Evaluation of Heat Conduction Microcalorimetry in Pharmaceutical Stability Studies
(2) Methods to evaluate the microcalorimetric response

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INTRODUCTION

In preformulation and formulation work on pharmaceutical preparations preliminary testing of stability often requires high temperatures and therefore suffers from the uncertainty of extrapolation to room temperatures. (These methods of calculation of stability are only valid if the mechanism of reaction remains unchanged over the temperature range studied). Since with isothermal heat conduction microcalorimetry the intensity of heat flow (dq/dt) is related to the concentration of sample, enthalpy of reaction and the rate constant, the rate of degradation of a sample can sometimes be calculated at close to normal storage conditions.

The objective of this study was to determine the rate constants and to evaluate the precision and accuracy of microcalorimetric data for the hydrolysis of acetylsalicylic acid (ASA) at different temperatures and pH values. Furthermore, the microcalorimetric response was evaluated by two additional methods.

EXPERIMENTAL

180 mg ASA was dispensed into 100ml 0.01M buffer solution giving a 0.01M ASA solution ranging from pH 1.9 to 7.5. 2.40g of the solution was then placed in disposable microcalorimetric glass containers. Measurements were conducted at 40 and 50 °C, as described in Application Note 22005 using 2277 Thermal Activity Monitor, TAM, equipped with twin ampoule measuring units.

Evaluation of Results

Degradation of ASA is followed by an enthalpy of reaction (ΔH) which is exothermic. Microcalorimetric data can be related to the enthalpy of reaction by:

$$dq/dt = \Delta H(-d[ASA]/dt) = \Delta H\, k\, [ASA]$$

Integration of the equation yields:

$$\ln(dq/dt) = \ln(dq/dt)_{t=0} - k\,t$$

The Arrhenius relation was used to determine the activation energy, Ea and further extrapolate the rate constant to 25 °C; the rate constant k being proportional to the gradient. Substitution of Ea into other equations allows the calculation of thermodynamic quantities for the transition state.
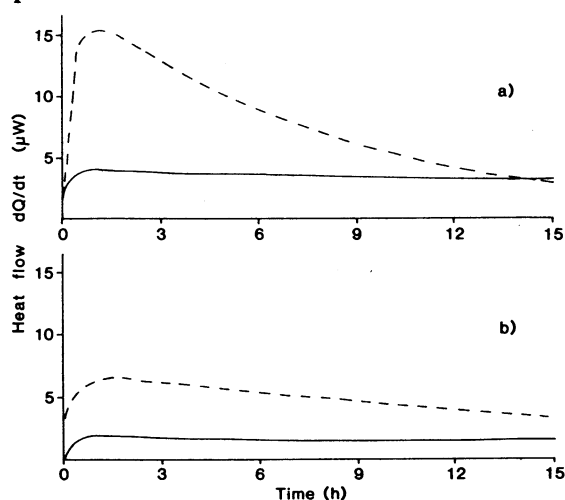

Figure 1. Primary heat flow-time curves for ASA hydrolysis at pH 2.4 (———) and pH 5.4 (- - - - -) at (a) 50.0 °C and (b) at 40.0 °C.

RESULTS AND DISCUSSION

The rate constant-pH profiles

The primary heat flow curves for the hydrolysis of ASA at pH 2.4 and 5.4, at 40 and 50 °C are shown in fig 1. Results clearly show that the reaction rate is much higher at pH 5.4 than at pH 2.4, which is the pH of maximum stability. Results (application note 22005) have shown the rate constant to be linear between 4-17h.

Plots of the logarithms of the mean rate constants as a function of pH, reveal similar results as to reported values at other temperatures. The precision and correlation of individual results were in general higher at 50 °C and at higher pH values where higher heat flow was detected. The mean rate constant at 50 °C and at pH 2.4 was determined to be 16.9×10^{-3} /h. This correlates well with the rate constant obtained by Garrett, Ref b), using conventional techniques at 50.3 °C and at pH 2.5 which was 17.4×10^{-3} /h. Garrett also reported a plateau rate constant of 127 $\times 10^{-3}$/h at pH 5.0 at 50.3 °C, compared with results obtained in this study showing values of 123×10^{-3} /h at pH 4.8 and 50.0 °C.

Table 1 shows the high correlation of microcalorimetry with spectrophotometric methods used to calculate thermodynamic constants.

Method	pH	Activation energy, E_a (kJ mol^{-1})	Frequency factor, A ($\times 10^{-10}$)(h^{-1})	Entropy, ΔS^* (J mol^{-1} K^{-1})	Enthalpy, ΔH^* (kJ mol^{-1})	Gibb's free energy, ΔG^* (kJ mol^{-1})	Equilibrium constant, K^* ($\times 10^{19}$)
Micro-calorimetry	1.1 [a]	71.9 (5)	3.33	−120	69.4	105	3.75
Spectro-scopy	1.1 [b]	69.5 (4)	1.21	−128	67.0	105	3.70
Micro-calorimetry	4.8	75.3 (2)	18.0	−106	72.8	104	5.27
Spectro-scopy	5.0 [b]	73.6 (4)	10.4	−110	71.2	104	5.84

Table 1. Comparison of thermodynamic quantities for the transition state for ASA hydrolysis at two pH levels and 25°C

The heat flow-pH profiles

An additional approach to characterize the stability of ASA was to examine the heat flow at a defined time which would reduce the need for the calculation of rate constants. Figure 1 shows the higher rate of initial heat flow for a fast reaction as compared to that for a slow reaction. Plots of mean heat flow with pH values showed similar correlations of reaction rates as shown by the rate constant-pH profiles, although less information is available with these type of plots.

The heat quantity-pH profiles

Calculation of the total heat flow (Q) over a defined time period would enable the differentiation between slow and fast reactions since the initial total heat flow would be larger for a fast reaction. Results for the total heat quantity versus pH plots show similar profiles as the rate constant-pH profile.

Comparisons

Results therefore show the similarity of the three methods of characterising the degradation of ASA (fig 2). Data using heat flow and heat quantity profiles were obtained within 4h and could be used to predict the pH region of maximum stability even at 40°C. In addition unlike the mean rate constant method, these methods show better precision at pH of maximum stability.
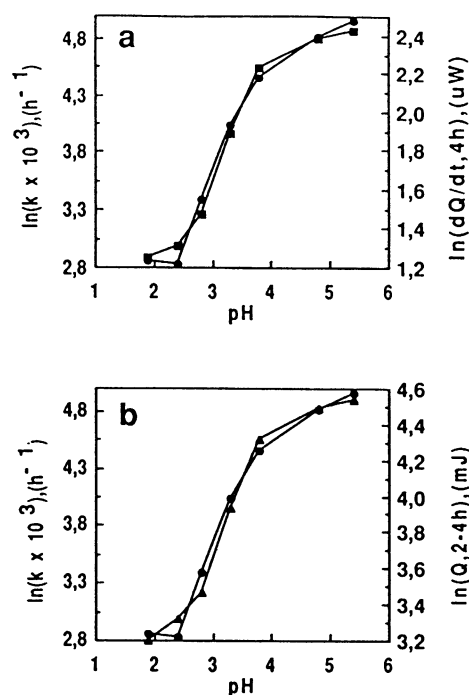
CONCLUSION

Microcalorimetry can thus be used to provide accurate and precise information on the stability of products while yielding the rate of decomposition. In particular, the degradation rate constant for ASA was calculated and found to correlate well with conventional techniques. The heat flow and heat quantity profiles gave much faster and more precise information than the rate constant profile. The technique can also be used for solids as well as solutions.

REFERENCES

a) ThermoMetric Application Note 22005

b) E.R. Garrett - J. Am. Soc. 79:3401-3408 (1957)

c) M. Angberg, C. Nyström, S. Castensson - Int. J. Pharm. 61: 67-77 (1990)

NOTE

This is the second of two papers on this study.

Application Note written by M. Shafiq, Thermomeric AB.

Figure 2. Comparison between the rate constant-pH (●) and (a) the heat flow (4h) profile (■) and (b) the heat quantity (2-4 h) profile (△) for ASA hydrolysis at 50.0 °C.