



Drug Stability Testing by Isothermal Heat Conduction Microcalorimetry: Some Examples

M. Shafiq

J. Suurkuusk

Thermometric AB, Jarfalla Sweden

INTRODUCTION

Most methods for the determination of the rate of decomposition of drugs (stability and thus shelf life) involve elevated temperature measurements as with DSC and DTA techniques, in which the rate is extrapolated to the storage temperature. The use of such methods although rapid is only valid if the mechanism of reaction remains the same over the temperature range studied.

It would be advantageous if measurements could be performed at room temperatures. However, current methods of measurements at room or close to room temperatures are unable to detect the rate of degradation of slow processes. Indeed, the difficulty is even more apparent in solid state kinetics for which there is a distinct lack of sensitive techniques.

Since all chemical and physical processes are accompanied by heat flow, it is possible with highly sensitive isothermal heat conduction microcalorimeters to measure slow decomposition rates (1-2% per year) of solid samples at room temperatures. The data can be obtained rapidly, efficiently, without sample treatment and without destroying the sample. The technique therefore affords the possibility of evaluating the stability of newly formulated material, effects of excipients, stabilisers, light and impurities as well as providing information on dissolution rates. Furthermore, the data gives an insight into the nature of degradation products. Some typical examples are shown below. The theoretical aspects for evaluation of stability can be found in a separate application note.

EXAMPLES

Figure 1 shows the data for two different lots of Lovastatin collected at 70°C. Results clearly show the susceptibility of lot 1 to an autocatalytic oxidation which does not occur with lot 2. Subsequent high-performance liquid chromatographic (HPLC) analysis of the same lots stored at room temperature for six months showed that lot 1 underwent a significant amount of degradation, while lot 2 did not.

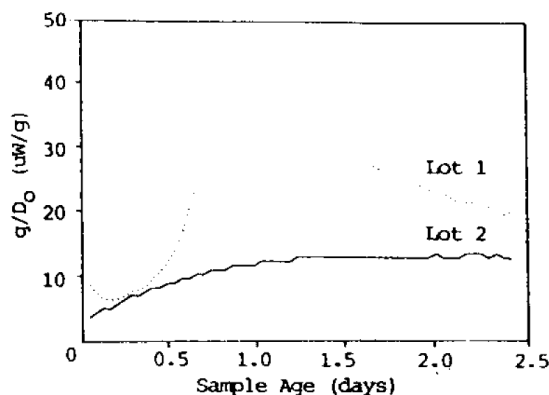


Fig 1. Calorimetric data on two different lots of Lovastatin.

Similar results were observed for the autocatalytic oxidation of three different lots of a derivative of Lovastatin at 50°C (fig 2). The data shows that the induction period, time to maximum heat rate and the maximum heat rate varies from lot to lot. The area under the curve represents the total amount of degradation, and is therefore concentration dependent.

In another series of experiments on a lot of Lovastatin, the effect of temperature on the rate of autoxidation was studied. Fig 3 shows the effects of increasing the storage temperature between 50 and 70°C. Although most pharmaceutical preparations are kept much below these temperatures, it is important to know the period of storage at certain temperatures before a significant amount of degradation has occurred or indeed before the accumulation of toxic degradation products.

Classical chemical analyses of degradation rates usually take weeks if not months to acquire. Table 1 shows the sensitivity of TAM even at room temperatures in assessing reaction rates of pharmaceutical formulations. TAM data was found to correlate well with established chemical methods of analysis. Indeed TAM data revealed the presence of unstable preparations which had been presumed to be stable.

The stability of ampicillin in solution has also received attention recently. The effect of pH and temperature on the rate of degradation was assessed. Fig 4 shows that the rate followed a pseudo first order process over 45h at constant pH and temperature. The degradation rate constant was calculated from the slope of the line. Additional experiments at other temperatures allowed the calculation of rate constants at these temperatures which were then substituted into the Arrhenius equation from which the activation energy was calculated.

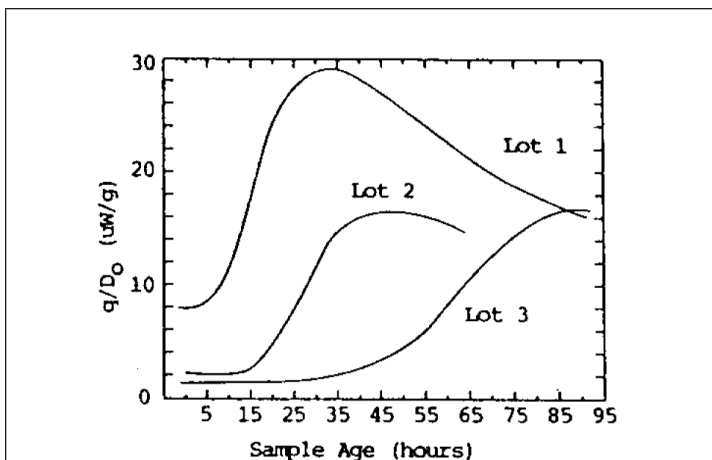


Fig 2. Calorimetric data on three different lots of a derivative of Lovastatin at 50°C.

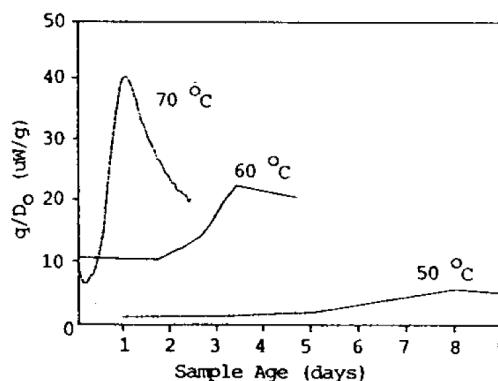
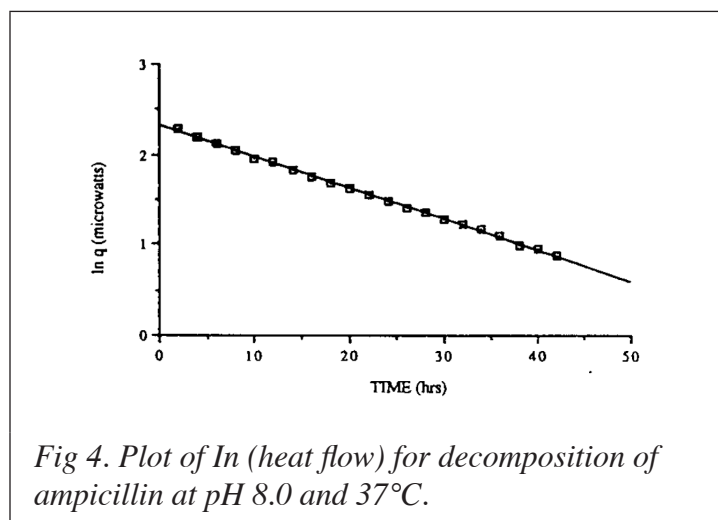


Fig 3. The effect of temperature on the kinetics of autoxidation

Stability of pharmaceutical formulation	Reaction rates			
	% mo ⁻¹ Chemical aiur (estimated)		μW/g Microcalorimetric (heit flow)	
	25°C	37°C	25°C	37°C
Cephllothin Sodium Amorphous solid, 0.3% H ₂ O	0.2	0.9	3-5	9.2
Cephllothin Sodium Amorphous solid, 2.0% H ₂ O	1.4	6.7	5.7	20.5
Crystalline A. stable salt	“stable”	“stable”	0.74 (“unstable”)	3.1 (“unstable”)

Table 1. Heat output and estimated reaction rates for three pharmaceutical preparations.



It is evident from the above data that microcalorimetry is sensitive enough to detect the slow rate of degradation of many pharmaceutical formulations. Indeed from this data it is clear that the rate of degradation and hence shelf life can be calculated. Microcalorimetry is undoubtedly an added resource for the formulation chemist as well as being one of very few techniques that can be used for solid state kinetic studies at close to room temperatures.

REFERENCES

1. Hansen L.D., Lewis E.A, Eatough D.J., Bergstrom R.G., DeGraft-Johnson D. - Pharmaceutical Research 6 (1): 20-27, **1989**.
2. Pikal M.J., Dellerman K.M. - Int. J. Pharmaceutics 50: 233-252, **1989**.
3. Oliyai R., Lindenbaum S. - Int. J. Pharmaceutics 72: **1991** (In Press).