



An investigation of calibration methods for solution calorimetry

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Abstract

Solution calorimetry has been used in a number of varying applications within pharmaceutical research as a technique for the physical characterisation of pharmaceutical materials, such as quantifying small degrees of amorphous content, identifying polymorphs and investigating interactions between drugs and carbohydrates or proteins and carbohydrates. A calibration test procedure is necessary to validate the instrumentation; a few of the suggested calibration reactions are the enthalpies of solution associated with dissolving Tris in 0.1 M HCl or NaCl, KCl or propan-1-ol in water. In addition, there are a number of different methods available to determine enthalpies of solution from the experimental data provided by the calorimeter, for example, the Regnault–Pfaundler's method, a graphical extrapolation based on the Dickinson method, or a manual integration-based method. Thus, the aim of the study was to investigate how each of these methods influences the values for the enthalpy of solution. Experiments were performed according to the method outlined by Hogan and Buckton [*Int. J. Pharm.* 207 (2000) 57] using KCl (samples of 50, 100 and 200 mg), Tris and sucrose as calibrants. For all three materials the manual integration method was found to be the most consistent with the KCl in water (sample mass of 200 mg) being the most precise. Thus, this method is recommended for the validation of solution calorimeters.

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1. Introduction

Solution calorimetry has been used in a number of varying applications within the area of pharmaceutical research and is rapidly becoming an indispensable technique for physically characterising pharmaceutical materials. For example, solution calorimetry has been used to quantify small degrees of amorphous content (Hogan and Buckton, 2000); identify polymorphs (Souillac et al., 2002b) and investigate interactions between a drug and a carbohydrate (Chadha et al., 2002) or a protein and carbohydrate (Souillac et al., 2002a).

A prime requirement of any analytical procedure is to ensure that experimental results obtained in different laboratories are directly comparable. It is therefore essential that solution calorimeters should have an accepted calibration test procedure to ensure that all experimental data comes from qualified instruments. Ideally, a test system should be robust, simple to operate and only require materials that are readily available and need no or little preparation prior to use (Willson et al., 1999). There has been some discussion about the use of calibrants to assess the performance and accuracy of the solution calorimeter. A few of the suggested calibration reactions are the enthalpies of solution associated with the dissolution of Tris in 0.1 M HCl (Hill et al., 1969), KCl or NaCl in water (Archer and Kirklin, 2000) and propan-1-ol in water (Olofsson

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et al., 2000). In addition to a range of possible calibration materials, there are a number of different methods available to determine enthalpies of solution from the experimental data provided by the calorimeter. For example, in the case of a solution calorimeter operated under semi-adiabatic conditions, the enthalpy of solution can be determined from the temperature offset data using: (i) the Regnault–Pfaundler’s method (Wadsö, 1966), (ii) a graphical extrapolation based on the Dickinson method (Wadsö, 1966), or (iii) an integration-based method (Willson, 2002). Thus, the aim of the present study was to investigate how each of these three methods influence the values for the enthalpy of solution determined for a number of different test materials, and based on these results to recommend the most appropriate method and calibrant in order to validate semi-adiabatic solution calorimeters.

In addition, as the integration method has the extra benefit of converting the temperature offset data into power time plots, it was also planned to investigate the relevance of these plots in the characterisation of the dissolution profile of active pharmaceutical ingredients.

2. Experimental methods and material

A Thermometric Precision Solution Calorimeter 2225 S/N 71, SolCal, (Thermometric AB, Sweden) was used to determine the heats of solution of the following samples: sucrose (Tate and Lyle, UK) in distilled water, Tris (trihydroxymethylaminomethane) >99.8% from Aldrich in 0.1 M hydrochloric acid, potassium chloride (KCl, Standard Reference Material 1655, National Bureau of Standards certificate) in distilled water. The KCl was dried for over 24 h at 423 K in an oven and samples of 50 mg, 100 mg and 200 mg were analysed. The drying process was further investigated by thermogravimetric analysis (TA Instruments TGA 2950). During this analysis 15 mg of the KCl sample were held at 423 K again for 24 h, with the mass recorded continuously as a function of time throughout this period.

The experimental procedure was carried out according to the method described by Hogan and Buckton (2000). Briefly, the solution calorimeter was thermostated in a Heto precision water bath. Between 50 and 200 mg (depending on solute and set of

experiments) of sample were placed in glass crushing ampoules. The ampoules were double-sealed with beeswax, placed in the calorimeter and after an appropriate equilibration time broken into 100 ml of solvent. In the case of the 25 ml vessel, 25 ml of solvent was used. The solution calorimeter monitored the change in temperature during this process via a thermistor incorporated in the reaction vessel. Each sample was run a minimum of three times with the stirrer within the calorimeter being set at 500 rpm.

Three different calculation methods were used to analyse the data, and the results from the different approaches are discussed in turn in the following sections.

3. Results and discussion

3.1. Sample preparation

Samples of KCl were analysed thermogravimetrically at 423 K for 16 h to simulate the drying process. After the samples had been brought to a temperature of 423 K, there was no weight loss that might correspond with the evaporation of water. There was a slight fluctuation in the mass of the sample over the 16 h period (the coefficient of variance (%cv) of the baseline was 2.0×10^{-2}). This was less than the fluctuation observed when the experiment was carried out using an empty sample pan (%cv 7.7×10^{-2}), and was thus considered to be an instrumental artefact. The National Bureau of Standards (NBS) recommends that the KCl sample is dried at 800 K for at least 4 h, but it has been suggested in the literature that drying at a temperature above 600 K could be unnecessary (Archer and Kirklin, 2000).

3.1.1. Raw data

A typical response from the SolCal is shown in Fig. 1, the calorimeter records the fluctuation of temperature as a function of time. The calorimeter used was operated under semi-adiabatic conditions, so the initial temperature was offset, typically by 200 mK, from the air bath temperature of 25 °C (298.15 K). The baseline sections in Fig. 1 were used to check that the observed temperature increase conformed to an exponential decay, which is the condition that is assumed for the heat flow equations (Section 3.2). Before and

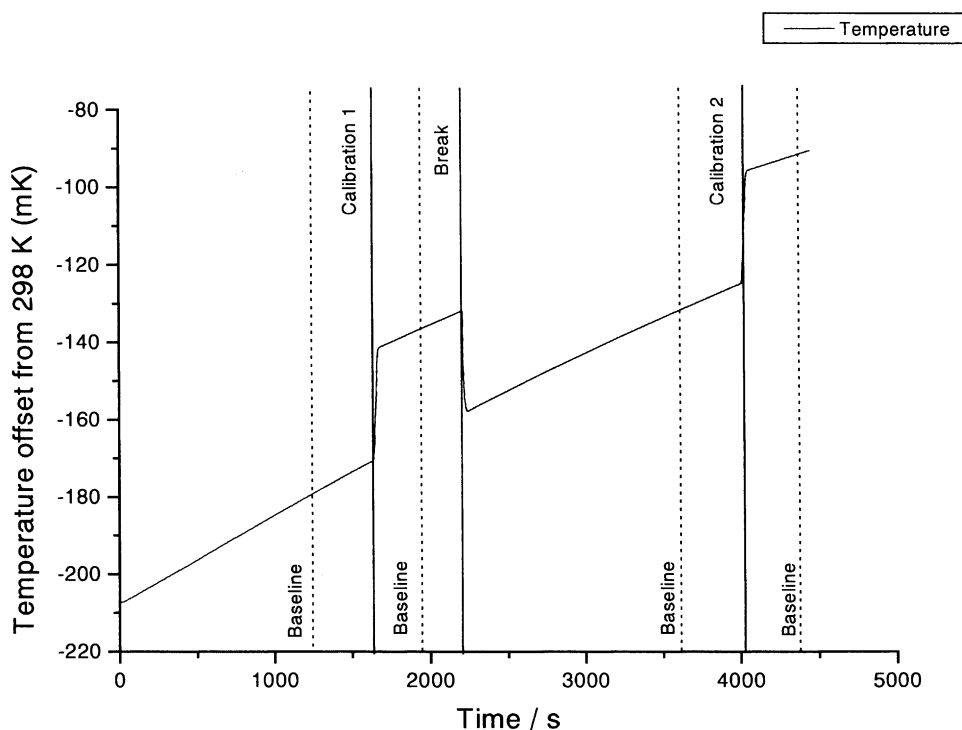


Fig. 1. An example of a typical response from the solution calorimeter, showing temperature against time.

after the ampoule was broken, the calorimeter was calibrated electrically with known amounts of heat supplied to the solution via an electrical heater. From these calibrations and the baseline sections, three different analysis methods were used to determine values for the enthalpy of solution when the sample ampoule was broken into the 100 ml of solvent contained in the calorimeter vessel, marked “Break” in Fig. 1. A number of different processes can be initiated when the ampoule is broken, in addition to the formation of a solution, so the “Break” section is referred to as the reaction section of the temperature offset data.

Typically, the temperature offset during the “Break” section in the KCl and sucrose experiments remained below zero. By analysing a series of electrical calibrations, with some below zero and some above zero, it was discovered that the temperature offset did not have an obvious effect on the value of the heat flow. Using an electrical input set at 10 J, the average was taken of 10 calibrations (5 were below zero and 5 above) and this was 10.047 J (%cv of 0.026).

3.2. Data analysis

A new user of a solution calorimeter is confronted with a number of complex equations that allow the conversion of the recorded temperature offset into the associated change in enthalpy for the process under study. The purpose of the following section is to introduce the reader to the basic concepts of the data analysis, and to summarise the three methods used by the authors to determine the enthalpies of solution quoted in this paper. For the full derivations, the reader is directed to the original papers cited in the text below. The present discussion centres on the calculations associated with the calorimeter used by the authors, but the approaches are transferable and are currently used, or can be used, with most of the solution calorimeters available on the market.

In the specific case of an adiabatic calorimeter, no heat is exchanged between the calorimetric vessel and its surroundings (Wadsö and Goldberg, 2001). When a process or reaction occurs in the calorimetric vessel,

the quantity of heat evolved or absorbed, Q (J), is equal to the product of the temperature change, ΔT (K), and the total heat capacity of the calorimetric vessel, C (J/K), given in Eq. (1).

$$Q = C\Delta T \quad (1)$$

However, Eq. (1) describes an ideal situation, as all calorimeters typically suffer some heat transfer between their vessel and the surroundings. The SolCal conforms to this observation especially as it was operated under semi-adiabatic conditions for the study reported in this paper. Thus, Eq. (1) cannot be applied without a prior calibration experiment, whereby a known amount of heat is supplied to the system, usually via an electrical heater, and the resultant change in temperature is used to determine a calibration constant, ε . Furthermore, the assumption made in Eq. (1) is that the measured temperature change arises solely from the reaction taking place in the vessel, but there are other contributions to the observed change in temperature, ΔT_{obs} . The heat caused by stirring the solution, the heat generated by the thermistor and heat leakage all contribute to the observed change in temperature. Therefore, ΔT_{obs} is expressed by:

$$\Delta T_{\text{obs}} = \Delta T_{\text{corr}} + \Delta T_{\text{adj}} \quad (2)$$

where ΔT_{corr} is defined as the corrected temperature change for the reaction (or calibration) and is the temperature change that would be observed if the reaction (or calibration) was carried out in an ideal adiabatic calorimeter with no other contributions to the temperature response. ΔT_{adj} is defined as the temperature change from all other factors that contribute to ΔT_{obs} . In order to determine the value of ΔT_{adj} for a particular experiment two further parameters are required.

A typical experiment combines both calibrations and the reaction under investigation within the same run, and connecting these sections are regions termed baselines (Fig. 1). These baseline sections clearly show the underlying exponential decay from the initial temperature offset, of approximately 200 mK, in the direction of the air bath temperature. This decay is described by Eq. (3):

$$T = T_{\infty} + \Delta T_{\text{norm}} e^{-t/\tau} \quad \text{where } \Delta T_{\text{norm}} = T_0 - T_{\infty} \quad (3)$$

where T is the temperature of the contents of the calorimetric vessel at time t , recorded by the thermistor. T_0 is the starting temperature and T_{∞} is the temperature that the vessel would approach if the temperature was recorded for an infinitely long time, i.e. the value of T at $t = \infty$. T_{∞} is commonly described as the constant steady-state temperature of the reaction vessel. The calorimeter time constant, τ , relates to the thermal “leakage” of the vessel and it reflects the rate at which the temperature of the solution within the vessel approaches the steady-state temperature, T_{∞} . The time constant is measured in seconds and can also be expressed as $\tau = \varepsilon/k$, where k is the heat exchange coefficient.

The first operation during the data analysis is therefore to fit data from the baseline sections to the exponential temperature function, Eq. (3). These baselines, shown in Fig. 1, are recorded both before and after each calibration and the break sections. Fig. 1 clearly illustrates the exponential decay of the offset temperature towards T_{∞} within the baseline sections. A multi-parameter least-square minimising fitting routine, part of the software accompanying the High Precision Solution Calorimeter (Thermometric, 1996), was the specific method used to generate values for both T_{∞} & τ from the temperature and time data, as T_0 is known from the beginning of each baseline section. At this point the different methods of analysis diverge with respect to which parts of the baseline are used to determine T_{∞} & τ , and by which method of integration is used during the reaction.

In the Regnault–Pfaundler’s method, which is based on the reaction dynamics of the break (Wadsö, 1966), T_{∞} and τ are calculated from baseline sections immediately before and after the break. The value of ΔT_{adj} , the sum of the contributions to the temperature change from other factors, is determined from the following integral:

$$\Delta T_{\text{adj}} = \int_{t_{\text{start}}}^{t_{\text{end}}} \frac{1}{\tau} (T_{\infty} - T) dt \quad (4)$$

where t_{start} is the time of the break or calibration start and t_{end} is the time when the reaction section is finished, therefore $t_{\text{end}} - t_{\text{start}}$ is the time associated with the reaction or calibration period. The corrected temperature change is calculated by subtracting ΔT_{adj} from the observed temperature change

(Eq. (2)). ΔT_{corr} is determined for both the break and calibrations sections, giving $\Delta T_{\text{corr, reaction}}$ and $\Delta T_{\text{corr, calibration}}$, respectively. Once $\Delta T_{\text{corr, calibration}}$ has been determined from the calibration sections of the experiment, where a known amount of heat, $Q_{\text{calibration}}$, is supplied to the system via the electrical heater, it is relatively straightforward to calculate a calibration constant, ε , using Eq. (5) given below.

$$\varepsilon = \frac{Q_{\text{calibration}}}{\Delta T_{\text{corr, calibration}}} \quad (5)$$

The above is a rearrangement of Eq. (1), where ε is the effective heat capacity of the system. Unless there are major differences in the post and pre-break values, an average ε value is determined. For the break section, the corrected change in temperature for the reaction, $\Delta T_{\text{corr, reaction}}$ and ε , can be used to determine the unknown quantity of heat evolved or absorbed during the reaction, Q_{reaction} , using Eq. (6) given below:

$$Q_{\text{reaction}} = \varepsilon \Delta T_{\text{corr, reaction}} \quad (6)$$

In the present case Q_{reaction} represents the formation of solution, so dividing this value by the amount of solute used gives the enthalpy of solution, $\Delta_{\text{sol}}H$ (kJ mol^{-1}). The Regnault–Pfaundler’s method is frequently used when the heat of reaction is small, and is referred to as the Dynamics of Break method.

The second calculation method is a model based on the reaction dynamics of the electrical calibrations and uses the baseline data associated with either the pre- or post-break calibrations to calculate values of T_{∞} and τ . This is carried out, as explained above, by fitting these baselines to Eq. (3). Subsequently, the method uses the graphical extrapolation method of Dickinson (Wadsö, 1966) to determine the corrected temperature change, ΔT_{corr} , with the assumption that the rate of heat evolution during a reaction is truly exponential. Eqs. (5) and (6) are applied in a similar way to the previous method to give the enthalpy of solution. This method is referred to as the Dynamics of Calibrations method. Both the Dynamics of Break and Dynamics of Calibrations methods are offered as options in the software accompanying the high precision solution calorimeter.

The third method involved manual integration of the data using OriginTM software, after the calorimetric response, given as the temperature change against time,

was converted to heat flow. The software requires a value for the thermistor time constant in order to carry out the calculations. The thermistor time constant is different from the calorimeter time constant, as it is a measure of the lag between the temperature change caused by the reaction and its detection by the thermistor situated in the calorimeter vessel. Therefore, the thermistor time constant is required to dynamically correct for the dullness or the inertia of the thermistor at the beginning of the reaction or calibration. It is defined by the user and typically has a value within the range of 1–10 s. Fig. 2 shows the dynamically corrected heat flow signals determined from the observed temperature changes (using a thermistor time constant of 2 s), against time. The conversion of the temperature offset data to heat flow which is based on Eq. (7) given below, was carried out using the Thermometric software.

$$-\frac{dQ}{dt} = \varepsilon \left(\frac{dT}{dt} + \frac{1}{\tau}(T - T_{\infty}) \right) \quad (7)$$

where dQ/dt is the heat flow (power) due to the solution reaction or electrical calibration, and is defined as negative for exothermic reactions. Eq. (7) is based on the Tian equation (Wadsö and Goldberg, 2001) and in a similar way to Eq. (3) assumes that, if left to continue to infinity, the temperature of the reaction vessel will reach the constant steady state T_{∞} by exponential decay.

The Thermometric software allows the data to be exported and plotted as a curve representing power against time. Peaks are seen that correspond to the input from the electrical calibrations and the solution process of the sample after the ampoule is broken. If the peaks are integrated to give the area under the curve, this will give the value, in joules (J), of the power input of the calibration and heat of solution of the sample respectively. Dividing this latter value with units of joules by the sample mass of the solute, the enthalpy of solution in J/g can be obtained, which in turn can be converted to J/mol.

The selection of the thermistor time constant was based on the analysis of the calibration section of the experiment before and after the break. The calibration peaks in the heat flow signal, produced by the electrical heater, were integrated, the areas of which should be equivalent to the amount of heat, in joules,

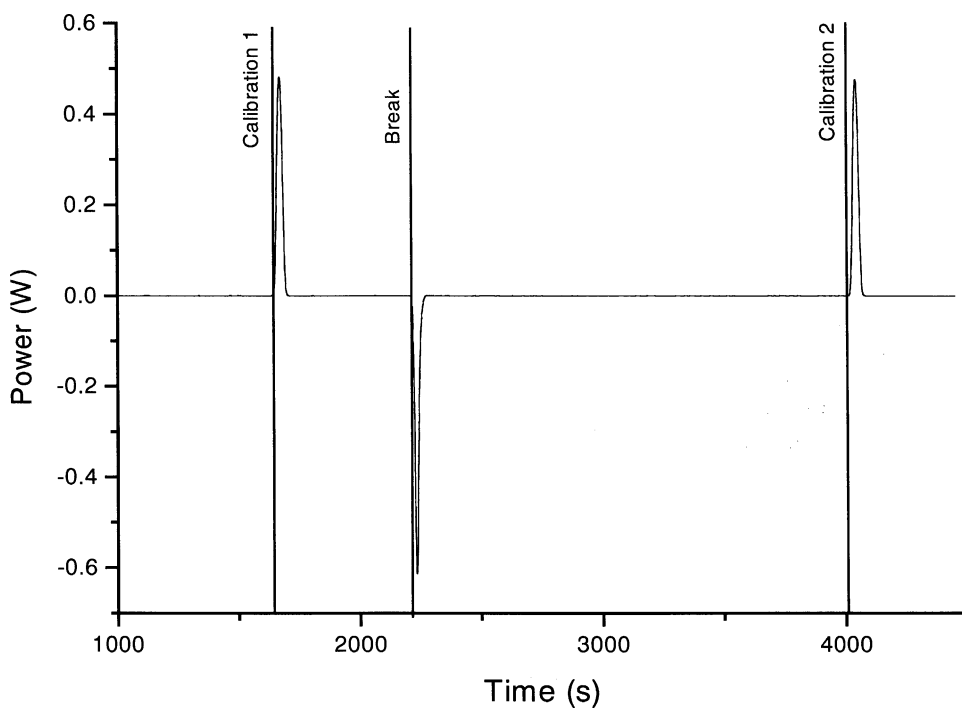


Fig. 2. An example of the response from the solution calorimeter where the signal has been converted into power (heat flow) against time.

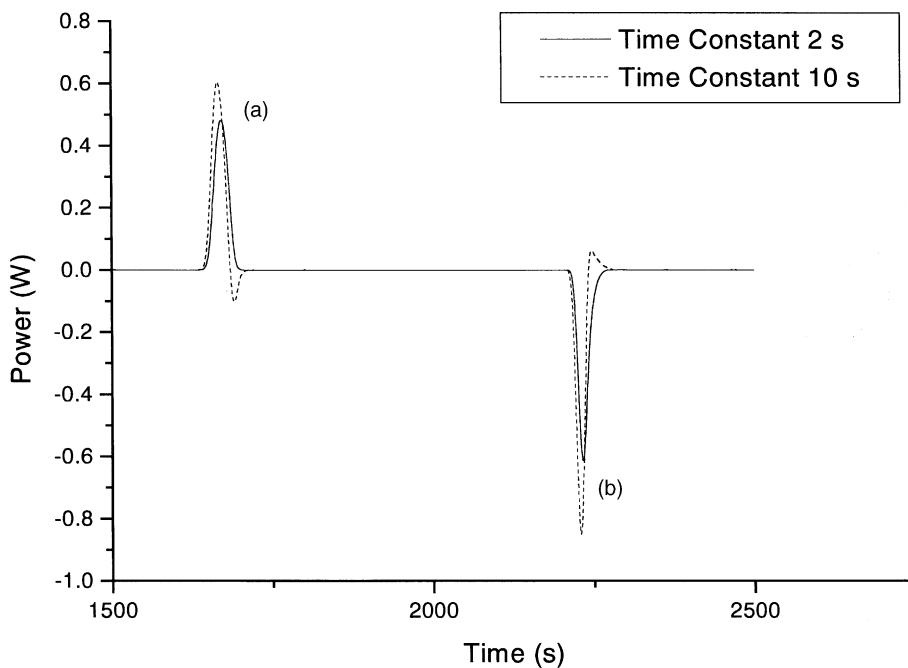


Fig. 3. The effect of the thermistor time constant on the shape of the power/time curve corresponding to (a) an electrical calibration and (b) the solution process of the sample.

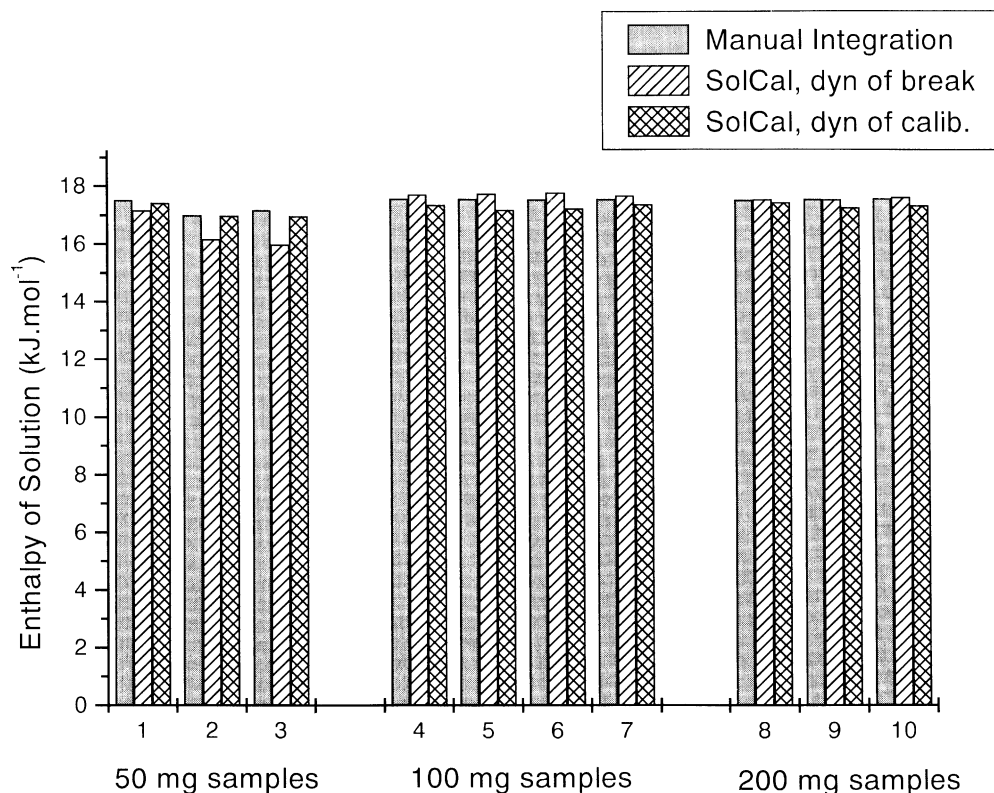


Fig. 4. A comparison of the three different methods of calculating the enthalpy of solution for KCl, of three different sample masses, in water. The variation in enthalpy between the three methods as well as between the samples themselves decreases as the sample mass increases.

supplied to the solution. The amount of heat supplied from the heaters was calculated, from the heater voltage, current and resistance. Different thermistor time constants were used to produce heat flow signals and it was found that these affected the shape of the curve. If larger values were chosen for the thermistor time constant, the peak tended to be narrower with the tail crossing the baseline to form an additional small peak in the opposite direction. Although this did not have a great effect on the area as long as both peaks were included in the integration, the shape of the peak is important for information about the dissolution process. A thermistor time constant of 2 s gave calibration peak areas that matched the number of joules supplied by the heater and produced a single peak, therefore this thermistor time constant was used to determine the heat flow signals shown in Fig. 2. Fig. 3 shows the effect that the thermistor time constant has on the shape of the peaks.

3.3. Potassium chloride

The results obtained for the dissolution of KCl in water are shown in Fig. 4. The enthalpies of solution in joules per mole are shown for a total of ten experiments, grouped into sample masses of (200 ± 1.088) , (100 ± 3.860) and (50 ± 0.675) mg. The data from the solution calorimeter were analysed using the three different, previously detailed, methods and these results are shown for each sample. The figure shows that the results were more reproducible when a sample mass of 200 mg was used compared to 50 mg. Analysis showed that the significant difference between the groups of different mass was caused by the 50 mg sample group, there was no significant difference between the 100 mg and the 200 mg sample mass groups. If the average of the enthalpies of solution is calculated, excluding the 50 mg samples, these values are (17.556 ± 0.019) , (17.664 ± 0.086) and (17.316 ± 0.084) kJ/mol for the

manual method of integration, the SolCal dynamics of break and SolCal dynamics of calibration respectively. Statistical analysis by ANOVA showed that this difference between the methods was significant ($P < 0.05$) and also that the effect of using different sample masses was significant ($P < 0.05$). The method of manual integration was shown to be the most consistent and have the least associated variance in the values. The method of manual integration was also shown to produce the enthalpies of solution that were closest to the certified value of 17.584 ± 0.05 kJ/mol (Uriano, 1981). Use of this method of analysis has an additional benefit in that it can provide information about the rate of dissolution of the sample. If the power/time curve of the experiment is integrated manually and the results of this integration are plotted, a curve is obtained that shows cumulative heat flow with time (Fig. 5). Individual points on this curve can be calculated as a percentage of the total heat flow (area under the curve) and as such, the point in time where the heat flow is

at 50% can be taken as T_{50} of the dissolution process. Such findings suggest that solution calorimetry could be used in dissolution studies for fast dissolving pharmaceutical materials provided they can fit into the ampoule. For example, a comparison could be made between the dissolution processes resulting from various dosage forms, such as microspheres, self-emulsifying drug delivery systems (SEDDS) (Porter and Charman, 2001), or powdered material destined for capsules. However, knowledge of the particle size and particle size distribution would be required for the detailed interpretation of such dissolution data.

Unless otherwise specified, the rest of the results shown in this paper have all been calculated using the manual method of integration.

The KCl supplied by the National Bureau of Standards (NBS) was a standard reference material and has a certified value for its enthalpy of solution in water when performed under certain standard conditions (Uriano, 1981). As it was not possible to carry

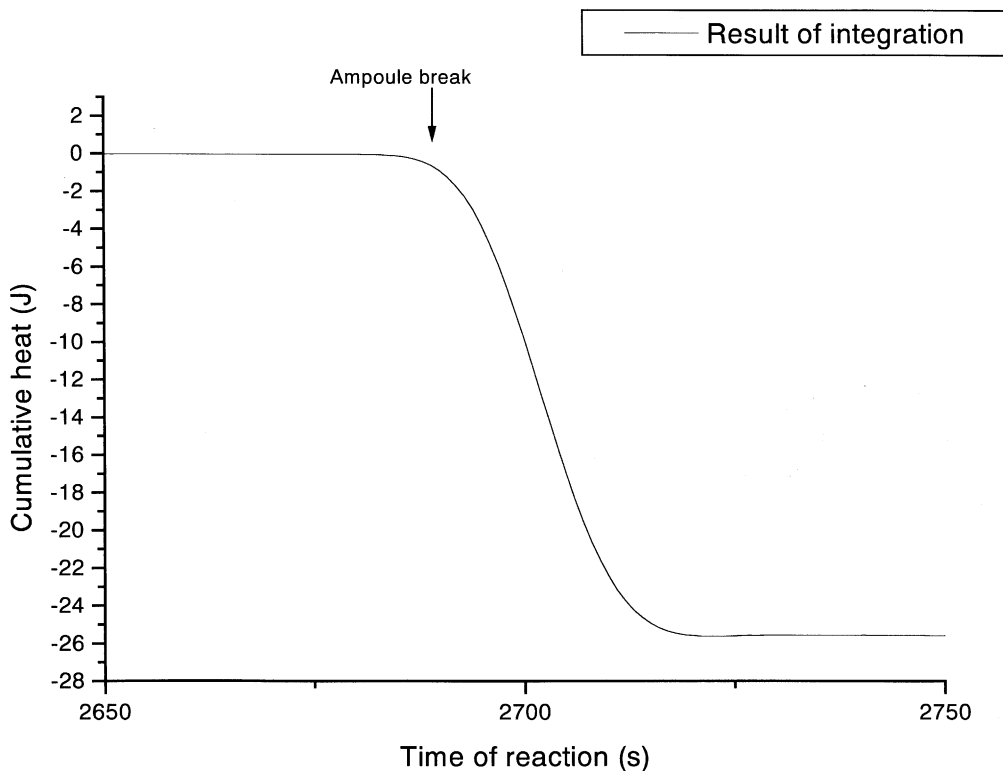


Fig. 5. The result of the integration of the power time curve of an experiment plotted as cumulative heat flow. The time corresponding to half of the total heat flow can be regarded as T_{50} .

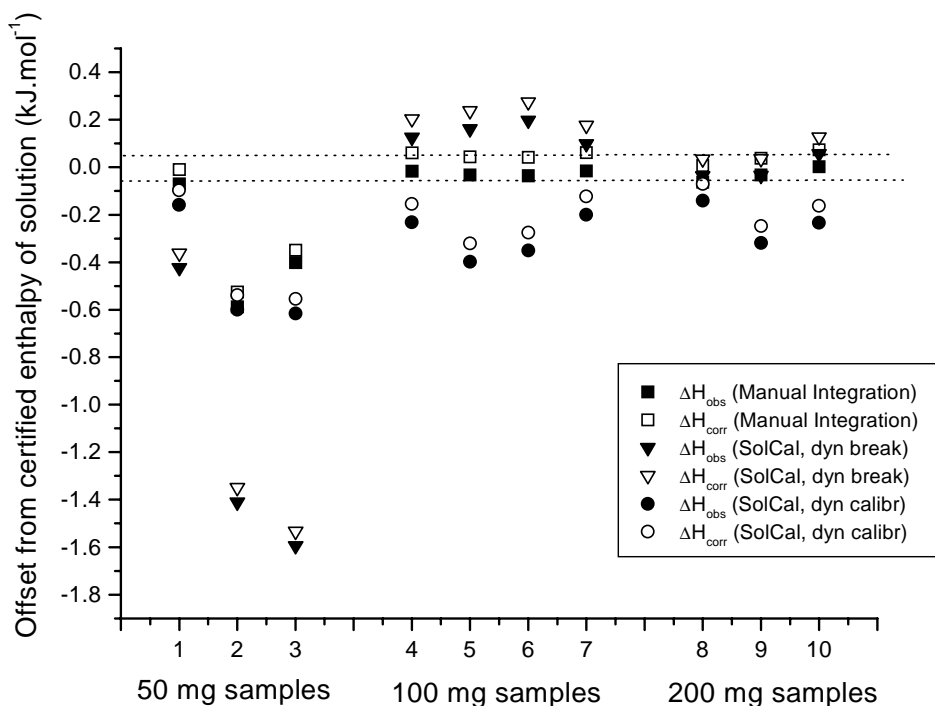


Fig. 6. The offsets of the results of the KCl in water experiments from the certified enthalpy of solution (17.584 ± 0.05) kJ/mol were determined by subtracting this value from the observed enthalpies. The dotted line shows the limits of the certified value. The results are compared using the three different methods of analysis and three different sample masses, and also incorporate the recommended NBS corrections in the enthalpy.

out the experiments at the exact conditions specified, it was necessary to make corrections to the measured enthalpy values. These procedures involved correcting for the molality, the energy of condensation and the energy of vaporisation and are further explained in the NBS certificate for the standard reference material 1655. The effect of these corrections can be seen in Fig. 6. The same figure also shows how the values of the enthalpies of solution compare to the certified value specified by the NBS. The data are obtained by subtracting the certified enthalpy from the measured enthalpy, and this offset is compared across all the samples using all the methods of analysis, with and without corrections.

It can be seen that the least variability is observed with the highest sample mass, which is to be expected because the certified enthalpy value refers to a molality of 0.111 M, so the smaller samples require a larger correction factor.

The NBS certificate also recommends that the sample masses should be corrected using a buoyancy factor. This factor has not been incorporated in the results shown here because it was calculated that the effect this would have on the enthalpy of solution is to decrease it by approximately 0.008 kJ/mol throughout, and this value is smaller than the variability found in the data. The possible error that could occur from the weighing out of the samples (± 0.01 mg) was calculated. The effect that this has on the enthalpies of solution in terms of %cv, were only 0.0004, 0.0013 and 0.005% for the sample masses of 200, 100 and 50 mg, respectively, and hence these were not incorporated into the results.

3.4. Comparison of calibrants

Using all three methods of analysis, the enthalpies of solution for KCl, Tris and sucrose are shown in

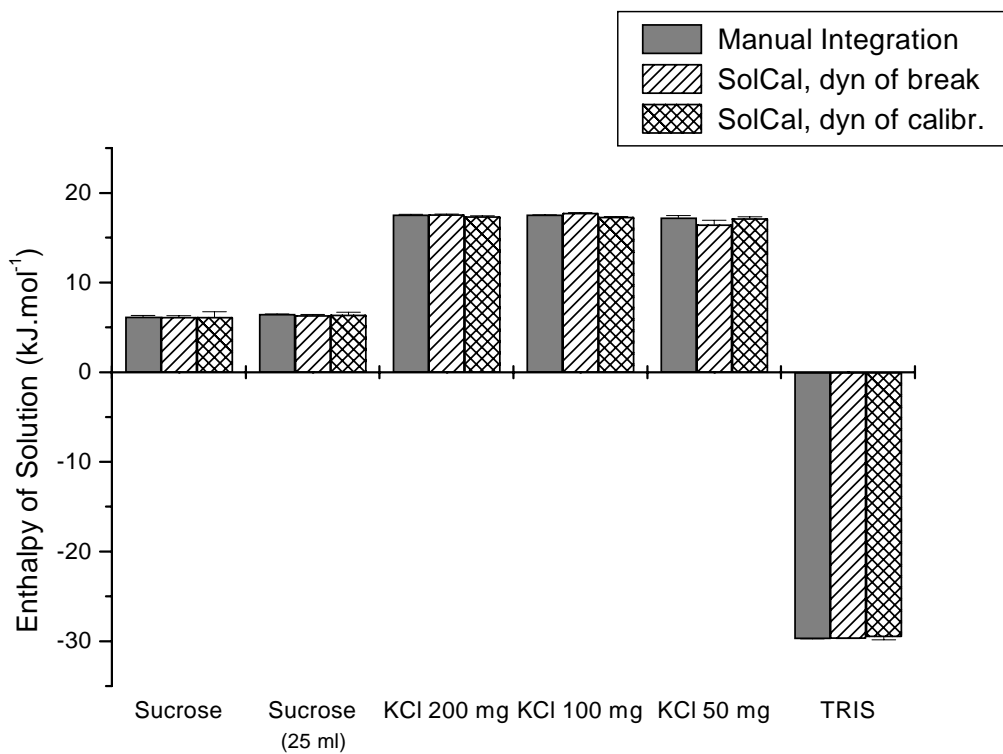


Fig. 7. A comparison of the three methods of analysis across all the samples used as calibrants in this study. For sucrose $N = 6$, but using the 25 ml vessel, $N = 3$. For KCl, 50 mg $N = 3$, 100 mg $N = 4$, 200 mg $N = 3$. For Tris, $N = 6$. The error bars represent the standard deviation.

Fig. 7. The enthalpies of solution calculated by manual integration are compared to literature values in Table 1. Sucrose experiments were carried out using a 25 ml vessel as well as the 100 ml vessel, the

results compare favourably to those reported previously (Table 1). The experimental data show that the dissolution of 200 and 100 mg KCl samples produced the more reproducible enthalpies, so the data

Table 1

A summary showing some of the calibrants that have been used in solution calorimetry and a comparison of the values of the enthalpies of solution found in the literature to those determined in this study using the manual integration-based method of analysis

Calibrant	Enthalpy (kJ/mol)	Reference	Measured enthalpy (kJ/mol)
KCl in water	17.584 ± 0.050	Uriano (1981)	17.556 ± 0.019
	17.22	CRC Handbook (1986)	
	20.14	Salveti et al. (1996)	
Tris in 0.1 M HCl	-29.75 ± 0.02	Hill et al. (1969)	-29.72 ± 0.02
Sucrose in water	6.172 ± 0.158	Gao and Rytting (1997)	6.167 ± 0.153
	6.43	Salveti et al. (1996)	
Propan-1-ol in water	-10.16 ± 0.02	Olofsson et al. (2000)	
KF in water	-17.73	Salveti et al. (1996)	
NaCl in water	4.213 ± 0.012	Archer and Kirklin (2000)	

obtained from the 50 mg samples have not been included in the values in Table 1. The values for Tris are also highly reproducible and correlate well with the previously reported data (Hill et al., 1969). Table 1 illustrates that the values reported for the heat of solution of a given calibrant show variability, although this would probably be reduced if certified samples were used in all cases. It is also likely that introducing one standard method of analysing the data from the solution calorimeter could reduce this variability further.

For all three calibrants, the literature value was subtracted from the observed value of the enthalpy to calculate the offsets and these were compared. Analysis by ANOVA showed no significant difference between the methods of analysis for the data from all three calibrants, but the difference between the offsets from the three calibrants was significant ($P < 0.05$). However, when the offsets were standardised as a percentage of the enthalpy they were offset from, the difference between the calibrants was not significant ($P > 0.05$).

4. Conclusions

The observed %cv of the enthalpies of solution obtained by the dissolution of KCl in water decreased as a function of the sample mass. Experiments using 50 mg of KCl did not show acceptable reproducibility, so a minimum of 100 mg should be used although, if possible, 200 mg would be preferred.

KCl (standard reference material) would appear to be an ideal material to act as a calibrant, although the experimental results obtained in this study have shown that Tris also has a reproducible enthalpy of solution. The variance in the enthalpy of solution of Tris was larger than that found with KCl samples, however it is useful to include an exothermic as well as an endothermic reaction standard in any calibration procedure.

Sucrose has a relatively reproducible enthalpy of solution. In contrast to KCl, sucrose does not need to be dried beforehand and can be used as received. It also does not need to be stored in a desiccator and there are no corrections that need to be made to the enthalpy of solution and it is also cheap and easy to use. However, sucrose is not as robust a calibrant as

KCl because it does not have a standard certified enthalpy of solution, but is an ideal sample to use for the purpose of a spot check for the performance of the solution calorimeter. From these results, the calibration test system that produced the most consistent results was KCl in water (sample mass of 200 mg) using the manual integration-based method of analysis. Since this procedure provides the most reproducible enthalpies, it is recommended that this should be the minimum procedure that should be carried out prior to undertaking further studies to ensure that the data between different solution calorimeters are validated and thus comparable.

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