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The stability of benzoyl peroxide formulations determined from isothermal microcalorimetric studies

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Abstract

Recent developments in the analysis of microcalorimetric data output allow the possibility of determining both thermodynamic and kinetic parameters for complex reaction systems. Such experiments routinely take around 50 h, hence qualifying for the description rapid. The methods have earlier been applied to a study of the stability of benzoyl peroxide itself in aqueous suspension. This paper reports the results of isothermal microcalorimetric study of the stability of benzoyl peroxide in the presence of a wide range of excipients and in formulated materials. The results are shown to assist in formulation design, are achieved rapidly and are derived from direct experimental study of the complex systems themselves. That is, no ancillary information is required nor are the studies invasive or destructive.

Keywords: Calorimetry; Benzoyl peroxide; Formulation excipients; Stability

1. Introduction

Benzoyl peroxide (BPO) is commonly used in topical formulations for the treatment of acne and, more recently, athlete's foot. It is available as a lotion, cream, liquid, bar or mask with concentrations of 1, 2.5, 5 and 10% (Chellquist and Gorman, 1992). These formulations may contain water, propylene glycol, isopropyl myristate, acetone or alcohol as solvents. The choice of solvent, in part, influences the stability of the product. For example, in 10% gel preparations, those prepared with alcohol (40%) were less stable (loss of 50% of active following 90 days storage at 40 °C) than those in 6% laureth surfactant (20% loss), and those in 5% propylene glycol (10% loss) and there was no reported loss of active in formulations containing 10% acetone (Bollinger et al., 1977).

In another paper (Zaman et al., 2001), we described the isothermal microcalorimetric determination of the rate constants for the degradation of

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crystalline benzoyl peroxide presented in the experiment as a 75% aqueous suspension of the solid material. The rate constants and activation enthalpy for the degradation process at temperatures covering storage conditions (20–45 °C) were reported from direct, non-invasive, non-destructive study of the material as received from the supplier. By contrast the UV studies that supported the investigation were conducted at higher temperatures (55–90 °C) in aqueous solution and sampling was required to allow for analysis of produced benzoic acid. The advantages of direct study of the heterogeneous system of the solid suspension are obvious and lead directly to the possibility of examining excipient choice in formulation studies through isothermal microcalorimetric investigations of putative systems. Here, the advantages sought include not only those cited above but, in addition, the capacity of the isothermal microcalorimeter to accept a system for study which is largely independent of the physical form of the sample, solid, suspension, cream, ointment, solution etc.

This paper reports the outcomes of such a study in which some formulation components were examined as individual additions to benzoyl peroxide and some in which complete placebo preparations and commercial formulations were also examined. The results suggest a serious role for microcalorimetry in shortening the formulation/excipient selection process.

2. Experimental

The procedures and data analyses were as described in the earlier paper (Zaman et al., 2001). The instrument used was a MicroDSC III supplied by Setaram (Setaram S.A., Caluire, France) and it was operated in the isothermal mode according to the manufacturer's instructions. The instrument is a differential calorimeter, i.e. the sample is evaluated against the performance of (usually) an inert reference. For the studies reported here the material in the reference ampoule is specified in the tables describing the results. Where an inert reference is used this is either water for the aqueous solution based systems or talc for suspended BPO systems and preparations. For commercially available products the reference ampoule sometimes contained a placebo preparation. Placebos are not necessarily wholly stable and the reaction rate constants for these systems have also been evaluated (against a water or talc reference). All calorimetric experiments were conducted for a minimum of 24 h and most were run for 48 h. As so many experiments were conducted over such time periods it is not reasonable to display raw data. However, all the outcomes were analysed as first order kinetic reaction rates since simple plots of ln(power output) versus time were linear (Zaman et al., 2001; Willson et al., 1995; Beezer et al., 2001).

All materials used (shown in the following tables) were supplied by GlaxoSmithKline Consumer Healthcare (Weybridge, UK) and were used as received. The solubility of BPO was determined following long term (1 week) storage in the study solvent system by filtration and subsequent starch/iodine titration.

3. Results and discussion

3.1. Studies in aqueous solution

Microcalorimetric experiments were performed on BPO, combinations of formulation excipients plus BPO, and separately on BPO plus Pluronic P234. These studies were performed at 40 °C where, given the temperature dependent structural properties of Pluronic 234 (Gaisford et al., 1998) it is known that aggregates exist. The data listed in Table 1 reveal that almost all the added excipient combinations contribute toward stabilising the BPO degradation reaction at this temperature (40 °C) with both 5% propylene glycol, 2.5% glycerine, 0.15% Monawet and 5% Pluronic 234 systems resulting in rate constants something under two orders of magnitude lower than that for BPO alone. The exception to the stabilising effect is that of the 1% Sipernat system. Sipernat is a silica preparation and will act as Lewis Acid because of the presence at its surface of silanol groups and these may contribute to the enhanced (by about an order of magnitude) degradation rate observed.

Table 1
Microcalometric kinetic stability studies of degradation of BPO in the presence of excipients in water at 40 °C

Excipient	First order rate constant, k (s^{-1})
–	$2.00\times10^{-7}\pm7.13\times10^{-9}$
2% Polytrap	$1.04\times10^{-7}\pm2.64\times10^{-9}$
1% Sipernat	$1.11\times10^{-6}\pm1.51\times10^{-8}$
0.15% Monawet	$3.40\times10^{-8}\pm1.62\times10^{-9}$
5% Propylene glycol: 2.5% Glycerine: 0.15% Monawet	$8.42\times10^{-9}\pm6.76\times10^{-10}$
5% Propylene glycol: 2.5% Glycerine: 2% Polytrap	$3.41\times10^{-7}\pm3.75\times10^{-9}$
Pluronic[a] P234	$7.24\times10^{-9}\pm5.00\times10^{-10}$

[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.

3.2. Saturated solution studies

Topical preparation dermal transport can be influenced by a range of factors and perhaps the most significant is the thermodynamic activity of the drug/compound present in the formulated material. Maximal thermodynamic activity can be achieved through the use of saturated solutions. For example, permeability has been shown (Twist and Zatz, 1986) to remain constant through silicone membranes for saturated solutions of parabens in the presence of a variety of excipients. Thus, it was of interest to investigate the stability of BPO in saturated solutions in the presence of excipients. Table 2 describes the results of both solubility determinations and the first order rate constants for BPO degradation under approximately controlled pH conditions and in the absence and presence of excipients. At pH $\approx$5.1 none of the excipients has a marked effect on the solubility of BPO except for Carbopol. For Polytrap the observed rate constant was essentially the same as that in aqueous solution. Monawet, Sipernat and Xanthan gum containing systems, however, produced significantly lower rate constants (ca one order of magnitude lower than that found for aqueous solution at that pH). These excipients are of unrelated physical and chemical form providing different properties in formulated materials. It is notable that Carbopol (a thickening agent) yields the highest saturated solubility (by one order of magnitude greater than that in aqueous solution) and also results in the highest rate constant, two orders of magnitude greater than that found in aqueous solution.

It is not possible to draw general conclusions about the reasons for the differences in the determined rate constants since the excipients themselves have diverse physical and chemical properties. However, as noted in another paper (Zaman et al., 2001) microcalorimetry does permit a direct and rapid evaluation of the effects on stability of a wide range of excipients.

3.3. Studies on formulated products

The rate parameters for the degradation of an aqueous suspension of 75% crystalline BPO was reported in the earlier paper (Zaman et al., 2001)

Table 2
Relationship between the saturated solubility of benzoyl peroxide and rate of degradation at 40 °C by isothermal microcalorimetry

Excipient	PH	Saturated solubility (g l^{-1})	First order rate constant for degradation k (s^{-1})
Unadjusted pH	3.47	5.50×10^{-4}	$5.12\times10^{-9}\pm1.19\times10^{-9}$
Adjusted pH	5.77	1.44×10^{-3}	$1.92\times10^{-8}\pm1.33\times10^{-9}$
Monawet	5.08	1.39×10^{-3}	$2.54\times10^{-8}\pm9.53\times10^{-10}$
Sipernat	5.14	1.60×10^{-3}	$2.36\times10^{-9}\pm6.27\times10^{-10}$
Polytrap	5.19	1.24×10^{-3}	$1.25\times10^{-8}\pm2.14\times10^{-9}$
Germall II	5.20	4.00×10^{-4}	$9.44\times10^{-8}\pm2.49\times10^{-9}$
Carbopol	5.09	1.48×10^{-2}	$1.25\times10^{-6}\pm1.88\times10^{-7}$
Xanthan gum	5.29	4.98×10^{-3}	$2.73\times10^{-9}\pm9.69\times10^{-10}$

Glycerin: propylene glycol 2.5: 5% in 0.5 ml water with pH adjusted as required. Benzoyl peroxide was added at the saturated solubility indicated. All experiments were carried out using a water reference.

Table 3
Microcalorimetric kinetic stability studies of solid BPO and formulations

Temperature (°C)	Solid BPO (reference talc)	2.5% (reference talc)	Placebo (reference talc)	2.5% (reference placebo)	1% (reference w/o carbopol)
15	–	–	$5.03\times10^{-8}\pm2.30\times10^{-8}$	–	–
20	$1.16\times10^{-9}\pm1.01\times10^{-8}$	$2.61\times10^{-9}\pm1.01\times10^{-8}$	$5.16\times10^{-8}\pm1.60\times10^{-8}$	$1.59\times10^{-8}\pm1.12\times10^{-8}$	$1.11\times10^{-9}\pm7.51\times10^{-10}$
25	$4.33\times10^{-9}\pm3.59\times10^{-9}$	$1.36\times10^{-8}\pm2.51\times10^{-8}$	$5.29\times10^{-8}\pm8.73\times10^{-9}$	$2.04\times10^{-8}\pm7.76\times10^{-10}$	$2.57\times10^{-9}\pm6.41\times10^{-9}$
30	$6.85\times10^{-9}\pm1.33\times10^{-8}$	$2.34\times10^{-8}\pm1.64\times10^{-8}$	$5.65\times10^{-8}\pm8.91\times10^{-8}$	$3.93\times10^{-8}\pm1.38\times10^{-9}$	$4.01\times10^{-9}\pm6.07\times10^{-9}$
35	$2.00\times10^{-8}\pm2.83\times10^{-8}$	$5.27\times10^{-8}\pm6.36\times10^{-9}$	$6.94\times10^{-8}\pm7.14\times10^{-8}$	$4.34\times10^{-8}\pm1.25\times10^{-8}$	$5.42\times10^{-9}\pm3.34\times10^{-9}$
40	$5.84\times10^{-8}\pm2.53\times10^{-8}$	$3.43\times10^{-7}\pm2.11\times10^{-8}$	$1.20\times10^{-7}\pm7.70\times10^{-9}$	$1.29\times10^{-7}\pm1.22\times10^{-9}$	$1.31\times10^{-9}\pm6.52\times10^{-8}$
45	$1.07\times10^{-7}\pm8.49\times10^{-9}$	$7.68\times10^{-7}\pm1.94\times10^{-7}$	$1.89\times10^{-7}\pm3.68\times10^{-8}$	$1.35\times10^{-7}\pm1.04\times10^{-9}$	$1.74\times10^{-8}\pm8.90\times10^{-10}$
E_a (kJ mol^{-1})	138 (±7)	172 (±14)	5 (±2), 82 (±3)	72 (±9)	84 (±6)

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

and in particular the activation energy was determined to be 138 kJ mol^{-1}. This value provides a reference point against which to estimate the performance of formulated products containing BPO. Formulated BPO is contained within a complex assembly of excipients and it is essential to determine the performance characteristics of the base formulation in the absence of BPO before attempting to study the effects of particular excipients within the formulation on the stability of the product. Table 3 lists the rate constants determined over the temperature range 15–45 °C for both placebo and formulated BPO systems.

Inspection of the data for the placebo, using talc in the reference ampoule, shows a break in the $\ln k$ versus $1/T$ (Arrhenius) plot between 30 and 35 °C (Fig. 1). This indicates a change in the nature of the reaction(s) that proceeds in the placebo. Formally, it is possible to calculate an activation energy of 5 kJ mol^{-1} for temperatures of 15–30 °C and of 82 kJ mol^{-1} for the reaction above 30 °C. Of course, a formal measure of 5 kJ mol^{-1} for E_a indicates a reaction process which is essentially independent of temperature. However, note that the rates of reaction over this 'low' temperature range are easily determined via microcalorimetry and, indeed, are on the same order as that determined for BPO suspensions alone. A much more temperature dependent reaction occurs at 'high' temperature with an activation energy of 82 kJ mol^{-1}. We have not attempted to analyse the nature of these complex reactions.

Table 3 also displays the results of a study on a product containing 2.5% BPO, again using talc as the reference material. Here, however, the Arrhenius plot is linear over the temperature range 20–45 °C. The calculated activation energy is 172 kJ mol^{-1} (cf. E_a for aqueous suspension of BPO

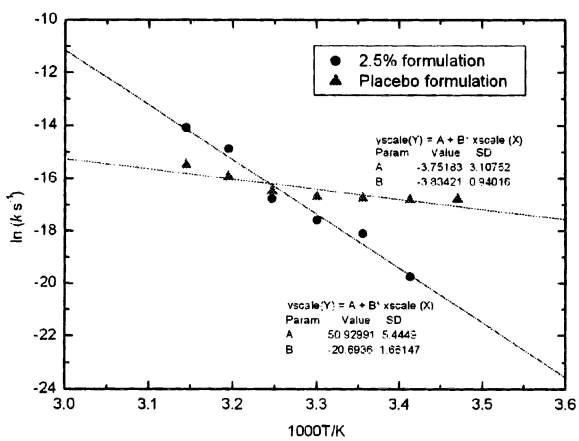

Fig. 1. Arrhenius plot showing 2.5% and host formulations.

is 138 kJ mol^{-1}). Interestingly, the rate constant for the reaction(s) in the commercial product are lower than the placebo reaction rate constant from 15 to 30 °C and higher over the temperature range 30–45 °C. This observation implies that the presence in the formulation of BPO improves the stability profile of the product over the lower temperature range. It is possible that this occurs because of some effect of pH control exerted by the presence of the BPO in the product. Interestingly, the stabilising effect occurs within the normal temperature of storage range. These findings also emphasise the problem of projecting from rate constants determined at high temperature to estimates of rate constants at appropriate storage temperatures.

3.4. Studies using the placebo vehicle as reference

It is not simple to arrange experimental protocols that probe the fundamental role of a single excipient in a formulated product containing many components. There are three broad strategies that can be adopted. One is to evaluate the kinetic behaviour of a complete product against a reference of a placebo formulation. This will have the consequence of assuming that the presence of the active does not influence either the nature or the rate of the reactions in the placebo. That this may not be entirely true is suggested by the results discussed above from studies on commercial products where the reference was the inert material talc. The second is to record and analyse the output from the formulated material against an inert reference material such as that used in these studies—talc. A third possibility that can be used to probe the role of a particular excipient is to omit it from a formulation and use this as the reference material for study of the complete product. Results from experiments based on these three approaches are described below.

The results of studies using the placebo vehicle as reference for a 2.5% BPO product are displayed in Table 3. Note here that the rate constants are slightly increased at each temperature over those determined for this same product using talc as the reference. A linear Arrhenius plot can be formed from these data and it results in a value for the activation energy of 72 kJ mol^{-1}. It is interesting to note that the rate constants at each temperature are for first order processes and that these are obtained from subtraction of the placebo reactions from the overall signal resulting from the product's reactions. Hills (2001) has recently shown that complex parallel/sequential reactions of the same order can appear as an apparent (overall) reaction of that same order. It is not possible without extensive chemical analysis to interpret these observations at a molecular level, although, the ability to determine reaction rate constants directly on the (complex) product sample is of considerable significance.

A further exploration of the role of excipients in controlling degradation reactions was undertaken through a study of a 1% BPO formulated material using a 1% preparation without Carbopol as reference. This was done since, as noted in Table 1, Carbopol much improved the solubility of BPO in aqueous solution. Hence, this excipient, it was felt, may affect the determined reaction rate constants when present in a formulation. It is apparent that the absence of Carbopol results in lower rate constant values across the temperature range of study. However, the calculated activation energy is determined as 84 kJ mol^{-1}—a value close to (within experimental error) for that found for the 2.5% formulated product.

The results from 'excipient exclusion' experiments using talc as reference material for a 1% BPO product are displayed in Table 4. The experiments were designed to allow comparison of products with and without a particular excipient as recorded against a common, and inert, reference. As noted above Carbopol was selected because it enhanced the solubility of BPO in aqueous solution and Sipernat was selected because it enhanced the degradation rate of BPO in aqueous solution (see Table 1).

Curiously, the results for the Carbopol experiments show a break in the respective Arrhenius plots (see Fig. 2) in both the presence and absence of this excipient. The rate constants and the calculated activation energies are, within experimental error, the same. The higher activation energy is observed for the lower temperature regime—this observation is the opposite of that found for the

Table 4
Microcalorimetric kinetic stability studies of formulations containing BPO

T (°C)	1% BPO w/o carbopol	1% BPO with carbopol	1% BPO w/o sipernat	w/o BPO w/o carbopol	w/o BPO sipernat
20	$2.66\times10^{-9}\pm7.21\times10^{-9}$	$1.61\times10^{-8}\pm4.89\times10^{-9}$	$9.15\times10^{-9}\pm1.92\times10^{-8}$	$2.10\times10^{-8}\pm1.03\times10^{-8}$	–
25	$1.80\times10^{-8}\pm2.20\times10^{-8}$	$3.41\times10^{-8}\pm4.73\times10^{-9}$	$3.92\times10^{-8}\pm1.99\times10^{-7}$	–	$1.74\times10^{-8}\pm3.15\times10^{-8}$
30	$3.97\times10^{-8}\pm2.36\times10^{-7}$	$4.44\times10^{-8}\pm5.63\times10^{-8}$	$4.86\times10^{-8}\pm2.14\times10^{-8}$	–	$1.83\times10^{-8}\pm2.47\times10^{-8}$
35	$3.99\times10^{-8}\pm2.17\times10^{-8}$	$5.03\times10^{-8}\pm5.57\times10^{-8}$	$8.45\times10^{-8}\pm1.21\times10^{-7}$	$3.59\times10^{-8}\pm3.82\times10^{-8}$	$2.60\times10^{-8}\pm1.04\times10^{-8}$
40	$4.24\times10^{-8}\pm7.12\times10^{-9}$	$5.66\times10^{-8}\pm2.81\times10^{-8}$	$9.54\times10^{-8}\pm8.27\times10^{-8}$	$5.78\times10^{-8}\pm1.08\times10^{-8}$	$2.56\times10^{-8}\pm2.98\times10^{-8}$
45	$7.03\times10^{-8}\pm7.63\times10^{-9}$	$5.96\times10^{-8}\pm7.71\times10^{-8}$	$1.20\times10^{-7}\pm1.41\times10^{-7}$	$5.79\times10^{-8}\pm3.63\times10^{-8}$	$3.44\times10^{-8}\pm1.40\times10^{-8}$
E_a (kJ mol^{-1})	201 (±46), 28 (±14)	222 (±), 16 (±2)	34 (±6)	212	46 (±6), 27 (±7)

All experiments were carried out with a talc reference. First order rate constants (s^{-1}).

placebo formulation. These data imply that the same processes occur in both the presence, and absence, of Carbopol, i.e. Carbopol has no effect upon the reaction processes. The determined activation energies are significantly different from those determined in the other BPO systems investigated. They are, however, rather close to the rate constants and activation energies determined for a placebo in the absence of not only BPO but also Carbopol. Note too, that no such break is observed in the same experiment conducted on a 2.5% BPO product (see Table 3). This indicates that there is a significant difference in reactive behaviour between 1 and 2.5% BPO preparation the reasons for which are unknown but which are clearly related to BPO content.

Table 4 also describes the results for study of a preparation made without BPO and without Carbopol. Here, interestingly, again two kinetic regimes were found, one again with an activation energy of 212 kJ mol^{-1} and the other of 46 kJ mol^{-1}. Thus, it would seem that the high activation energy mechanism proceeds independently of Carbopol and of BPO (see Table 4) and is, therefore, the result of reactions taking place between other constituents of the formulation. Note that from the detail in Table 3 that whilst the placebo formulation for the 2.5% product also showed two kinetic regimes the associated activation energies are quite different from those found for the 1% preparation.

Omitting Sipernat from the formulation also resulted in kinetic regimes of different activation energies although in this case these were of quite modest values. Excluding both BPO and Sipernat from a preparation led to a single kinetic behaviour of rather low activation energy. In this case, therefore, one must conclude that it is the Sipernat that contributes to different mechanistic

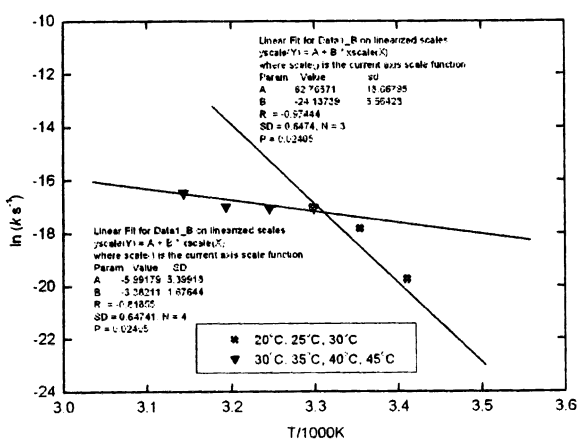

Fig. 2. Arrhenius plot for 1% BPO formulation in the absence of Carbopol.

Table 5
Microcalorimetric kinetic studies for glycerine containing formulations

Temperature (°C)	2.5% glycerine pH 3.95	2.5% glycerine pH 4.75	20% glycerine pH 3.94	20% glycerine pH 4.79
20	$1.38\times10^{-8}\pm1.53\times10^{-8}$	$9.97\times10^{-8}\pm1.10\times10^{-8}$	$8.53\times10^{-8}\pm2.25\times10^{-8}$	$1.73\times10^{-8}\pm7.73\times10^{-9}$
25	$2.48\times10^{-8}\pm4.26\times10^{-8}$	$3.34\times10^{-8}\pm9.16\times10^{-9}$	$3.64\times10^{-8}\pm1.02\times10^{-8}$	$2.07\times10^{-8}\pm9.38\times10^{-9}$
30	$2.71\times10^{-8}\pm1.18\times10^{-8}$	$3.38\times10^{-8}\pm7.76\times10^{-8}$	$1.13\times10^{-8}\pm2.62\times10^{-8}$	$2.18\times10^{-8}\pm3.29\times10^{-8}$
35	$3.35\times10^{-8}\pm1.81\times10^{-8}$	$4.18\times10^{-8}\pm4.12\times10^{-8}$	$3.42\times10^{-8}\pm7.44\times10^{-8}$	$2.54\times10^{-8}\pm1.16\times10^{-8}$
40	$1.17\times10^{-8}\pm9.81\times10^{-9}$	$4.34\times10^{-8}\pm3.57\times10^{-8}$	$4.10\times10^{-8}\pm1.59\times10^{-7}$	$3.28\times10^{-8}\pm1.32\times10^{-6}$
45	$5.84\times10^{-8}\pm7.16\times10^{-8}$	$4.48\times10^{-8}\pm1.42\times10^{-8}$	$5.18\times10^{-8}\pm2.86\times10^{-8}$	$9.02\times10^{-8}\pm1.76\times10^{-8}$
E_a (kJ mol^{-1})	41 ($\pm$5)	38 ($\pm$14)	46 ($\pm$20)	43 ($\pm$12)

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

behaviour at the higher and lower temperature ranges.

Notably, over all the results shown in Table 4 there are only modest differences in the values of the observed rate constants—it is only their relative variation with temperature that leads to the differences in calculated activation energies.

Tables 5 and 6 show the results of studies in which glycerine was used to modify the viscosity of the BPO preparations instead of Carbopol and in which Aerosil was used instead of Sipernat. The glycerine results show a modest activation energy with no break observable over the temperature range in the rate constants. These measured rate constants are, again, of the same order as those noted above. The activation energies cluster around 40 kJ mol^{-1} (cf. 172 kJ mol^{-1} for a 2.5% BPO preparation). Glycerine does not appear to offer any advantage over Carbopol in formulated materials (this was confirmed by conducting conventional long-term stability tests at GSK, Weybridge).

Likewise, the results from experiments using Aerosil again reveal activation energies clustering around 40 kJ mol^{-1} but this time there are breaks in the Arrhenius' plots.

From conventional studies it is known (GSK internally reported data) that the production of benzoic acid is constant in quantity irrespective of the BPO amount present in the sample. That is, 10, 5 and 2.5% BPO preparations produce the same quantity of acid over equal time intervals. pH is likely to affect the rate of degradation of benzoyl peroxide since the produced benzoic acid will, in aqueous based systems, ionise. In a limited set of experiments (Table 7) pH was controlled by addition of HCl/NaOH as appropriate. The data show that at higher pHs the rate of reaction is somewhat reduced as would be expected. Experiments with addition of glycerine and of propylene glycol did not show any significant improvement in the degradation rate.

4. Conclusions

Microcalorimetry has been shown to be effective in the examination of both raw and formulated products of BPO. Direct, non-invasive and

Table 6
Microcalorimetric studies of 1% BPO formulation in the presence of Aerosil COK-84

T (°C)	1% BPO with aerosil and without carbopol
20	$1.27\times10^{-8}\pm5.79\times10^{-9}$
25	$2.44\times10^{-8}\pm4.12\times10^{-8}$
30	$3.12\times10^{-8}\pm4.29\times10^{-8}$
35	$3.67\times10^{-8}\pm7.44\times10^{-9}$
40	$3.82\times10^{-8}\pm1.22\times10^{-8}$
45	$4.48\times10^{-8}\pm5.83\times10^{-8}$
E_a (kJ mol^{-1})	95, 18 ($\pm$2.72)

Talc reference cell was used. First order rate constants (s^{-1}).

Table 7
The effect of pH and excipients on the degradation of benzoyl peroxide in water

Excipient	T (°C)	pH	First order rate constant k (s^{-1})
–	40	2.34	$1.54\times10^{-8}\pm7.90\times10^{-10}$
–	40	4.29	$6.50\times10^{-9}\pm7.40\times10^{-10}$
–	40	7.24	$3.88\times10^{-9}\pm3.26\times10^{-10}$
–	20	–	$1.17\times10^{-8}\pm1.72\times10^{-9}$
Glycerine	20	–	$3.29\times10^{-9}\pm2.9\times10^{-10}$
Propylene Glycol	20	–	$6.08\times10^{-9}\pm6.68\times10^{-10}$

0.013 g of BPO in 0.5 ml water were taken and pH adjusted. Ionic strength was maintained with 0.01 M NaCl.

non-destructive testing of samples has allowed comparison of the effects of alteration in the amount of active present and in the choice of excipients. It appears that the base formulation, the placebo, has a reaction rate that is affected by temperature having a low activation energy at relatively low temperatures and a significantly higher activation energy at higher temperatures. Such behaviour is not shown by either solid, suspension phase BPO nor by 2.5% BPO preparations. 1% BPO products do, however, show a break in the Arrhenius' plots. Thus, it may be that, as noted above, at the relatively low temperatures the BPO itself contributes to stabilising the material whereas, as the temperature rises the process has a much higher activation energy—perhaps the result of affects of the BPO, in this regime, on the excipient's interactions.

Interestingly, therefore, these data confirm that projecting stability data to storage conditions from 'high' temperature data can result in mis-assignment of rate constant values (k) at the lower temperature. For example, the most extreme case reported here is that for a 1% BPO system with Carbopol (Table 4, where the reference was talc) where the two calculated activation energies are very different from each other ('low' temperature, 222 kJ mol^{-1}; 'high' temperature, 16 kJ mol^{-1}). A calculation of the first order rate constant expected at 20 °C from the data accumulated between 30 and 45 °C results in a value for k which is around nine orders of magnitude in error. This arises solely from the dependence of k values on temperature over the two ranges (there is no proof, nor indeed investigation, of the nature of the reaction(s) that take place within these regimes). However, note that the real, directly determined value for k at 20 °C is of the same order as those over the 'high' temperature range. These same conclusions can be drawn for much of the other data reported in the tables and thus, they underline the importance of direct determination of these parameters at the required environmental conditions.

Comparison of rate constant values for the various excipients studied in the work this reported here allows selection of those with the lowest rate constants (however, note the cautions expressed above about the temperature dependence of rate constants).

The results reported here also highlight an interesting calorimetric experiment design problem—that of the selection of reference material for use in differential calorimeters such as that used in this work. The issue of the selection of inert/placebo/formulation without a particular excipient as the reference material raises fundamental questions about the bases of calorimetric experimental design. These issues will be addressed in subsequent papers.

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