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Pharmaceutical microcalorimetry: recent advances in the study of solid state materials

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Abstract

This paper discusses the theory and experimental application of microcalorimetry to the study of solid state reactions of pharmaceutical importance. The practical example selected is that of formulated products containing benzoyl peroxide – a treatment for acne and athlete's foot. A newly developed procedure for data analysis is outlined and preliminary results from chemometric-based analysis of complex solid state reaction schemes is presented. Finally, the microcalorimetric requirements for such stability studies are contrasted with the newly emerging multi-channel "chip calorimeters" that operate in the nano range (watts, material, concentration) with high throughput potential.

Keywords: Microcalorimetry; Stability; Solid state; Chemometric; "Chip" calorimeters

1. Introduction

For some time now it has been possible [1,2] to determine *directly* from microcalorimetric data (power-time) n the order of reaction, k the rate constant, $\Delta_R H$ (hereafter H for simplicity) the reaction enthalpy, K the equilibrium constant (and hence G and S) and, as the protocol requires study of the reaction system at at least three temperatures, the activation energy E_a. The described procedures [1,2] were developed principally for solution phase reactions. They have been used to analyse data for solution phase systems [3], complex reactions [4], raw drug materials [5] and formulated pharmaceutical materials [6]. They are of particular interest in the study of long term stability (shelf life) – again, particularly here, in the stability of drugs and medicines.

For complex reaction systems (which we must expect most drug/medicine degradation reactions to be) the individual reactions must be integral in order. The overall order can be non-integral and, initially, the only complex reaction systems amenable to study were those [4] for which prior knowledge of the mechanism was available. This requirement is a rather severe limitation on the exploitation of microcalorimetric stability determinations. In addition, that solid state reactions are not described by integral reaction orders but through non-integral fitting parameters [7,8] that indicate a mechanism for the solid state reaction process is another rather significant limitation. It is the purpose of this paper to outline new approaches that may ameliorate some of these limitations.

Importantly too, microcalorimetric determinations of stability offers significant time saving relative to traditional high temperature storage studies – these take months to years to complete [9]. By contrast microcalorimetric study may require [1,2], at the storage conditions of interest, only some 50 h to yield the appropriate rate constant data.

2. Solid state reactions

The Ng equation [7]

$$\frac{d\alpha}{dt} = k(1-\alpha)^n \alpha^m$$

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is claimed to be capable of describing most solid state reactions. This equation has been the basis of a very recent [10] theoretical treatment of microcalorimetric data to yield *directly* values for k and α and, thereafter, for H. However, before this analysis can be performed, in common with protocols for analysis of solution phase data, it is necessary to determine values for the fitting parameters n and m in the Ng equation [7] (order parameters for solution phase reactions). A simple procedure has been outlined [11] to achieve this end – it is based on taking well separated pairs of data points over the experimental observation period (anything from 12 to 50 h normally).

The Ng equation [7] can be modified to yield a calorimetric equation through setting Q as the total number of joules involved in the reaction to time $t = \infty$ and q as the number of joules involved in the process up to any time t. Thus, α can be set equal to q/Q and the equation now becomes:

$$\frac{dq}{dt} = kQ\left[1 - \left(\frac{q}{Q}\right)\right]^n \left(\frac{q}{Q}\right)^m$$

This equation can be solved [10], by taking, again, paired data points throughout the data set, to yield values for Q and k. Note Q is not measured – it is calculated from the observed data set (over, relatively, short time periods).

The theoretical development [10] was supported by simulated solid state reaction data which showed that it would be possible to analyse data satisfactorily for extents of reaction as low as $\alpha = 0.01$. The procedures outlined are model free save for the requirement that the data are analysed through the basic Ng equation [7] – there is no imposed restriction on the appropriate values of n and m.

3. Practical results

The most extensively investigated system is that of benzoyl peroxide (BPO) in both its raw and formulated product forms [5,6]. Table 1 shows the outcomes for investigation of the effects of single excipients on the degradation of benzoyl peroxide. It can be seen that 1% Sipernat decreases the stability of BPO – it is a Lewis acid. All the others appear to contribute to stability or have little effect. Notably BPO in the presence of 5% propylene glycol, 2.5% glycerine, 0.15% Monawet and of 5% Pluronic 234 yield rate constants some two orders of magnitude lower than that of BPO alone. Table 2 shows some data for formulated materials where it can be seen that there are, for many of the study systems, two different, temperature dependent kinetic regimes. This outcome is also illustrated in Fig. 1. Listed in Table 2 are the derived activation energies.

Table 1
Microcalorimetric kinetic stability studies of degradation of BPO in the presence of excipients in water at 313 K

Excipient	First-order rate constant, k (s^{-1})
–	$2.00 \times 10^{-7} \pm 7.13 \times 10^{-9}$
2% Polytrap	$1.04 \times 10^{-7} \pm 2.64 \times 10^{-9}$
1% Sipernat	$1.11 \times 10^{-6} \pm 1.51 \times 10^{-8}$
0.15% Monawet	$1.40 \times 10^{-8} \pm 1.62 \times 10^{-9}$
5% Propyfene giycol:2.5% glycerine:0.15% monawet	$8.42 \times 10^{-9} \pm 6.76 \times 10^{-10}$
5% Propylene glycol:2.5% glycerine:2% polytrap	$3.41 \times 10^{-7} \pm 3.75 \times 10^{-9}$
Pluronic[a] P234	$7.24 \times 10^{-9} \pm 5.00 \times 10^{-10}$

[a] M(PO)-2250 M(EO)-1500. T_m 33.43 and $MW_{Pluronic} = 3750$. 5 mg ml^{-1} in water cooled to 4 °C.

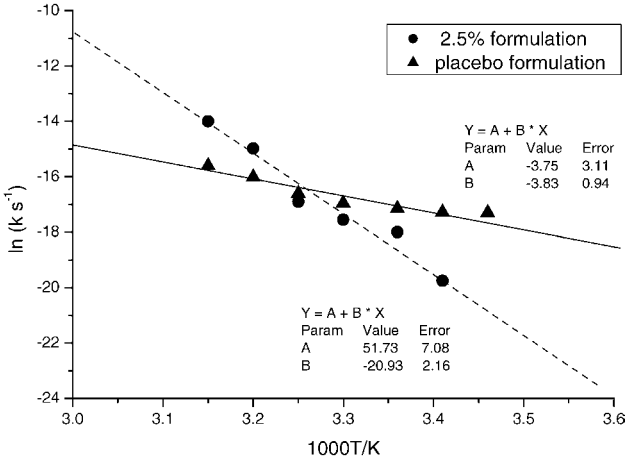

Fig. 1. Arrhenius plot showing 2.5% and host formulations.

It is normal practice to determine stability from high temperature storage studies [9], i.e. storing a formulation at temperatures ~50 °C at defined relative humidity. Extrapolation from rate constant data at these elevated temperatures to the storage temperature of interest is then performed. By contrast microcalorimetry has the sensitivity [1,2] to determine the appropriate rate constant at the selected storage conditions – say 20 °C and 75% RH. Using the microcalorimetric data for the formulated materials at the higher temperatures allows calculation of the rate constant expected at 20 °C. A 1% BPO formulation in the presence of Carbopol shows a "low" temperature (<30 °C) activation energy of 222 kJ mol^{-1} and a "high" temperature (>30 °C) activation energy of 16 kJ mol^{-1}. Prediction of the rate constant at 20 °C from the "high" temperature data results in an error in that rate constant of 9 orders of magnitude. The overall conclusions of the study [5,6] were; that experimentation was fast – 24 h was sufficient to identify k; direct measurement was possible at the selected storage conditions of interest; excipient choice was simplified; quantitative results allowed for real comparisons between different formulated materials.

4. Chemometric approaches

As noted above, to date, the study of complex reaction systems has relied [4] on prior knowledge of the mechanism of a reaction to allow calorimetric solutions to be found. The essence of the procedures outlined here is that they are use-

Table 2
Microcalorimetric studies of solid BPO and formulations (first-order rate constants (s^{-1}))

Temperature (°C)	Solid BPO (reference talc)	2.5% (reference talc)	Placebo (reference talc)	2.5% (reference placebo)	1% (reference w/o carbopol)
15	–	–	$5.03 \times 10^{-8} \pm 2.30 \times 10^{-8}$	–	–
20	$1.16 \times 10^{-9} \pm 1.01 \times 10^{-8}$	$2.61 \times 10^{-9} \pm 1.01 \times 10^{-8}$	$5.16 \times 10^{-8} \pm 1.60 \times 10^{-8}$	$1.59 \times 10^{-8} \pm 1.12 \times 10^{-8}$	$1.11 \times 10^{-9} \pm 7.51 \times 10^{-10}$
25	$4.33 \times 10^{-9} \pm 3.59 \times 10^{-9}$	$1.36 \times 10^{-8} \pm 2.51 \times 10^{-8}$	$5.29 \times 10^{-8} \pm 8.73 \times 10^{-9}$	$2.04 \times 10^{-8} \pm 7.76 \times 10^{-10}$	$2.57 \times 10^{-9} \pm 6.41 \times 10^{-9}$
30	$6.85 \times 10^{-9} \pm 1.33 \times 10^{-8}$	$2.34 \times 10^{-8} \pm 1.64 \times 10^{-8}$	$5.65 \times 10^{-8} \pm 8.91 \times 10^{-8}$	$3.93 \times 10^{-8} \pm 1.38 \times 10^{-9}$	$4.01 \times 10^{-9} \pm 6.07 \times 10^{-9}$
35	$2.00 \times 10^{-8} \pm 2.83 \times 10^{-8}$	$5.27 \times 10^{-8} \pm 6.36 \times 10^{-9}$	$6.94 \times 10^{-8} \pm 7.14 \times 10^{-8}$	$4.34 \times 10^{-8} \pm 1.25 \times 10^{-8}$	$5.42 \times 10^{-9} \pm 3.34 \times 10^{-9}$
40	$5.84 \times 10^{-8} \pm 2.53 \times 10^{-8}$	$3.43 \times 10^{-7} \pm 2.11 \times 10^{-7}$	$1.20 \times 10^{-7} \pm 7.70 \times 10^{-9}$	$1.29 \times 10^{-7} \pm 1.22 \times 10^{-9}$	$1.31 \times 10^{-9} \pm 6.52 \times 10^{-8}$
45	$1.07 \times 10^{-7} \pm 8.49 \times 10^{-9}$	$7.68 \times 10^{-7} \pm 1.94 \times 10^{-7}$	$1.89 \times 10^{-7} \pm 3.68 \times 10^{-8}$	$1.35 \times 10^{-7} \pm 1.04 \times 10^{-9}$	$1.74 \times 10^{-8} \pm 8.90 \times 10^{-10}$
E_a (kJ mol^{-1})	138 (±7)	172 (±14)	5 (±2), 82 (±3)	72 (±9)	84 (±6)

First-order rate constants (s^{-1}).

ful – that is, they can/will find application in the real world of the Pharmaceutical Industry. In this context medicines are to be regarded as complex reagents the stability associated reactions of which are likely to be complex. So, an iteration [1] or pre-knowledge strategy [4] is unlikely to be productive. Recently [12], we have been pursuing a chemometric approach to the analysis of microcalorimetric power-time data. This study based upon simulated data [12] for complex sequential and parallel reaction schemes suggests that deconvolution of the overall (i.e. recorded) power-time output into that representing the constituent individual reactions is indeed possible. The study is now being extended to experimental study of reactions that are commonplace within pharmaceutical preparations, e.g. the Maillard reaction [13].

5. Commentary

To achieve the outcomes described above for long term stability data analysis requires a sensitive and stable instrument. The studies described are conducted over relatively, for microcalorimetry, long time periods – up to 50 h [1,2]. The operation of a typical isothermal heat conduction microcalorimeter such as a Thermal Activity Monitor (TAM, Thermometric AB, Järfalla, Sweden) is such that the required equilibration procedures mean that the first hour of calorimetric information on the system is not available. The instruments themselves are large although sample size is small – this is a result of the need to build the instruments so that they can withstand small environmental changes and have highly efficient heat conduction pathways in order to maintain the necessary ($\pm 1 \times 10^{-4}$ K) isothermal conditions. Thus, these instruments cannot be used for study of rapid processes. They are, however, absolutely the instruments of choice for the study of stability.

The growth in the number of compounds now synthesised through combinatorial chemistry procedures and the appearance of rapid bioscreens suggests the need for a new range of calorimeters suited to the demands of “high throughput”.

There is a new range of instruments appearing on the market that have no claim to long term stability, that could not be used for stability (shelf-life) studies, that have little effective long term stability themselves but that have enormous potential for rapid screening purposes.

Veeco [14] makes an eight cantilever nanocalorimeter based on atomic force technologies in which the cantilevers are coated with another metal hence making them into bi-metallic strips and therefore calorimeters. Xensor [15] make “chip” calorimeters 20 mm^2 in area which are cheap (€200 or so) and can be combined to make arrays to produce, in principle, multi-calorimeters composed of any number of these units. Vivactiss [16] has 96, 384 and 1536 well plates that are composed of multiple differential nanocalorimeters. All these calorimeters require nanolitres of reagents at nanomolar concentrations. The speed of re-

sponse and high throughput rates they allow are going to revolutionise screening and the study of binding reactions. The problems will be; making *quantitative* deductions from these instruments; handling the volume of data efficiently and intelligently; finding methods that utilise the high throughput potential to secure not just *H* but also *G*. These challenges will, if met, allow the real exploitation of calorimetry in this area – that of dealing with closer to in vivo systems than is now possible.

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