

## A SIMPLE, SWIFT AND PRAGMATIC APPROACH IN THE USE OF SMALL SCALE LABORATORY TESTS TO DEFINE SAFE DRYING CONDITIONS FOR MANUFACTURING SCALE PRESSURE FILTERS<sup>†</sup>

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It is relatively straightforward to determine the worst-case, self-heating 'onset' decomposition temperatures for liquids of low viscosity when scaling up from laboratory to plant of known size and natural cooling characteristics, as there are usually insignificant temperature gradients within the bulk mass of the liquid. However, the same cannot be said for solids (powders) or highly viscous liquids as these inherently have relatively poor thermal conductivity resulting in insulating effects that vary greatly depending upon the size and shape of the bulked mass. Frank-Kamenetski model has been used and reported extensively in the literature, considering the balance between the heat of decomposition and the heat loss solely by thermal conduction and can be manipulated to give a critical layer thickness or volume at any temperature of interest. The approach adopted within AstraZeneca's development plants for the specification of safe bulk drying of Active Pharmaceutical Ingredients (API) and their intermediates is discussed with the main focus being on pressure filter drying. The various lab techniques and the respective sensitivities are used along with conservative estimations of various physico-chemical parameters to extrapolate, quickly and safely to larger-scale operating conditions. These conservative predictions are compared against larger scale test data as an initial step to ongoing corroboration of this simple pragmatic approach.

### INTRODUCTION

Self-heating of bulk powders typically arises through one of two mechanisms or perhaps even a combination of both: i) decomposition of the molecule itself/self-reaction or ii) oxidation of the molecule from the surrounding air if present/combustion. A wide variety of larger scale laboratory techniques are available for the assessment of the thermal stability hazards associated with the drying of bulk solids. These tests amongst others include diffusion cell, aerated cell, air over test (Gibson, 1995) and Bowes-Cameron cage tests (referred to as the basket test for the remainder of this paper) (Bowes, 1981). In an ideal world of unlimited budget, time and material availability these tests would be performed prior to drying any material on a significant scale to obtain a comprehensive knowledge of the system stability. In reality where often the material quantities needed for these larger scale laboratory tests are simply not available and there is an emphasis of the business to work smarter in a continuous improvement driven environment to drive down costs and development time, it is not feasible to sanction such testing on a routine basis. An inherent problem also with these larger scale tests can be the melting of the material before any self-heating detection is possible which is caused by the relatively poor sensitivity of the test methods.

Usefully from a safety perspective, operations carried out within AstraZeneca's development plants are almost always carried out under a nitrogen atmosphere with drying operations performed in enclosed equipment, either at reduced pressure (following a rigorous leakage testing pro-

cedure, sometimes accompanied by the supply of a low flow of nitrogen) or by blowing the filter cake dry using high purity nitrogen at atmospheric or positive pressure. It is considered therefore, despite recently confirmed evidence of self-ignition under reduced volume fractions of oxygen (Schmidt, 2003 & Lohrer 2004), that oxidative decomposition will not lead to a significant extent of self heating and therefore generally need not be considered in the assessment of bulk stability. In any case, small scale tests (e.g. DSC, Carius tube) have a quantity of oxygen available in the ullage space on sealing the test sample capsule and it is considered reasonable to assume that extrapolation of such data that may exhibit some exothermic oxidative decomposition is a worst case.

In the past the safe drying of bulk solids within pressure filters was often based on the decomposition temperature observed in the small scale screening tests. In practice this approach requires a large difference between the temperature at which self-heating is initially detected (onset temperature) in the screening test and the proposed drying temperature. Judgement is also required in interpreting the thermal profile of the substance. Often caveats were written into a Basis of Safety for drying, introducing the concept that only 'thin layers' could be dried safely, which is rather qualitative and interpretation of the dimension of a thin layer could vary considerably. It has therefore been necessary to develop a fast and pragmatic quantitative approach in which extrapolation of the data obtained from the various small-scale testing equipment available within AstraZeneca is used to derive conservative drying conditions for bulk manufacture without compromising safety.

<sup>†</sup>AstraZeneca retain all registered and unregistered Intellectual Property Rights.

### AVAILABLE EQUIPMENT

The nature by which AstraZeneca was formed back in 1999 from the merger of the Swedish Astra and UK Zeneca groups has meant that a variety of lab equipment is available with varying sensitivities. Generally, as the sensitivity of the equipment increases, the time taken to complete a typical test also increases. The starting point for any investigation is to therefore perform an initial evaluation with one of the rapid, lower sensitivity tests (e.g. DSC, Carius tube) and then where appropriate carry out further testing with more sensitive equipment (ARC, C80, TAM). An overview of the equipment and how it is operated within AstraZeneca is given below:

#### DIFFERENTIAL SCANNING CALORIMETER (DSC) – HEAT FLUX TYPE

The sample (typically 5 mg) is sealed in a high pressure gold plated crucible and ramped at a pre-set temperature rate of 5 K/min. Calibration of the temperature difference between the sample and a reference cell allows the heat flow to be measured as a function of time and temperature.

#### CARIUS TUBE

The sample (typically 10 g) is charged to a glass Carius tube (ca. 35 ml volume), connected via a link to a pressure transducer and ramped at a pre-set temperature rate of 2 K/min. The temperature is monitored with respect to the furnace temperature allowing the detection of self-heating and pressure build-up as a function of time and temperature.

#### ACCELERATING RATE CALORIMETER (ARC)

In this pseudo-adiabatic test the sample (typically 4–7 ml) is sealed in a hastelloy or titanium bomb, connected via a link to a pressure transducer. The bomb is placed in a temperature-controlled oven that tracks the sample temperature to minimise heat losses. Measured data are self-heating and pressure build-up versus time or temperature.

#### SETARAM C80

The Calvet micro calorimeter uses a typical sample size of 0.5 g. The sample is placed in a glass vial, which itself is placed in a high-pressure hastelloy vessel fitted with a pressure transducer. The sample is usually heated to 250°C using a pre-set temperature rate of 0.5 K/min or 0.05 K/min in order to achieve a higher sensitivity. Measured data are heat flow and pressure versus time or temperature.

#### THERMAL ACTIVITY MONITOR (TAM)

Samples are typically encased in 4 ml glass vials with a typical sample size of around 1.0 g. Multiple isothermal measurements of power output as a functional of temperature are usually carried out over a least 24 hours with

Thermometric 3206 mini-calorimeters with temperature control provided by an oil-filled TAM III 3101 Thermostat.

#### EXTRAPOLATION OF SCREENING TESTS SENSITIVITIES

If the sensitivity of the equipment is known, and the assumption is made that the decomposition proceeds via standard *n*th order kinetics with a conservative activation energy, a conservative (i.e. high) power output at the temperature of interest can be calculated according to:

$$q(T) = q_s(T_{\text{onset}}) \cdot \exp\left(\frac{E}{R} \left[ \frac{1}{T_{\text{onset}}} - \frac{1}{T} \right]\right) \quad (1)$$

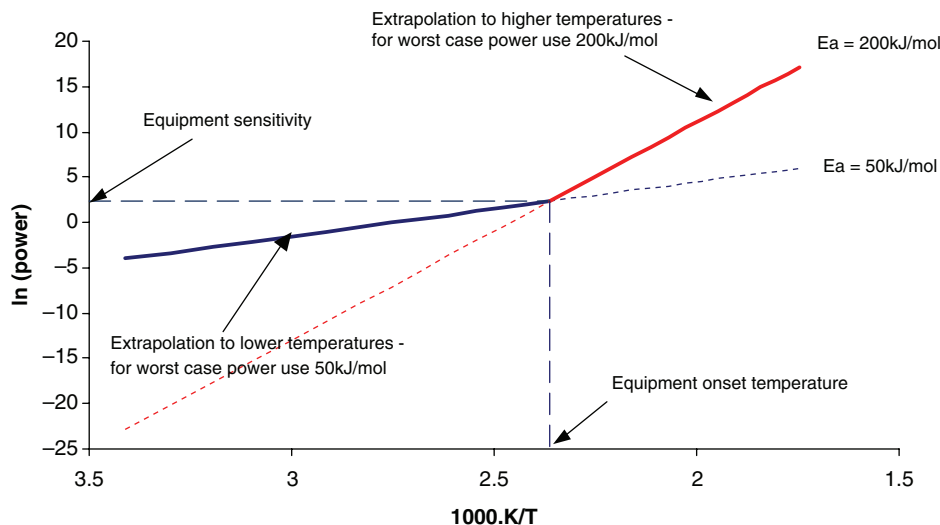
where  $q_s$  is the specific practical sensitivity of the calorimeter at the onset temperature  $T_{\text{onset}}$ ,  $E$  is the activation energy,  $R$  is the universal gas constant,  $q$  is the specific heat generation rate at the temperature  $T$ , of interest.

The activation energy is an important factor in reaction kinetics and is essential for the extrapolation of kinetic data to different temperatures. Synthesis reactions show typically activation energies between 50 and 100 kJ/mol. Decomposition reactions tend to be more temperature dependent than synthesis reactions, i.e. have higher activation energies reaching up to 160 kJ/mol (Stoessel, 2008). Many nitro based explosives reach even higher activation energies, such as the military explosive RDX with 200 kJ/mol (Cooper, 1996). Activation energies below 50 kJ/mol may indicate mass transport phenomena.

In order to extrapolate power output conservatively, a low value for the activation energy (50 kJ/mol) is used when calculating heat output at temperatures below the measured test temperature. In contrast, a large value (200 kJ/mol) is used when extrapolating to higher temperatures to ensure a conservative result (as illustrated in Figure 1). Where concern remains regarding the validity of such extrapolations from the higher temperatures of the screening tests to the lower bulk scale operating temperatures of interest, or the obtained results are too conservative to be applied, then more realistic data can be obtained by the running isothermal tests in a sensitive experimental heat conduction calorimetry test (e.g. TAM) at or just above the proposed operating temperature. This approach

**Table 1.** Practical equipment sensitivity as operated and evaluated within AstraZeneca

Equipment	Practical sensitivity/W/kg
DSC	20
Carius tube	5
ARC	1
C80	0.5–1
TAM	0.001–0.005



**Figure 1.** Extrapolation of heat generation rate using activation energy

is well known (Bunyan, 2003) and whilst the test may be relatively time consuming (typically in the order of 1–5 days), the material requirements are typically no more than 1–5 g.

**USE OF “SCALE FACTORS” SUBTRACTED FROM INSTRUMENT ONSET TEMPERATURES**

In determining a generally worst-case self-heating “onset” temperature for large volumes of non-viscous liquids, by using a conservative extrapolation combined with heat loss data from typical process vessels, standard “scale factors” or “safety factors” are often subtracted from the “onset” of thermal activity as detected in a screening instrument. This area has been extensively reviewed previously with the “DSC 100 K rule” being especially widely referred to. Rowe (2002), has suggested specific and generally conservative factors for some other commercially available thermal screening tests, specifically presented are factors of 50–75 K for the Carius tube test and 30 K for the ARC test. Whilst the occasional pitfalls of this simplistic approach are well known, (Hofelich, 2002), and it is appreciated that in most cases the resulting maximum operating temperatures will be somewhat over-conservative, it is usually an effective approach for the screening of a large number of processes and as such is widely applied within the R&D chemical and pharmaceutical industries. However as will be shown, use of simple “scale factors” designed for R&D plant-scale quantities of liquids equate only to relatively small volumes of bulk solids.

**FRANK-KAMENETSKII MODEL**

The stability of a mass of material depends on the balance between the kinetics of the heat generating process and

the heat transfer properties of the system. The system may pose a hazard if the heat generating process (decomposition) exceeds the heat transfer to the environment so that self-heating would occur which in turn accelerates the heat generation exponentially. Depending on the exothermicity of the decomposition, this self-heating could lead into thermal explosion.

For solids and highly viscous liquids, heat transfer to the environment via natural convection is at best very limited so that the main heat transfer mechanism to the environment is via heat conduction.

To assess the hazard of the drying process, this heat balance needs to be solved in order to define an envelope of safe operation. This problem, i.e. a reactive solid as heat source and heat transfer solely via conduction, was addressed and solved by Frank-Kamenetskii in the 1930s. It is not intended to treat the Frank-Kamenetskii model in detail here as there is extensive literature available on this subject (e.g. Bowes, 1984).

The Frank-Kamenetskii model is based on the following assumptions:

- Heat generation occurs within the bulk mass with a temperature dependence of the heat generation rate according to the Arrhenius law.
- The heat transfer occurs solely via conduction following the second Fourier law.
- The surface temperature of the bulk mass is identical with the ambient temperature.
- Reagent/solid consumption is neglected.

The neglecting of reagent consumption simplified the kinetic description of the heat generation term by making it pseudo zero order.

**Table 2.** Critical dimensionless parameter  $\delta_c$

Geometry	$\delta_c$	$r$
Infinite slab	0.88	Half of layer thickness
Infinite cylinder	2.00	Cylinder radius
Sphere	3.32	Sphere radius

Frank-Kamenetskii identified a critical dimensionless parameter  $\delta_c$

$$\delta_c = \frac{E}{RT_0^2} \frac{q(T_0) \cdot r^2}{a \cdot c_p} \quad (2)$$

where  $r$  is a characteristic length of the geometry,  $a$  is the thermal diffusivity (=thermal conductivity/density/specific heat capacity),  $c_p$  is the specific heat capacity,  $E$  is the activation energy,  $R$  is the universal gas constant,  $q$  is the specific heat generation rate and  $T_0$  is the ambient temperature.  $\delta_c$  is dependent on the geometric shape of the bulk mass. Examples are shown in Table 2.

At  $\delta_c$  the heat generation equals the heat transfer to ambient. For values larger than  $\delta_c$ , the heat generation rate exceeds the heat transfer rate to ambient resulting in uncontrolled self-heating.

Providing the geometry, kinetic parameters, physical properties of the bulk mass are known or conservatively estimated one can determine the highest ambient temperature at which no hazardous self-heating could occur. Alternatively, the largest critical length  $r$  for a given maximum ambient temperature  $T_0$  can be determined.

$$r = \sqrt{\frac{\delta_c \cdot \frac{RT_0^2}{E} \cdot c_p \cdot a}{q_s(T_{\text{onset}}) \cdot \exp\left(\frac{E}{R} \left[\frac{1}{T_{\text{onset}}} - \frac{1}{T_0}\right]\right)}} \quad (3)$$

In equation 3,  $r$  is a characteristic length of the geometry,  $a$  is the thermal diffusivity,  $c_p$  is the specific heat capacity,  $E$  is the activation energy,  $R$  the universal gas constant,  $q$  is the specific heat generation rate and  $T_0$  is the ambient temperature,  $T_{\text{onset}}$  is the temperature at which self-heating is initially detected in the screening instrument,  $\delta_c$  the geometric factor.

During development the kinetic data and the physical data of the bulk mass are typically not available but need to be conservatively estimated. Conservative extrapolation of the heat generation rate to the temperature  $T_0$  using activation energy has already been described above. The  $c_p$  of organic solids was reviewed in literature and it was concluded that for material with an unknown  $c_p$ , a value of 1300 J/kg/K is regarded as a reasonable estimate. Values for the thermal diffusivity were also reviewed in literature. Grever (1994) stated that powders typically have a thermal diffusivity of around  $2 \cdot 10^{-7} \text{ m}^2/\text{s}$  and Kotoyori (2005) reports measured values in the order of  $1 \cdot 10^{-7} \text{ m}^2/\text{s}$  for “organic powdery materials”. Due to

this uncertainty and the desire to use a conservative value for the thermal diffusivity it was intended to use a different approach to define a conservative thermal diffusivity.

The thermal diffusivity is the thermal conductivity divided by the density and specific heat capacity. In the absence of a thermal conductivity value of the bulk mass, the relatively low value for nitrogen (0.026 W/mK) is deemed suitably conservative for the application of pressure filter drying particularly under the conditions of hot nitrogen blowing. With an average bulk density of 500 kg/m<sup>3</sup> and a specific heat capacity of 1300 J/kg/K this gives a thermal diffusivity of  $4 \cdot 10^{-8} \text{ m}^2/\text{s}$ . To the authors’ knowledge, no thermal diffusivity of a lower value has been reported for an organic material, and is hence regarded as conservative.

### POTENTIAL PITFALL 1 – EXTRAPOLATION

When calculating the critical length according to equation 3 based on estimated data for the kinetics and physical properties, data needs to be chosen so that the critical length for a given geometry will be conservative, i.e. small. To achieve this it is important to consider that the activation energy parameter is included in both the numerator and denominator of equation 3. In cases where no extrapolation of temperature is needed, e.g. where TAM data is used, or the extrapolation is towards higher temperatures then a high activation energy will give the conservative value for  $r$ . In cases where an extrapolation to lower temperature is necessary and the extrapolation is significant, i.e. more than 25 K for drying temperatures below 100°C, then the exponential function for the extrapolated heat generation rate is dominating yielding a conservative  $r$ , i.e. a small activation energy is used. For an extrapolation to lower temperatures over a range of up to 25 K then values for the activation energy between 50 and 200 kJ/mol may give a more conservative value for the critical length; (this is illustrated in Figure 4).

### POTENTIAL PITFALL 2 – KINETICS

The Frank-Kamenetskii model neglects any reagent consumption, which makes the kinetic term only dependent on temperature. For “normal reactions” with nth order kinetics, i.e. an isothermal reaction rate that is highest at the beginning and will decay with progressing reagent consumption, this assumption is conservative. However, for decomposition reactions, it is not uncommon that the isothermal reaction rate goes through a maximum, which indicates a pseudo autocatalytic decomposition process.

The main problem with “autocatalytic” decompositions is that the onset temperature of the decomposition in thermal screening experiments depends on the thermal history of the sample. This means that the decomposition onset temperature of freshly produced sample in a thermal screening experiment could be significantly above an older/aged sample. It is therefore very important to ensure that the tested samples are representative and due judgement used when applying the obtained data.

**Table 3.** Drying temperature 25°C

Instrument (Onset)	Critical thickness (thermal diffusivity $4 \times 10^{-8} \text{ m}^2/\text{s}$ )	Critical thickness (thermal diffusivity $1 \times 10^{-7} \text{ m}^2/\text{s}$ )
DSC (125°C)	14.6 cm	23.2 cm
Carius (85°C)	12.6 cm	19.9 cm
ARC (55°C)	11.3 cm	17.9 cm

**Table 4.** Drying temperature 50°C

Instrument (Onset)	Critical thickness (thermal diffusivity $4 \times 10^{-8} \text{ m}^2/\text{s}$ )	Critical thickness (thermal diffusivity $1 \times 10^{-7} \text{ m}^2/\text{s}$ )
DSC (150°C)	11.4 cm	18.0 cm
Carius (110°C)	10.8 cm	17.1 cm
ARC (75°C)	11.0 cm	17.4 cm

**APPLICABILITY OF SCALE FACTORS BASED ON LIQUID SYSTEMS?**

In the tables below are presented the calculated maximum cake thickness across the range of drying temperatures as are typically used for pharmaceutical intermediates, based only on simple subtraction of the typical AstraZeneca scale factors as are used for liquids (100 K for DSC, 60 K for the Carius tube and 25 K for the ARC). As can be seen the results are in the order of just 10–20 cm, depending mostly upon the drying temperature and value for thermal diffusivity that is assumed. It is notable that at higher drying temperatures the cake thickness obtained on subtracting a standard factor decreases, albeit this does not overly impact upon the drying of pharmaceutical products, which tends to be operated between ambient and 80°C.

Tables 3–5: Critical cake thickness calculated by subtracting typical scale factors as used for liquids from detected onsets from DSC, Carius and ARC tests.

Calculations are based on an activation energy of  $50 \text{ kJ/mol}^{-1}$ , heat capacity of  $1300 \text{ J/kg/K}$  and relative sensitivities for the DSC, Carius tube and ARC respectively of  $20 \text{ W/kg}$ ,  $5 \text{ W/kg}$  and  $1 \text{ W/kg}$ , using the “infinite slab” model.

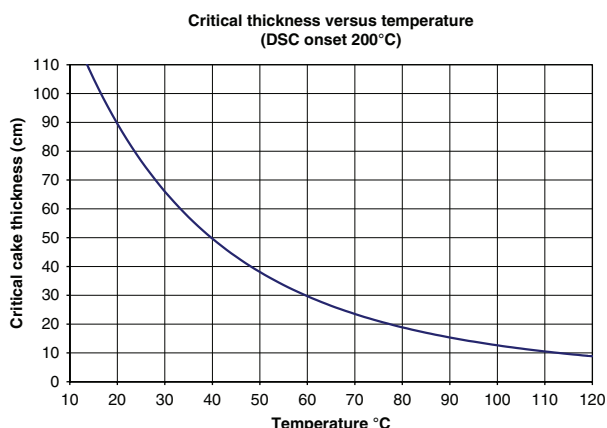
On considering the maximum cake depths calculated using conservative estimates for the required parameters, it is clear that operations carried out at the smaller pilot plant scale and dried in typical tray driers in layers of ~10 cm deep are still covered by the standard scale factors used for liquids.

However for larger scale operations typical of many later phase campaigns, it is not uncommon within AstraZeneca to process significantly deeper layers of material up to 50 cm or above. For larger quantities, it is apparent that a standard subtraction factor is inappropriate. As an illustration of this, for a material in which differential scanning calorimetry detects exothermic decomposition from 200°C, subtraction of a “scale factor” as large as 160°C may be required for a filter cake of a depth of 50 cm (assuming a typical thermal diffusivity of  $1 \times 10^{-7} \text{ m}^2/\text{s}$ ). The effect of larger scales of operation is quite pronounced as shown in Figure 2. (In general within AstraZeneca, DSC would not be used in isolation to support manufacture at such bulk scale quantities.)

In certain pilot-scale drying operations, depending upon the filter-dryers used, the geometry may sometimes deviate significantly from the infinite slab model with a seemingly significant proportion of the surface area of the batch being at the sides of the filter. The use of “cylinder” models has also been widely published, (Fisher, 1993 and references within), with use of a varying geometry factor dependent upon the relative height and radius. However as shown in Table 6 below, unless the geometry tends strongly towards the equi-cylinder case where the thickness of the filter cake approaches that of the diameter, the infinite slab models provides a convenient but not over-conservative limit for general application which can be generally stated into safety reports without the need for prior identification of specific processing equipment.

**Table 5.** Drying temperature 80°C

Instrument (Onset)	Critical thickness (thermal diffusivity $4 \times 10^{-8} \text{ m}^2/\text{s}$ )	Critical thickness (thermal diffusivity $1 \times 10^{-7} \text{ m}^2/\text{s}$ )
DSC (180°C)	9.0 cm	14.3 cm
Carius (140°C)	9.5 cm	15.0 cm
ARC (105°C)	10.8 cm	17.1 cm



**Figure 2.** Critical cake depth versus temperature for DSC onset of 200°C

**CORROBORATION WITH LARGE SCALE DATA**

In order to corroborate the extrapolation of the data acquired from the screening test equipment to bulk plant operation, it was thought prudent to compare the modelled predictions against actual large-scale data. A wealth of larger-scale test data was accessible, however, for the majority there was no accompanying screening test data and unfortunately representative material was not available for retrospective testing. An extensive search of the resources available identified two compounds (A & B) with both larger scale and screening data available and although non-pharmaceutical related compounds, were of similar physical form to the materials processed within AstraZeneca and therefore considered a suitable substitute. With the main focus of the work on the self-decomposition of the molecule rather than the combustion, the availability of air in some of these larger scale tests (e.g. basket) although not ideal did provide a worse case for comparison.

**COMPOUND A**

Compound A is a powdered formulation that gave identical onset temperatures when tested in an aerated cell both in air

and in nitrogen indicating that the decomposition and associated self-heating is not changed significantly by the presence of air, presumably associated with the formulation containing a chemical oxidant. The self-heating characteristics of the system being independent of air availability, make it an ideal test system allowing a consistent comparison of the self-heating data across all tests, i.e. the screening tests and the sealed large-scale oven test (450 litres of material contained within a cubic flexible intermediate bulk container, FIBC with polythene liner) where air availability is limited and also the basket test data (2.5, 5, 10 and 20 cm) where no restriction on the air availability is imposed.

The large-scale oven test consists of an 8 m<sup>3</sup> bespoke design oven of an air recirculation design with temperature control and air extraction. The sample is contained within the oven, which is heated to a preset temperature. Self-heating of the sample is monitored using five thermocouples typically placed on the central vertical axis from the centre to the top surface.

In a basket test the critical self-heating temperature of the powder is defined for a range of different volumes of cubic baskets of increasing unit dimension. A plot of log (Volume/Surface Area) versus reciprocal absolute temperature should yield a straight line allowing extrapolation to bulk quantities. Figures 3 and 4 indicate a reasonably good fit for the basket tests which when extrapolated to the large-scale oven test is coincident with the measured data point suggesting an excellent correlation. Figure 3 also and most importantly indicates that the modelled data (thermal diffusivity 4 × 10<sup>-8</sup> m<sup>2</sup>/s) is always conservative (i.e. predicting lower critical volume-surface area ratios) when extrapolated to both temperatures above and below the onset temperature measured in the screening instruments.

Figure 4, uses a more typical value for thermal diffusivity (1 × 10<sup>-7</sup> m<sup>2</sup>/s) and indicates that the use of an activation energy of 50 kJ/mol for extrapolations limited to approximately 25 K below the onset temperature obtained from the screening tests does not yield the most conservative results. However as described earlier, the use of activation energies between 50–200 kJ/mol results in more conservative data, which importantly when applied illustrates conservatism throughout the range compared to the measured large-scale data.

**Table 6.** Variation in critical cake thickness depending upon the geometry factor used; calculated values are based on a decomposition with a DSC-detected thermal onset of 150°C, drying temperature of 50°C and other assumptions as per Tables 3–5

Model	Critical thickness (thermal diffusivity 4 × 10 <sup>-8</sup> m <sup>2</sup> /s)	Critical thickness (thermal diffusivity 1 × 10 <sup>-7</sup> m <sup>2</sup> /s)
Inf. slab model (δ <sub>c</sub> = 0.88)	11.4 cm	18.0 cm
Diameter: 4 × depth (δ <sub>c</sub> = 1.00)	12.1 cm	19.2 cm
Diameter: 3 × depth (δ <sub>c</sub> = 1.09)	12.7 cm	20.0 cm
Diameter: 2 × depth (δ <sub>c</sub> = 1.36)	14.1 cm	22.3 cm
Diameter = depth (δ <sub>c</sub> = 2.78)	20.2 cm	31.9 cm

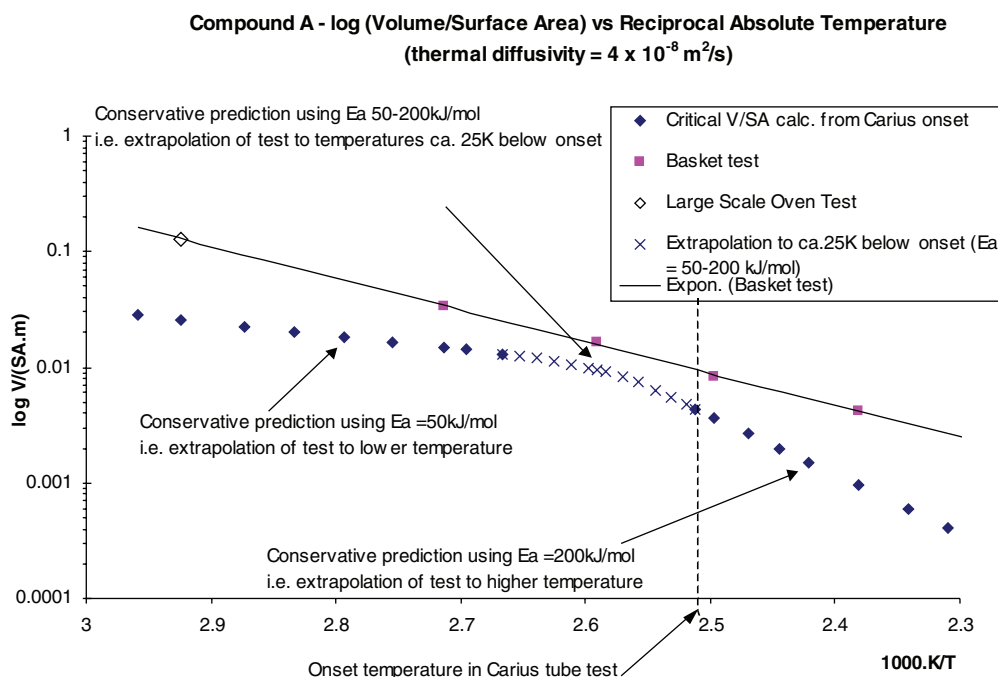


Figure 3. Compound A – Comparison of predicted and measured data (thermal diffusivity =  $4 \times 10^{-8} \text{ m}^2/\text{s}$ )

**COMPOUND B**

Compound B is a non-pharmaceutical powdered formulation and unfortunately no testing had been performed to evaluate the effect of air availability. It was therefore assumed that the unlimited air availability

present in the existing basket test data would at best give comparative data if self-reaction precedes combustion but would offer a worst case scenario should the alternative combustion pathway have a significant influence.

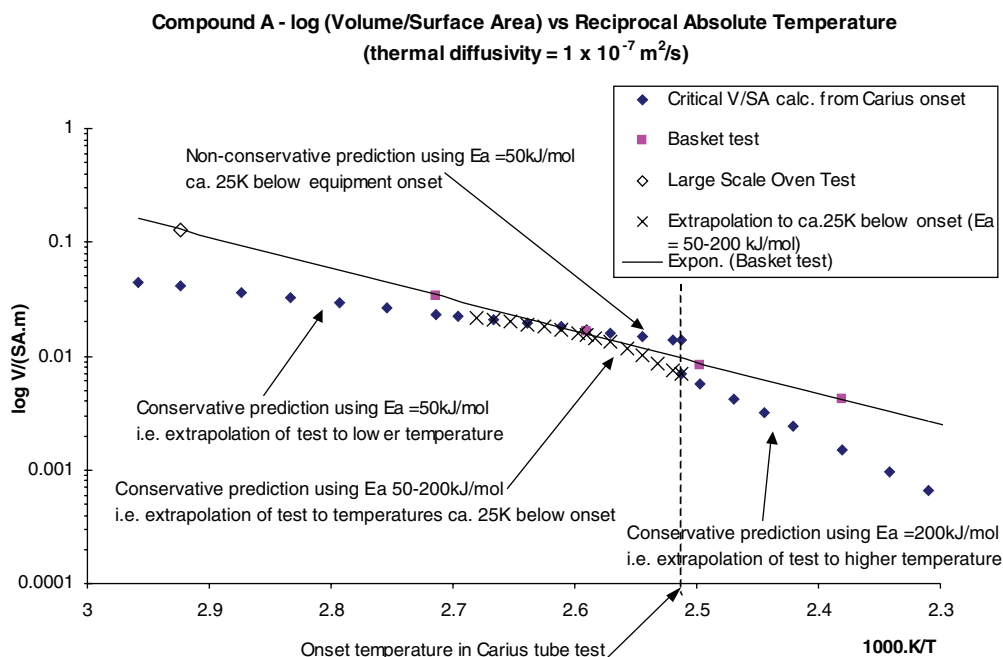


Figure 4. Compound A – Comparison of predicted and measured data (thermal diffusivity =  $1 \times 10^{-7} \text{ m}^2/\text{s}$ )

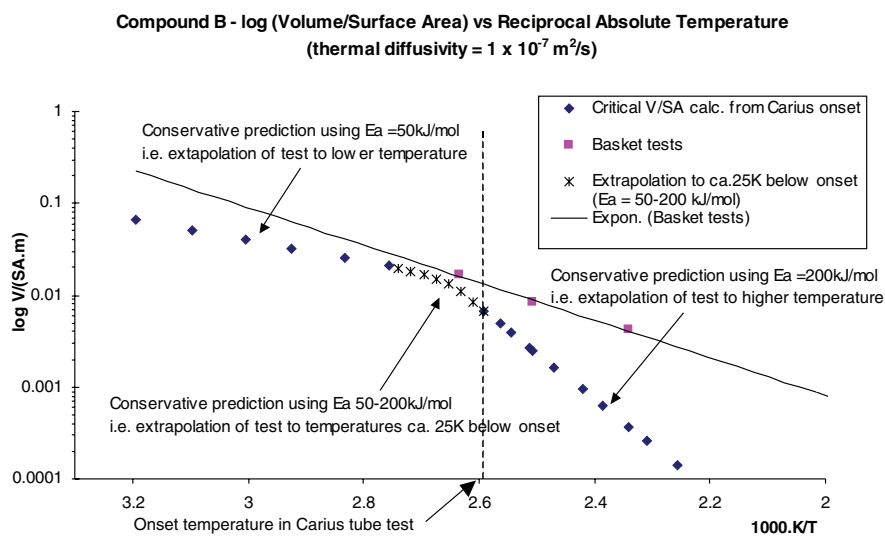


Figure 5. Compound B – Comparison of predicted and measured data (thermal diffusivity =  $1 \times 10^{-7} \text{ m}^2/\text{s}$ )

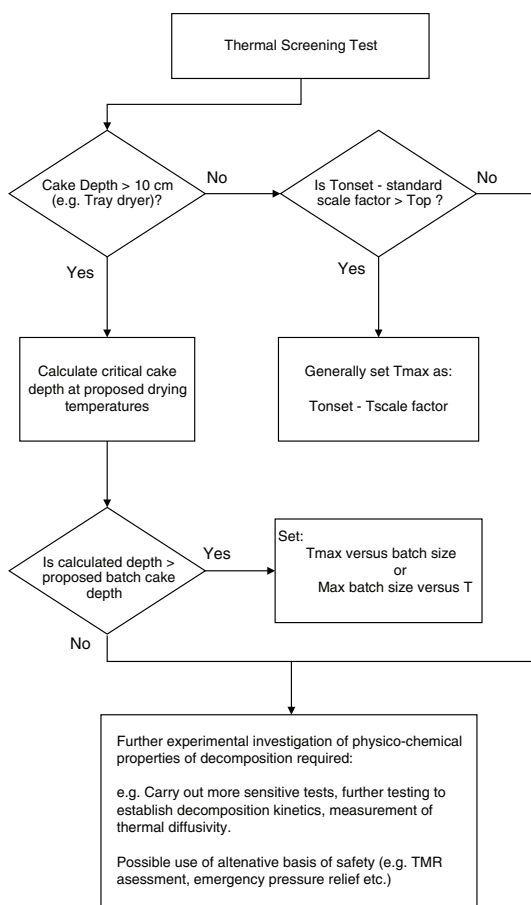


Figure 6. Scheme showing approach taken with the assessment of drying operations within AstraZeneca development plants. (Top: drying operation temperature, Tonset: self-heating onset temperature detected in screening test,  $T_{max}$ : maximum safe operating temperature)

Figure 5 shows the plot of log (Volume/Surface Area) versus reciprocal absolute temperature and yields a reasonable straight-line correlation of the basket test data allowing extrapolation to bulk quantities. The graph again illustrates that the modelled data even with use of the less conservative thermal diffusivity value ( $1 \times 10^{-7} \text{ m}^2/\text{s}$ ) is always conservative (i.e. predicting lower critical volume-surface area ratios) when extrapolated to both temperatures above and below the onset temperature measured in the screening instrumentation.

**CONCLUSIONS**

It is apparent that the commonly used practice of subtracting simple “scale factors” from thermal screening tests derived for assessment of non viscous liquid systems can be unsuitable for setting maximum operating temperatures for bulk quantities of solids. However with the use of conservative estimates for kinetic and physical properties for the decomposition reaction it can be shown that no additional consideration need be given to layers of less than 10 cm in depth provided that the operation is conducted under an inert atmosphere (i.e. a “thin layer” can be regarded as being up to 10 cm deep).

For thicker layers more typical of later phase R&D operations, assessment on an individual case basis is considered necessary, the general approach of which is shown schematically in Figure 6. Due judgement and consideration of properties such as autocatalysis is clearly needed however and it is not intended that this approach be used without due care and thought. However in most instances it has proven readily possible to further extrapolate, quickly and safely the results from small scale screening tests to larger-scale inert atmosphere operating conditions using the infinite slab geometry in the Frank Kamenetskii model.

Although limited, the large-scale data available indicated that the use of the model with the proposed



assumptions surrounding test equipment sensitivity and test material physico-chemical properties yields conservative critical drying conditions. The use of a more typical thermal diffusivity value of  $1 \times 10^{-7} \text{ m}^2/\text{s}$  still resulted in conservative data for the compounds tested, however in the absence of further larger-scale experimental data the more conservative value of  $4 \times 10^{-8} \text{ m}^2/\text{s}$  will continue to be adopted within AstraZeneca. As more data becomes available it is planned to further test the procedure with the expectancy to reduce conservatism in some of the assumptions.

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