is a salt of a weakly acidic drug (pK_a 4.2). Therefore, at lower pH ($\leq$ pH 6) both ionized and unionized forms contribute towards enthalpy of solution. However, at pH 7 and above the drug exists in completely ionized form and enthalpy of solution varies very little between pH 7–9 (50.24–50.48 kJ mol^{-1}) and corresponds to enthalpy of formation, $\Delta H_{\text{ion.}}$ of diclofenac anion from the acid in the solid form. At a particular pH enthalpy of solution can be represented by following equations.

$$\Delta H_{\text{sol}} = \Delta H_{\text{un}} f' + \Delta H_{\text{ion}} f''$$

$$\Delta H_{\text{sol}} = \Delta H_{\text{un}} f' + \Delta H_{\text{ion.}}(1 - f') \quad (1)$$

$$\Delta H_{\text{sol}} = f'(\Delta H_{\text{un.}} - H_{\text{ion.}}) + \Delta H_{\text{ion.}} \quad (2)$$

where f' and f'' represent the fraction of unionized and ionized form (Table 2) calculated from their ionization constants. It can be seen from Fig. 1 that a plot of ΔH_{sol} against f' is a straight line with intercept equal to $\Delta H_{\text{ion.}}$ and slope equal to $\Delta H_{\text{un.}} - \Delta H_{\text{ion}}$. The values of $\Delta H_{\text{ion.}}$ and $\Delta H_{\text{un.}}$ have been also calculated from Eq. (1) by solving simultaneous equations. The values from both the methods agree and are given in Table 3. The contribution to enthalpy of solution of ionized form is the sum of the enthalpy of solution of their unionized form $\Delta H_{\text{un.}}$ and it is enthalpy of deprotonation ΔH_{dp}.

Table 2
Fractions of un-ionized and ionized forms of DS and PC at various pH

pH	f'	F''
DS		
2	0.9937	0.0062
3	0.9407	0.0592
4	0.6134	0.3866
5	0.1333	0.8666
6	0.0156	0.9984
7	0.0016	0.9844
PC		
7	0.9996	0.0003
8	0.9693	0.0306
9	0.7597	0.2402
10	0.2403	0.7597
11	0.0306	0.9690
12	0.0030	0.9970

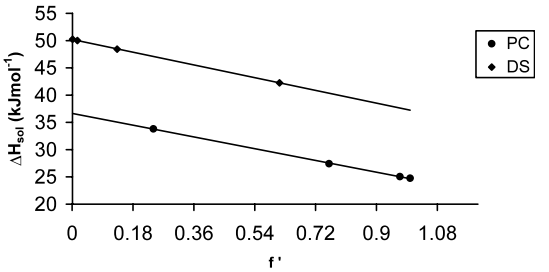

Fig. 1. Enthalpy of solution (ΔH_{sol} kJ mol^{-1}) vs. fraction of un-ionized drugs (f').

$$\Delta H_{\text{ion}} = \Delta H_{\text{un.}} + \Delta H_{\text{dp}} \quad (3)$$

The enthalpy of deprotonation for DS calculated from Eq. (3) is 13.03 kJ mol^{-1}. We are unable to determine the enthalpy of solution below pH 4 because of low solubility (lower than 1 mg ml^{-1}) as DS undergoes an intramolecular cyclization under the acidic conditions losing its activity [13].

The fraction of the drug existing in its unionized form in a solution is a function of both the

Table 3
Values corresponding to $\Delta H_{un.}$ and $\Delta H_{ion.}$ for DS and PC

$\Delta H_{un.}$ (kJ mol^{-1})			$\Delta H_{ion.}$ (kJ mol^{-1})		
Eq. (1)	Graph	Average value	Eq. (1)	Graph	Average value
DS					
37.10	37.23	37.17±0.05	50.18	50.22	50.20±0.02
PC					
24.67	24.59	24.63±0.05	36.62	36.38	36.50±0.13

dissociation constant of a drug and the pH of the solution. For very weakly acidic drugs ($pK_a < 8.0$), they are predominantly in the un-ionized form at all pH values between 1.0 and 8.0 [14]. The heat of solution of PC, a weakly acidic drug (pK_a 9.7) at pH 9 and 10 is due to the contribution from the *p*-acetamido phenolate ion and acetoaminophen molecule. The calculated values for $\Delta H_{ion.}$ and $\Delta H_{un.}$ are given in Table 3. Enthalpy of deprotonation, ΔH_{dp} of PC is calculated to be 11.87 kJ mol^{-1}.

Our experimentally determined molar enthalpy of solution values 24.66 kJ mol^{-1} at pH 6 is compared with the reported values 22.46 [7] and 23.75 kJ mol^{-1} at 303.15 K in water [15] obtained from van't Hoff plot of log solubility against the reciprocal of temperature for PC. The agreement with these values is not expected to be exact due to inherent weakness of van't Hoff plot method. However, our value compares well with data obtained by Lloyd et al. (1999), using technique of solution calorimetry at 310.15 K in water (Table 1). Beside this no other data are available for comparison with our results. The endothermic behavior of enthalpies of solution indicates little interaction of drugs with water.

The values of molar free energy of solution given in Table 4 calculated using the equation.

$$\Delta G = -RT \log s \quad (4)$$

where s is the molar solubility of drug.

The values of molar solubility (s) for DS at different pH [16] and PC [7] were taken from literature. The molar entropy of solution of both drugs was calculated from well known equation $\Delta G = \Delta H - T\Delta S$ and given in Table 4. No literature values are found for molar solubility of PC at pH other than pH 7. The positive values of entropy of solution indicate that the dissolution is largely entropically driven and this is attributed to the possible breaking of highly ordered structure of water surrounding the drug molecules.

Table 4
Molar free energies and molar entropies of solution for DS and PC

pH	ΔG_{sol} (kJ mol^{-1})	ΔS_{sol} (J K^{-1} mol^{-1})
DS		
4	30.88	36.69
5	25.24	74.80
6	19.30	99.01
7	13.36	118.90
8	11.88	123.88
PC		
5	–	51.01
6	–	52.23
7	8.458	52.56
8	–	53.49
9	–	61.13
10	–	81.74

3.2. Interaction studies between diclofenac sodium and paracetamol

Drug interactions occurring outside the body may be categorized as physical or chemical and may occur during formulation, storage as well as while mixing ingredients. These are manifested by precipitation or color changes. Occasionally in-vitro interactions occur without any observable change and can be determined quantitatively by determining their excess thermodynamic properties in solution [8]. Several methods for the

analysis of DS [17–21], PC [22–25] and their mixtures [26] dosage forms have been reported in literature. In order to find any interaction between these drugs in solution state, we have used the technique of solution calorimetry, which has wide advantages over other conventional techniques for the determination of interactions between drugs/excipients in both solid and solution state.

The excess molar enthalpies of solution of binary mixtures were calculated by equation

$$\Delta H_m^E = \Delta H_{sol} - [x_1\{f'_1\ \Delta H_{ion.} + f''_1\ \Delta H_{un.}\} + x_2\{f'_2\Delta H_{ion.} + f''_2\ \Delta H_{un.}\}] \quad (5)$$

ΔH_{sol}, molar enthalpy of solution of binary mixture; x_1, relative mole fraction of DS; x_2, relative mole fraction of PC.

In calculating mole fraction of drugs we ignore the solvent (buffer solution) and take into consideration only the amount of both the drugs. This is why we call these as relative mole fractions.

Eq. (5) represents the deviation of the system from ideality. For a non- interacting binary system ΔH_m^E should be zero. It is observed that the excess molar heats of solution of binary mixtures (ΔH_m^E) show exothermic behavior and magnitude of ΔH_m^E increases with pH (Table 5). This means that molar enthalpy of solution of the binary mixtures is less than the calculated one using the data obtained from the pure components. The small negative value of ΔH_m^E indicates some weak interaction between these drugs in solution and this may arise due to formation of intermolecular hydrogen bond between these two molecules. This tendency increases with the increase in pH when hydrogen from NH– can form hydrogen bond with oxygen of carboxylic anion of DS and phenolate ion of PC. This explains increase of exothermicity with increase in pH.

The value of excess molar enthalpies at various mole fractions are fitted to the Redlich–Kister regression equation

$$\Delta H_m^E = x_1 x_2 \sum_{i=0}^{n} h_i (x_1 - x_2)^i \quad (6)$$

h_i, magnitude of ith coefficients

Table 5
Molar enthalpies of solution [$\Delta H_{sol(m)}$] and excess molar enthalpies of solution [ΔH_{sol}^E] for the binary mixture of DS and PC at various pH

x_1	$\Delta H_{sol(m)}$ (kJ mol^{-1})	ΔH_m^E (kJ mol^{-1})
pH 5		
0.0868	26.65	−0.046
0.1762	28.73	−0.093
0.2496	30.43	−0.145
0.3222	32.12	−0.188
0.4540	35.21	−0.229
0.5430	37.35	−0.221
0.6554	40.08	−0.169
0.7404	42.14	−0.132
0.7810	43.14	−0.102
0.8770	45.46	−0.067
pH 6		
0.0868	26.77	−0.057
0.1762	28.98	−0.113
0.2496	30.78	−0.178
0.3222	32.58	−0.220
0.4540	35.88	−0.260
0.5430	38.15	−0.250
0.6554	41.03	−0.217
0.7404	43.24	−0.162
0.7810	44.30	−0.133
0.8770	46.76	−0.109
pH 7		
0.0868	26.84	−0.100
0.1762	29.13	−0.199
0.2496	31.01	−0.272
0.3222	32.86	−0.325
0.4540	36.23	−0.384
0.5430	38.48	−0.379
0.6554	41.37	−0.319
0.7404	43.55	−0.279
0.7810	44.58	−0.226
0.8770	47.03	−0.134
pH 9		
0.0868	29.41	−0.132
0.1762	31.48	−0.241
0.2496	33.14	−0.301
0.3222	34.79	−0.372
0.4540	37.79	−0.445
0.5430	39.81	−0.434
0.6554	42.37	−0.391
0.7404	44.30	−0.342
0.7810	45.22	−0.292
0.8770	47.40	−0.191

The values of the coefficients, h_i's has been determined by the method of the least squares along with standard deviations (S.D.) are given in

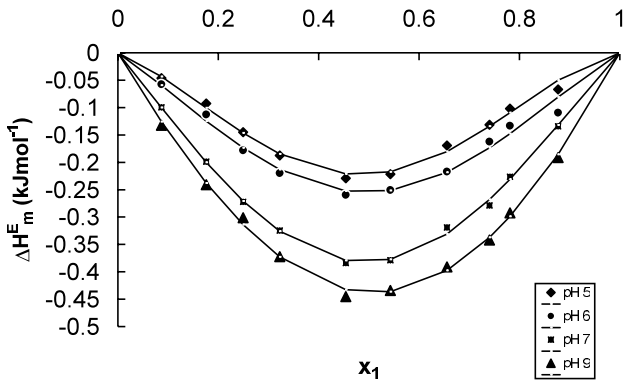

Fig. 2. Excess molar enthalpies of solutions of binary mixtures of DS and PC at pH 5, 6, 7, and 9. The solid lines were calculated using Eq. (6) and the experimental values represent points.

Table 6
Values of coefficients h_i in Eq. (6) along with the S.D. of $\Delta H^E{}_m$ for various mixtures of DS and PC at pH 5, 6, 7 and 9

pH	h_i (kJ mol^{-1})			S.D.
	h_0	h_1	h_2	
5	−0.889	0.097	0.617	0.011
6	−1.019	0.033	0.433	0.017
7	−1.529	0.062	0.455	0.008
9	−1.753	0.076	0.154	0.010

Table 6. The value of ΔH^E_m can be calculated at any mole fractions of drugs using the coefficients given in Table 6. In Fig. 2, the calculated excess molar enthalpy values are shown as solid curves and experimental values as points.

Thus the technique of solution calorimetry can be adopted for the routine analysis in quality control of finished dosage and raw materials in pharmaceutical industry with valuable results and serves as excellent alternative to HPLC technique [27].

4. Conclusion

The present study specifies that the technique of microcalorimetry has wide scope to characterize the pharmaceuticals by determining thermodynamic parameters. Calorimetrically determined enthalpy of solution for the above mentioned drugs in the present study indicates that the dissolution process is endothermic in nature which is accompanied by positive entropy of dissolution. The thermodynamic parameters of dissolution are independent of concentration but highly pH dependent. Moreover the technique of calorimetry is found to be a quantification method that could be used for the compatibility of admixtures of drugs and for simultaneous quantitative determination of both drugs in a mixture. The technique has been validated to study the interaction between DS and PC in solution state.

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