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Enthalpies of solution of paracetamol and sodium diclofenac in phosphate buffer and in DMSO at 298.15 K

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Abstract

We have been using a heat conduction microcalorimeter to measure enthalpies of dissolution of slightly soluble solids. Recently we did report the testing of the prototype and we are now extending the previous investigation to measurements with organic solvents.

In the present work we use DMSO due to its importance in the pharmaceutical industry. The importance of the applications of enthalpies of solution in organic solvents calls for the need to find a substance that can be used in the future for chemical calibration in these solvents. Attempts for proposing such a substance have also been a goal for our research group.

The enthalpies of solution of paracetamol and sodium diclofenac were measured in DMSO and in phosphate buffer (pH 6.91) at 298.15 K. We show that it is possible to obtain very good results with DMSO as solvent for these two drugs on our dissolution microcalorimeter. Nevertheless, due to their slow and low enthalpy of dissolution in this solvent, they cannot be seen as good candidates for test substances.

Keywords: Dissolution microcalorimeter; DMSO; Paracetamol; Diclofenac; Transfer enthalpies

1. Introduction

There is rising concern about the quality and safety of industrial products. Pharmaceutical drugs are one of the most delicate areas, due to human health concerns and the need for knowledge of many physical properties of these products, like the degree of crystallinity [1,2] or the existence of polymorphism [3–7], which can be related to biological properties of drugs [8].

Dissolution calorimetry is a powerful tool for gathering thermodynamic information that can be related to these properties [9,10]. It also allows the study of substances that are either very expensive or difficult to obtain in large amounts in high-purity form, due to its low detection limit.

Many drugs are not soluble in aqueous solvents and therefore the use of organic solvents is required. The performance of the present dissolution microcalorimeter has already been tested in our research group for formamide as a solvent, showing that the instrument was also very suitable for organic solvents after some minor technical adjustments [11].

In the present work we use DMSO [12] due to its importance in biological research [13–15] and in the pharmaceutical industry—it is a good solvent for many pharmaceutical products and it can penetrate cellular membranes without significant or permanent damage [16,17], making it an excellent carrier medium for different hydrophobic drugs. Further, from the viewpoint of calorimetric testing, we show that it is possible to obtain very good results with this solvent. The importance of the applications of enthalpies of solution in organic solvents calls for the need to find a substance that can be used in the future for chemical calibration in these solvents, as KCl [18] has been used when water is the solvent. Attempts for proposing such a substance have also been a goal for our research group.

Paracetamol (PC), an analgesic and antipyretic, and sodium diclofenac (DCF), an anti-inflammatory and analgesic drug, were chosen for various reasons: (i) their pharmaceutical importance as representatives of two important groups, (ii) they can be easily obtained in a high degree of purity and (iii) another study of their dissolution properties in phosphate buffer was available in the literature [19]. The enthalpies of solution of the two drugs were therefore measured in DMSO and in phosphate buffer (pH 6.91) at 298.15 K.

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2. Experimental

2.1. Instrument

The 20 mL dissolution vessel (Thermometric AB, Sweden) is a batch dissolution vessel of the insertion type, used with a twin heat conduction microcalorimeter (Thermometric AB, Sweden), which is positioned in a water bath of precisely controlled temperature ($\pm 5 \times 10^{-4}$ °C). The vessel is taken out from the calorimeter for inspection after each series of experiments and is cleaned and charged outside the calorimeter. Dissolution experiments are conducted with sample masses on the mg level (0.05–3 mg) and a solvent volume of 17.00 mL. The vessel has four injector guide tubes, three of which possess injectors, thus allowing the successive injection of three samples without opening the vessel. The guide tube without injector serves usually as a means of release of pressure upon sample "injection". In our case, we also use it as outlet for the wires of an insertion heater, when performing electrical calibration with an insertion resistor. The stirring speed was 70 rpm. The vessel was characterized with DMSO as a solvent as regarding stability, noise level and "empty cups" thermal effect according to the method described before [20]. The instrument was calibrated chemically by dissolution of potassium chloride (KCl) in water [21–23], and electrically by means of an insertion heater made at Lund University [24]. Data acquisition was performed through the SIGMA program (Sven Hägg, Lund University, Sweden).

2.2. Materials

The water used in dissolution measurements was produced by a Milli-Q filtration system, presenting a conductivity of 18.1 μS cm^{-1}.

KCl (Merk p.a., ≥99.5%) was dried under vacuum during 4 h at 70 °C [25]. The mass fraction of water was determined thereafter to be 0.027% (w/w) by Karl Fischer coulometry (KF737, Metrohm). Sodium diclofenac, sodium 2-[(2,6-diclorofenil)amino]benzenoacetatate (Sigma-Aldrich Química S.A., purity 98%), paracetamol, *N*-methyl-*p*-aminofenol (Sigma-Aldrich Química S.A., purity 98%) were used as received. All solid samples used in dissolution experiments were ground to homogenize the sample and then stored in a flask over silica gel inside a desiccator.

Potassium dihydrogen phosphate (Merk p.a., ≥99.5%) and dipotassium hydrogen phosphate (M&B, purity 99%) were used to prepare the buffer solution. A volume of 195.0 mL of a 0.2000 mol dm^{-3} solution of KH_2PO_4 was added to 305.0 mL of a 0.2006 mol dm^{-3} solution of K_2HPO_4 in a 1000.0 mL volumetric flask, and the total volume was made up with Milli-Q water. The pH of the buffer solution was measured with a pH meter, (Meter Lab. pH M 220) to be pH 6.91.

Dimethyl sulfoxide (Merck p.a., ≥99.5% by GC) was used as received. Its water content was determined by Karl Fischer coulometry to be 0.014% (w/w). To avoid water uptake it was always handled under dry-nitrogen. Periodical checks did not show any increase in water content.

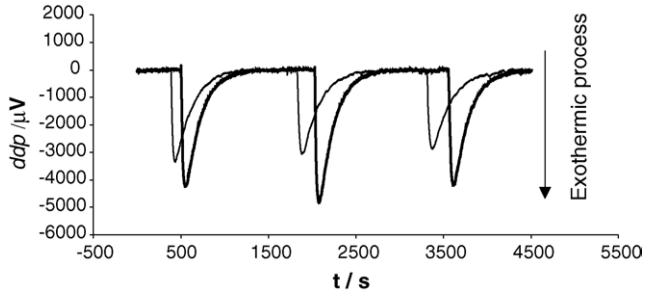

Fig. 1. "Empty cup" experiments in DMSO (bold) and water (light) at amplifier setting 30 μV.

2.3. Experimental procedure

In all experiments in water and in buffer the main tube (see Fig. 1, Ref. [20]) containing the stirring shaft was filled with water to minimize the gaseous phase and get therefore a shorter equilibration time and a better stability. In the DMSO experiments the inner tube was kept empty because water could not be used due to occurrence of liquid–vapour equilibria between the two solvents and the organic solvent could not be used because of its very low surface tension.

In all experiments the inner tube, all injector guide tubes and the cartridges were cleaned with water and ethanol and then dried with a flow of dry-nitrogen, to prevent problems due to humidity or some contamination from previous solvent [20].

Electric calibrations were performed in water and DMSO using an insertion heater connected to an electric battery and to an interface, which is computer controlled by the software SIGMA program (Sven Hägg, Lund University, Sweden). Electric pulses of $(5.000 \pm 0.003) \times 10^{-3}$ A were passed through the insertion heater for 10, 12 and 20 s for the 10, 30 and 100 μV amplifier settings, respectively. The insertion heater resistance of the two used heaters used in water and in DMSO were (50.915 ± 0.003) and (66.971 ± 0.003) Ω, respectively.

Blank experiments were performed to measure the thermal effect associated with the injection of an "empty cup". These experiments consisted in the injection of the sample cup holder into the solvent, without any substance [20]. Viton o-rings were used for the water experiments and Kalrez o-rings for DMSO. In the dissolution experiments the solid was pressed into tablets using a modest pressure. The detailed procedure used was described elsewhere [20]. Chemical calibration was performed through dissolution of KCl [20]. The calibration constant was calculated using enthalpies of dissolution reported in [21].

3. Results and discussion

Uncertainty values for all the results of the calorimetric measurements are reported as twice the standard deviation of the mean.

The results for the electrical calibration are presented in Table 1 for water and DMSO. Since the calorimeter is of the heat conduction type, the solvent shouldn't affect the values of the calibration constant. Accordingly, the values obtained for the two solvents at different amplifier settings agree within

Table 1
Calibration constants obtained in water and DMSO

Calibration	Amplifier setting (μV)	$\varepsilon^a \times 10^8$ (J (μV s)$^{-1}$)	n^b
Water			
Electric	10	2.12 ± 0.03	15
	30	2.16 ± 0.03	15
Chemical	30	2.25 ± 0.09	10
	100	2.26 ± 0.16	5
	300	2.26 ± 0.06	6
DMSO			
Electric	10	2.14 ± 0.02	16
	30	2.11 ± 0.02	19
	100	2.13 ± 0.01	14

[a] All values are corrected to the amplifier setting of 30 μV.
[b] Number of determinations.

the uncertainty limits. The calibration constant obtained from chemical calibration with KCl in water agrees with the electric calibration. Indeed the uncertainty is larger in chemical calibration as a result of a larger intrinsic variability. Therefore the calibration constant used thereafter was the overall mean of all calibration constants $(2.16 \pm 0.02) \times 10^{-8}$ J (μV s)$^{-1}$.

In the aqueous experiments the stabilization time was much shorter than in the DMSO experiments. This is due to the fact that the inner tube, which contains the stirring shaft, was filled with water in the experiments in aqueous media while it was empty in the DMSO experiments.

Blank tests were carried out in both solvents, and the effect is exothermic in both cases (Fig. 1). The larger amount of heat released in the DMSO experiments is a consequence of the higher friction that the Kalrez o-rings originate. Results are summarized in Table 2. The larger error for the first cartridge is due to a slightly different base that was used from another calorimetric cell, where the bottom part [20] was a little smaller, making the drop less reproducible. Nevertheless, the obtained results were within the experimental uncertainty and were therefore used.

The dissolution process for both drugs in phosphate buffer was fast and endothermic. The experiments in DMSO were more difficult to perform due to the slower dissolution reactions. Even so, the calorimeter provides good results for the enthalpies of dissolution of very small amounts of these drugs (∼1 mg) with DMSO as solvent. Due to a much smaller dissolution enthalpy in DMSO, in many experiments the balance between the "empty cup effect" (exothermic) and the dissolution process (endothermic) gave rise to a very small overall area (Figs. 2 and 3). This forced the need for more experiments in order to get a reliable value, as the amount of drug could not

Table 2
Thermal effect of "empty cup" injection

Cup	Water		DMSO	
	Q (mJ)	n^a	Q (mJ)	n^a
Cup 1	−16.8 ± 1.1	11	−22.6 ± 1.5	8
Cup 2	−16.4 ± 0.3	7	−22.2 ± 0.9	8
Cup 3	−16.4 ± 0.4	7	−20.5 ± 0.9	8

[a] Number of determinations.

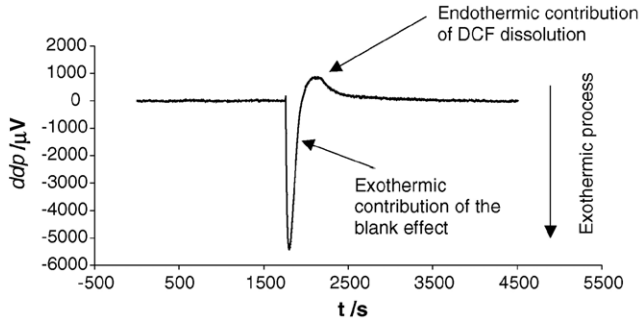

Fig. 2. Dissolution of a sample of 2.2136 mg of DCF in DMSO.

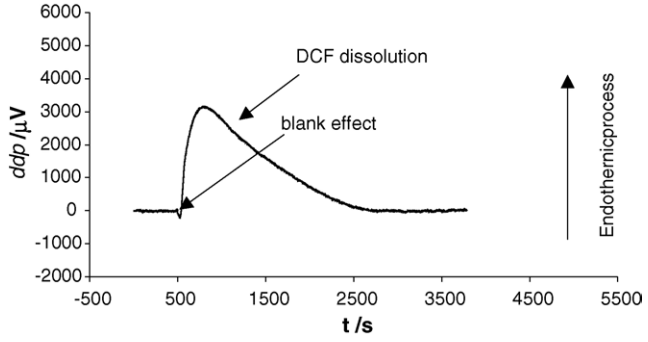

Fig. 3. Dissolution of a sample of 0.6141 mg of DCF in phosphate buffer (pH 6.91, T = 298.15 K).

be much increased due to solubility problems and dissolution time. The observed dissolution enthalpies did not depend on solute concentration—therefore, the results are taken as the infinite dilution enthalpies, $\Delta_{sol}H_m^\infty$. The results are presented in Table 3.

From the dissolution enthalpies in Table 3, the enthalpies of transfer of the drugs, at infinite dilution, $\Delta_{transf}H_m^\infty$, from phosphate buffer (pH 6.91) to DMSO, at T = 298.15 K were calculated. The values obtained were (-43.9 ± 1.6) and (-19.0 ± 0.6) kJ mol^{-1} for DCF and PC, respectively. The calculated transfer enthalpies show that the dissolution is enthalpically favoured in DMSO, probably due to the smaller cohesion energy of this solvent as compared to water, and therefore the

Table 3
Dissolution enthalpies, $\Delta_{sol}H_m^\infty$ of the two drugs in DMSO and phosphate buffer (pH 6.91), at T = 298.15 K

Solvent	Drug	$\Delta_{sol}H_m^\infty$ (kJ mol^{-1})	Difference (%)[a]	n^b
DMSO	DCF	2.7 ± 0.2		20[c]
	PC	1.89 ± 0.07		9
Phosphate buffer	DCF	46.6 ± 1.2 (50.24 ± 0.04[d])	7.8	5
	PC	21.0 ± 0.3 (24.76 ± 0.04[d])	17.7	6

[a] The values were calculated according to $[\Delta_{sol}H_m^\infty$ (Ref. [19]) $- \Delta_{sol}H_m^\infty] \times 100/\Delta_{sol}H_m^\infty$.
[b] Number of determinations.
[c] The higher number of determinations in this case was due to the evaluation of the concentration dependence of $\Delta_{sol}H_m$.
[d] Dissolution enthalpies obtained from Ref. [19] (phosphate buffer, pH 7, T = 310.15 K).

energy involved in creating a cavity to accommodate the solute is smaller.

Comparison of the obtained values with published ones [19] in the same buffer but at a different temperature (310.15 K) are in Table 3. From [19] a variation in pH from 6 to 7 only increases the dissolution enthalpy of PC and DCF of 0.10 and 0.23 kJ mol^{-1}, respectively. Therefore, the small difference in pH (our value was pH 6.91) can be neglected. Although the experiments in Ref. [19] were not carried at the same temperature ($\Delta T = 12$ K), it can be seen that the values are of the same order of magnitude and present the expected trend. It is well known that hydrophobic compounds have a high and positive ΔC_p value for their dissolution in water, which has been ascribed to the hydrophobic hydration [26–31]. In the case of DCF and PC, we can make a rough estimation of ΔC_p from the values reported in Table 3, leading to 303 and 318 J K^{-1} mol^{-1}, respectively. These estimates seem reasonable, if we consider the compounds' structure.

In summary, these results show that the enthalpy of dissolution of small amounts of these two drugs in DMSO could be determined with good precision in this calorimeter. Nevertheless the slow and energetically small dissolution processes do not allow us to consider them as good calibration substances when using DMSO as a solvent.

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