



Evaluation of Heat-conduction Microcalorimetry in Pharmaceutical Stability Studies

(1) Precision and accuracy for static experiments in glass vials

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INTRODUCTION

In the preformulation stage of pharmaceuticals, accelerated stability studies using data from DSC/DTA studies, combined with analytical techniques such as spectroscopy and HPLC are the normal methods used to collect data. The possibility to use isothermal heat conduction microcalorimetry to obtain rate constants at close to, or at room temperatures could therefore be of interest for reactions that follow the Arrhenius relationship.

The objective was to evaluate the precision and accuracy of the microcalorimetric system by measuring the rate constant at several temperatures and calculating the activation energy of the well documented hydrolysis of acetylsalicylic acid (ASA) in aqueous solution of pH 1.1.

EXPERIMENTAL

2.40g (0.010M) ASA solution and 2.40g 0.010M HCl, were dispensed into the disposable calorimetric glass containers, capped and then placed in the measuring and reference chambers respectively. Measurements were performed at 30, 35, 40, 45 and 50 °C. 2277 Thermal Activity Monitor - TAM equipped with twin ampoule measuring units was used in these studies.

Evaluation of results:

Degradation of ASA is followed by an enthalpy of reaction (ΔH) which is exothermic. The heat flow, dq/dt and the rate of degradation are proportional to the ASA concentration:

$$dq/dt = \Delta H(-d[ASA]/dt) = \Delta Hk[ASA] \quad (1)$$

This can also be written as:

$$\ln(dq/dt) = \ln(dq/dt)_{t=0} - kt \quad (2)$$

where the rate equation has been integrated and the heat flow (dq/dt) has replaced the concentration of ASA. A plot of $\ln(dq/dt)$ versus time gives a straight line; the gradient being proportional to k . The Arrhenius relation was used to determine the activation energy (E_a) and further extrapolate the rate constant to 25 °C.

RESULTS AND DISCUSSION

The heat flow curve for the degradation of ASA in aqueous solution of pH 1.1 at 45 °C is shown in Figure 1. A pseudo first order rate constant predominates in these conditions.

Evaluation of baseline stability

Several baseline experiments at 25 °C and 50 °C resulted in 0.07 and 0.14 μW baseline drifts respectively over 22h. Thus showing the baseline stability of TAM over long periods.

Evaluation of parallel reactions

TAM detected heat output from temperature and mechanical relaxation occurring in the rubber sealing material used in the glass ampoules. At 25 °C this effect declined rapidly, whereas at 50 °C the heat flow was 0.42, 0.29 and 0.22 μW after 2, 7 and 17h respectively.

Evaluation of the selected time period

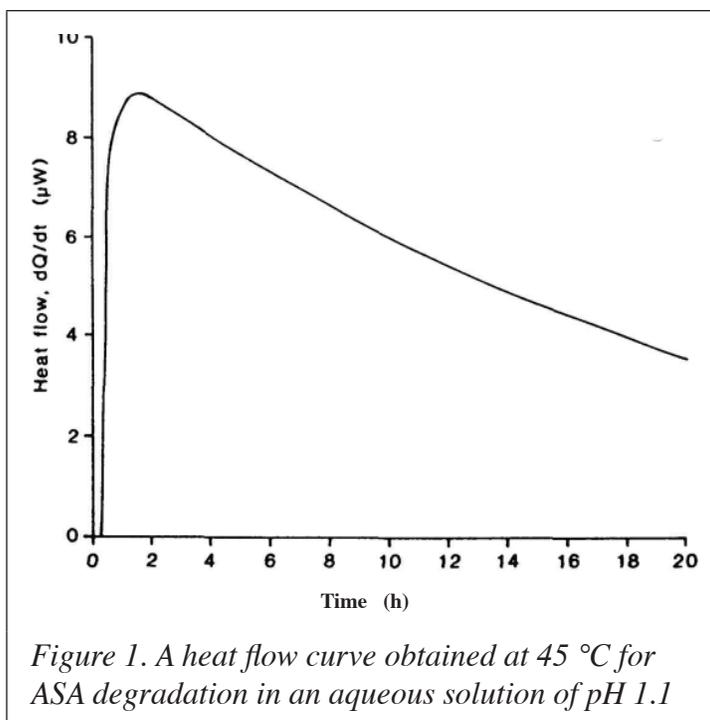
Results from previous experiments indicated that the best time for the rate constant determinations was between 4-17h. at 45 °C. Microcalorimetric results showed that the value of the rate constant did not significantly differ between 4-17h at 45 °C. This shows the linear rate of decomposition of ASA in aqueous solution at pH 1.1 between 4-17h. The time interval 7-11.5h was used for further evaluation.

Evaluation of precision

The precision of the results between 7-11.5h was found to increase with increase in temperature which corresponds to increased heat flow. The relative standard deviations were found to be less than 5% at 45 °C and 50 °C, but increased for lower temperatures.

Evaluation of accuracy

The Arrhenius plot was found to follow a linear relationship. This was extrapolated to 25 °C, and the corresponding rate constant was found to be close to that obtained by other techniques (table 1). The activation energy calculated from the means of the rate con-



stants at each temperature was similarly found to correlate well with the value from other methods (table 1).

Experimental technique	Reference	Activation energy (kJ/mol)	Rate constant at 25°C (h-1103)
Isothermal/ Spectroscopy	b)	69.5	8.06
Non-isothermal/ Spectroscopy	c)	70.6	8.23
Isothermal/ Heat-conduction microcalorimetry		71.9	8.41

Table L Comparison of experimental data and literature data for the degradation of ASA in an aqueous solution of pH 1.1.

COMMENTS

Although no conclusion was published for this part of the paper, it is clearly evident that microcalorimetric techniques particularly of the isothermal heat conduction type are valuable in determining the rate constants at close to real reaction conditions. Microcalorimetry therefore complements conventional assay techniques.

REFERENCES

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NOTE

This is the first of two papers on this study. Application Note written by M. Shafiq, ThermometricAB.