Process Safety Evaluations

Enabling a successful CDMO operation

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PharmaBlock

Thermal runaway in fine chemical production is one of the most perilous reasons for accidents. Once thermal runaway occurs in materials or reaction systems, it will inevitably lead to temperature rise, pressure increase, and eventually reaction runaway or even thermal explosion.

To prevent the occurrence of thermal runaway, it is necessary to explore the causes of thermal runaway accidents. It is additionally imperative to understand the heat release rate, adiabatic temperature rise, decomposition temperature of materials and other parameters. These parameters must be obtained through calorimetric technologies.

Process safety evaluations are essential

1. The necessity of thermal risk assessment via calorimetric technology

When the reactor size increases with production scale, the increase in cooling capacity is far less than the increase in heat generation rate. For example, when the laboratory scale is scaled up to the production scale, the specific surface area (surface area/volume) of the reactor is reduced by two orders of magnitude. On the laboratory scale, the cooling capacity may be as high as 1,000W/kg, while on the production scale it is only about 20-50W/kg (Data from HarsNet). Therefore, even if no exothermic effect was found on a laboratory scale, this does not mean that the reaction is safe on a larger scale. Therefore, empirical evaluations and theoretical calculations are often unreliable, and it is critical to use calorimetric technologies for accurate testing.

2. The significance of calorimetry technologies for material thermal stability

According to Japan's statistical analysis of accidents in batch reaction processes, the proportions of accidents in different processes is: accidents in reaction engineering ≥ 22.9%, accidents in storage ≥ 12.5%, accidents in transportation ≥ 10.1%, accidents in distillation ≥ 6.7%, and accidents in mixing = 5.8%. Incidents related to material stability (involving storage, custody, transportation, distillation, and mixing) accounts for 35.1% of the total. Therefore, accurate calorimetric analysis of the material needs to be carried out. The safety design of the process operation is very important.

The applications of calorimetry technologyies at PharmaBlock

Calorimetry technology refers to a type of technology that measures the relationship between a sample's temperature or its time under program controlled temperature and a certain atmosphere. Currently, the PharmaBlock process safety laboratory is

equipped with the following calorimetric equipment and software for material thermal stability:

Equipment	Main purposes	Obtained parameters
DSC	• Measure the heat absorbed by or released by the sample in a specified condition • Study compatibility • Study the material's decomposition kinetics	• Initial decomposition temp. • Heat release • Melting point • Glass transition
TGA	• Measure the relationship between the weight of the sample and the temperature or time under program control and certain atmosphere	• Weightlessness ratio • Weightlessness temp. • Decomposition residue • Decomposition component content
RSC (RSC-400A)	• Measure the temperature and pressure changes of the sample in linear heating, isothermal, and gradient heating modes	• Maximum temp. rise /maximum pressure rise rate • Gas production from material decomposition • Initial decomposition temp. • Pressure vs. temp. change data
ARC	• Measure the changes in sample temperature and pressure under adiabatic and programmed temperature control conditions • Study the material decomposition kinetics	• Initial decomposition temp. • Adiabatic temp. rise • Adiabatic induction period (TD24、TMRad) • Maximum temp. rise / maximum pressure rise

Software	Main purposes
Kinetics NEO	After the model-free or model kinetic analysis is performed, the reaction process can be simulated and predicted according to a certain temperature program on this basis.
CHETAH	This is mainly used to predict the energy release risk and chemical reaction heat of pure chemicals and mixtures. In addition, CHETAH can also be used to predict the flammability of chemicals, predict the enthalpy of combustion and combustion products.
Dynochem	Thermal analysis section: the process can be predicted and optimized based on RC1, DSC, and ARC data, and then amplified safely.

PharmaBlock case studies: material thermal stability research

Using the above equipment and software, the PharmaBlock process safety laboratory has tested the thermal stability of many substances. In the following section, the team would like to share some cases.

1. Dynamic testing and analysis by DSC

The DSC experiment of PB06483-01 used a 25uL disposable stainless steel gold-plated crucible (pressure resistance 15Mpa), and selected four different heating rates for testing. Specific experimental conditions, test curves, and heat release characteristic parameters are shown in Table 1 and Figure 1.
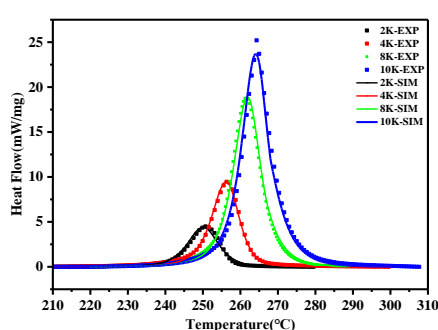

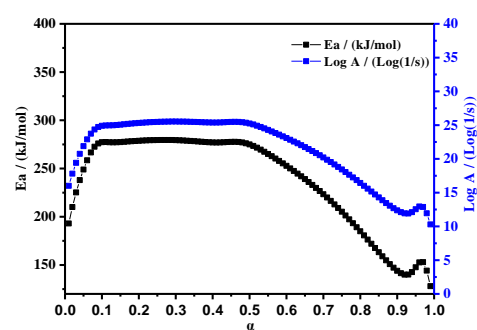Figure 1 Dynamic Test Curve and Fitting Curve of PB06483-01

Figure 2 The Relationship Between Ea, logA and α Obtained by Friedman

Table. 1 Dynamic DSC Test Conditions and Results of PB06483-01

β/（K/min）	m/(mg)	T_o/(℃)	T_{peak}/（℃）	$\triangle H_r$/(J/g)	Test range/（℃）
2	1.86	242.39	251.38	1411.09	
4	1.87	248.66	257.58	1455.36	
8	1.82	254.56	263.37	1516.45	100-350
10	1.83	257.62	266.66	1540.46	

2. Thermal decomposition kinetics based on dynamic DSC test

PharmaBlock substituted the obtained DSC data into the following formula to calculate the thermal decomposition kinetic parameters of PB06483-01 with equal conversion rate methods.

$$\ln\left(\frac{d\alpha}{dt}\right)_{\alpha,i} = ln[f(\alpha) \cdot A_\alpha] - \frac{Ea}{RT_{\alpha,i}}$$

The relationship between Ea、$ln[f(\alpha) \cdot A_\alpha]$ and α is shown in Figure 2 below.

It can be seen from Figure 2 that α is in the range of 0.1 - 0.5, the activation energy Ea varies between 274kJ/mol - 277kJ/mol, and the corresponding $ln[f(\alpha) \cdot A_\alpha]$ is between 24-25, and the values of these two parameters basically keep constant. Meanwhile α is in the range of 0.5-0.9, the activation energy Ea varies from 277kJ/mol to 144kJ/mol, and the corresponding $ln[f(\alpha) \cdot A_\alpha]$ is between 25-12.

From the above results, we can infer that the decomposition reaction mechanism of PB06483-01 does not follow a single mechanism function, and there are at least two continuous decomposition processes at work.

According to the above analysis, thermal decomposition of PB06483-01 has autocatalytic characteristics, so the autocatalytic model is chosen to calculate and accommodate, thereby obtaining the intrinsic decomposition characteristics of the sample. This in turn predicts the behavior of the sample under different scales and different environmental conditions.
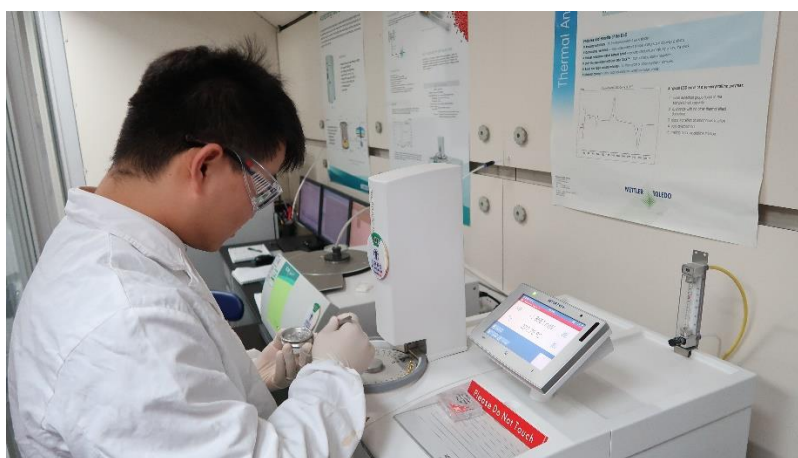
It can be seen from Figure 1 that the two-step autocatalysis model is suitable for the decomposition reaction mechanism of PB06483-01. The displayed values of the DSC curve at different heating rates are in good agreement with the experimental values of R^2=0.9969. The specific kinetic parameters obtained are shown in Table 2.

<div align="center">Table. 2 Kinetic Parameter Values</div>

Kinetic Parameters	Unit	Value
A→B: $\frac{d\alpha}{dt} = A * \alpha^n * (1 + P(1-\alpha)) * exp\left(\frac{-Ea}{RT}\right)$		
Ea	kJ/mol	251.600
Log(A)	Log(1/s)	21.919
n	-	0.674
P	-	1.499
B→C: $\frac{d\alpha}{dt} = A * \alpha^n * (1 + P(1-\alpha)^m) * exp\left(\frac{-Ea}{RT}\right)$		
Ea	kJ/mol	105.098
Log(A)	Log(1/s)	7.954
n	-	1.270
m	-	0.396
P	-	0.870

3. Intrinsic safety design based on dynamic DSC results

After obtaining the kinetic equation, we can learn the decomposition of the sample under any temperature mode (constant temperature, adiabatic, dynamic heating, or constant temperature storage) and at any magnitude. We can set the actual safe operating temperature (short-term storage temperature, baking temperature, concentration temperature, transportation temperature, etc.) for any process operation to be carried out, and even the decomposition rate under similar heating conditions. All the simulations are aimed to develop intrinsic safety strategies for actual production.

4. Dynamic testing and analysis by RSC

The RSC experiment of PB06483-01 uses 8ml titanium alloy balls and performs linear scanning at a heating rate of 2K/min. The specific experimental conditions, test curves, and heat release characteristic parameters are shown in Figure 3 and Figure 4.
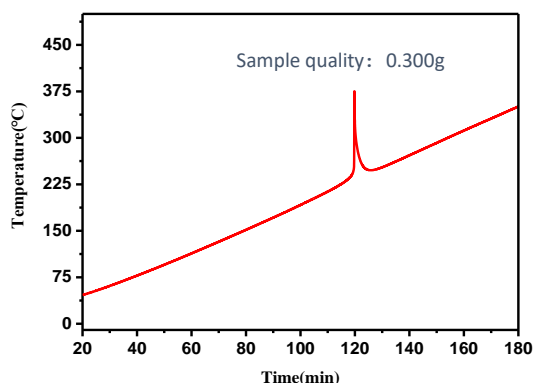

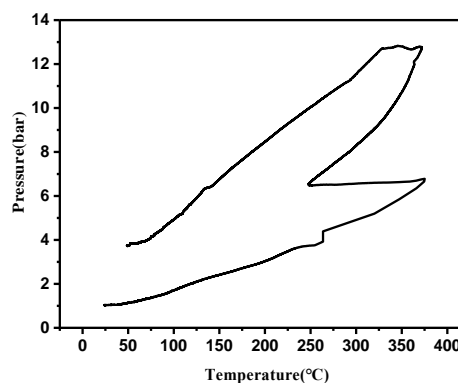Figure 3 Temperature-Time Curve of PB06483-01

Figure 4 Pressure-Temperature Curve of PB06483-01

It can be seen from Figure 3 and Figure 4 that under the RSC test conditions, PB06483-01 begins to release heat at 204.58°C; at the same time, when the temperature drops to 50°C at the end of the test, the residual pressure is 3.732bar, according to the formula below:

$$\frac{P_0 V_0}{T_0} = \frac{PV}{T}$$

The non-condensable gas production of PB06483-01 is calculated to be 68.88ml/g.

5. Material storage and transportation conditions intrinsic safety design by ARC

The ARC test of a substance uses 8ml titanium alloy pellets, and the test is carried out from 70-235°C in H-W-S mode. The specific experimental conditions, test curves, and heat release characteristic parameters are shown in Table 3 and Figures 5 and 6.
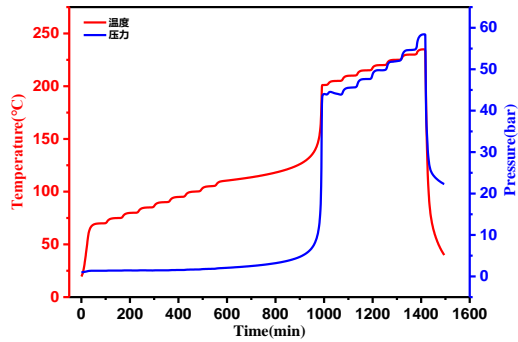

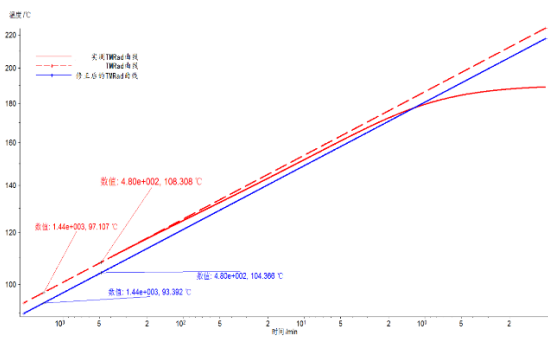Figure 5 ARC Test Temperature and Pressure Versus Time Curve

Figure 6 TMR Curve of Test Substance

Table. 3 ARC Test Conditions and Results of the Tested Substance (* means Ø revised)

Ø	$T_0/$ (℃)	dT/dt^*_{max} (℃/min)	$T_{mr}/$(℃)	dP/dt^*_{max} （bar/min）	$P_{max}/$(bar)	$\Delta T^*_{ad}/$(℃)	$T^*_{D24}/$(℃)	$\Delta H^*_r/$(J/g)
1.461	110.8	16.7	189.0	14.3	44.0	132.1	93.4	276.0

From Figure 6, the time required for the substance to reach the maximum temperature rise rate at any temperature can be calculated and different storage processes can be designed. For self-reactive substances stored in large quantities, SADT can also be calculated with the help of ARC data, according to the ability of SADT to set different transportation conditions.

TGA   DSC   FPCC   RSC

A glimpse into the future

Process safety evaluations should be the sum of a series of safety technologies and management methods for preventing and controlling emergencies specific to chemical processes. The evaluations involve design, construction, production, storage, transportation, and disposal of various links in the entire chain of chemical processes; it should not only be limited to the reaction processes or a few individual operating units.

At present, the process safety evaluations in most companies mainly focus on thermal risk, but the types of safety accidents that occur in the actual production processes are various (including fire, explosion, leakage, poisoning, corrosion, etc.). Therefore, safety evaluations should not only focus on the risk assessment of reaction heat, but also on fire prevention (lightning, ignition point, spontaneous ignition point, electrostatic measures, oxygen content control, etc.), explosion protection (explosion limit, minimum ignition energy, frictional impact sensitivity, etc.), and pressure venting to name just a few.

The process safety team at PharmaBlock is committed to applying calorimetric technologies to improve process safety management, emphasizing the use of thermal risk assessment technology and risk assessment data as the basis of the process safety system. At the same time, the team supports process optimization and amplification from a safety perspective, and finally achieves complete life cycle management of process safety.

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About PharmaBlock Process Safety Laboratory

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