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"THE EVALUATION OF SAFETY PERTAINING TO THERMAL AND REACTION PROCESSES IN THE PHARMACEUTICAL INDUSTRY"

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Abstract

Process Safety is study of hazards & managing risks that are involved in any type of Chemical reactions that are occurring at an industrial level. It is a step-by-step review of industrial operating procedures where it is undertaken to identify the potential causes (parameters like temperature, pressure, concentrations of reactants) and possible consequences of hazardous chemical releases. In our project we are using RSD (Rapid Screening Device) systems of Thermal Hazard Technology (THT) which help in the determination of optimum temperature for a particular reaction to take place & decomposition rate. Using a reference sample, we try to devise the operatable temperature range for production, for our desired samples loaded in the RSD. The 6 samples used hereare A, B, C, D, E, F along with the reference sample are tested are 20,30,40,50,60° C at regular time intervals to calculate the Decomposition rate. The graphs generated for Temperature Vs. time & Pressure are analyzed for the creating the process safety data analysis at production scale. Advance to this RSD the Thermal Hazard Technology Introduced ARC (Accelerating rate calorimeter). The ARC has specific features and advantages that make it unique and preferable to all other technologies that were available at this time - and today 30 years later this technology is still the number one choice for most people focusing in the area of quantifying exothermic reactions, effect of heat upon materials and simulating runaway reactions.

INTRODUCTION

Process safety is a crucial aspect of the pharmaceutical industry as it involves handling and processing hazardous materials, such as active pharmaceutical ingredients (APIs) and solvents, that can cause harm to people, property, and the environment if not handled appropriately. The goal of process safety in the pharmaceutical industry is to prevent accidents, incidents, and near-misses that can result in injuries, illnesses, or fatalities. Process safety in the pharmaceutical industry involves identifying potential hazards and assessing the risks associated with each step of the manufacturing process, from raw materials to finished products. It includes designing and maintaining safe and reliable equipment and facilities, developing and implementing robust procedures and guidelines, and providing appropriate training and supervision for employees. Some of the key process safety elements that are commonly applied in the pharmaceutical industry include:

1. **Hazard identification and risk assessment**: identifying and assessing potential hazards and risks associated with each step of the manufacturing process, from raw materials to finished products.
2. **Process design**: designing processes that eliminate or minimize the potential for hazardous events to occur.

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3. **Equipment design and maintenance**: ensuring that equipment is designed and maintained to prevent or mitigate the effects of any hazardous events that might occur.
4. **Operating procedures and guidelines**: developing and implementing operating procedures and guidelines that ensure safe and consistent operation of equipment and processes.
5. **Training and supervision**: providing appropriate training and supervision to employees to ensure they have the necessary knowledge and skills to operate equipment and processes safely.
6. **Emergency response**: Developing and implementing emergency response plans to ensure that appropriate actions are taken in the event of an accident or incident.

Process safety is a continuous effort that requires ongoing monitoring, review, and improvement to ensure that risks are continually reduced and controlled. Effective process safety management can help pharmaceutical companies to protect their employees, communities, and the environment, as well as to maintain a strong reputation for safety and quality. Process safety information is one of the concepts under Advanced Risk Assessment as shown in below figure.

Figure 1: Process Safety Management Elemnts

MATERIALS AND METHODS

Materials

- Sample (Distilled Residue) of VAM product- 15 g
- Tube Bomb- 1N
- Spherical high-pressure bomb- 1N
- Silicon oil- 5 ml
- Acetone, Toluene, Methanol

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EXPERIMENTAL METHODS

1. Rapid Screening device:

The rapid screening device has been designed as an entry level calorimeter able to screen material exhibiting exothermic or endothermic behavior rapidly and reliably. The RSD may be used by layer organizations who, rather than use expensive slower equipment, can quickly screen samples before deciding whether further investigation is needed. RSD would measure temperature and pressure and would operate over a wide temperature & pressure range. It would be low cost not only in initial outlay but also have minimal running costs.

Figure 2: Rapid Screening Device

PROCEDURE

Instrument Setup:

1. The main power supply ON indicates instrument and computer is ready to use. Prepare sample and charge appropriate amount of sample in the test bomb (I.e., 3 to 8 gm).
2. Fix the bombs to the caddy within the sample chamber.
3. Make sure that temperature channel and pressure channel should be connected on respective channels.
4. The heater is pulsed in order to keep the ramp rate at the point where the control thermocouple is at the rest rate.
5. By attaching the control thermocouple to similar thermal mas, the system will act to ramp accordingly thus taking account at the thermal mass of the sample.1.6 Samples with higher thermal mass will be heated at slightly lower rates.
6. Samples with higher thermal mass will be heated at slightly lower rates.

Principle:

1. The RSD test bomb made of Titanium or Hastelloy or Glass is used as test run analysis. Sample quantity is analyzed from 25 °C to 250° C and cooled to room temperature, here we used Hastelloy tube bomb.
2. A sample is charged into test bomb and heated step wise using electrical resistance heaters. The jacket is always held precisely at the same temperature.

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Figure 3: Hastelloy Tube Bomb

Figure 4: Sample Loading (Liquid)

Sample Preparation

1. Select the bomb based on its MOC compatibility with sample to be tested.
2. Distilled Residue sample of 6 grams is loaded in a Hastelloy cell.
3. Process temperature for distilled residue is 85°C
4. Weigh the empty test bomb using balance and tare the weight reading remove the test bomb from balance and insert (6 gm) material/sample into the test bomb check the weight of the test bomb with sample and use the value in the software to analysis.
5. Handle reaction mass and hygroscopic materials under nitrogen atmosphere in fume hood for sample preparation.

Figure 5: Sample Which Is Holded By Caddy

Figure 6: Caddy

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Test Cell/ Bomb type and its Heat capacity are:

1. Different type of MOC test cells are available like Titanium, Hastelloy, glass & Stainless steel.
2. During the analysis the heat capacities are to be given and they are : HC22:0.42 J/gK , Titanium:0.52 J/gK ,SS :0.42J/kJ/gK
3. HC22, Titanium and SS round test cells/bombs are in 10ml volume and can with stand up to 200 bar pressure.
4. HC22 and SS Low Phi bombs are of 65ml volume and can withstand up to 50bar pressure.
5. Test cell/bomb has to be selected as per MOC compatibility.

Preliminary observations:

1. Ensure that all electrical connections are secured.
2. Ensure the test bomb outer surface is cleaned after charging sample into it and is fitted properly to lid section.
3. Ensure all cables inside the ARC instrument are connected.
4. Ensure the sample thermocouple is placed properly to the test bomb.
5. Ensure pressure leak is removed before starting temperature program.

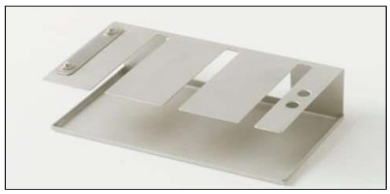

Figure 7: Thermocouple and Pressure Line

Startup Operation:

1. Switch on the power supply and switch on the CPU and monitor.
2. Double click this icon to run the RSD software.
3. Software starts to run and below window displays.
4. Always ensure the system settings as shown in window and click on the Test setup for new experiment.

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Parameters:

1. Sample Name : Distilled Residue
2. Sample Mass (g) : 6.00
3. Sample Heat Capacity (kJ/kg K) : 2.00
4. Test-cell Information : (Hastelloy)
5. Test-cell Mass (g) : 14.50
6. Test Mode : Ramp
7. Ramp Rate (°C/min) : 4.00
8. End Temperature (°C) : 250.00

Accelerating rate calorimeter

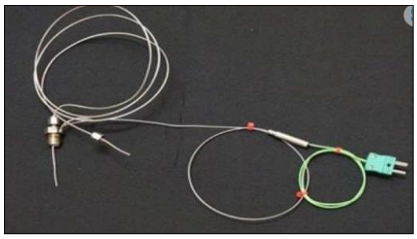

Figure 8: Accelerating Rate Calorimeter

The Chemical Processing Industry has been safer from its first availability in 1980! The ARC has specific features and advantages that make it unique and preferable to all other technologies that were available at this time - and today 30 years later this technology is still the number one choice for most people focusing in the area of quantifying exothermic reactions, effect of heat upon materials and simulating runaway reactions.

PROCEDURE:

1. Instrument Setup:

1. Door opens indicated sample under preparation/analysis stopped/analysis completed.
2. The main power supply "ON" indicates instrument and computer is ready to use.
3. Prepare sample and charge appropriate amount of sample in the test bomb (i.e. 3 to 8 gm).
4. Fix the test bomb to the top lid section and arrange sample sensor at the bottom clip.

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2. Principle:

Figure 9: Sample Loading(Solid)

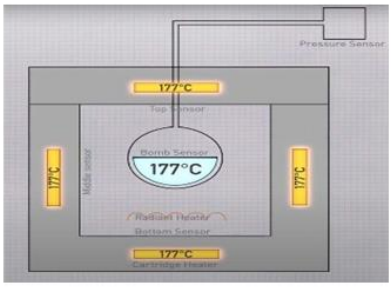

Figure 10: Working Mechanism of ARC

3. Sample Preparation:

1. Select the Test bomb based on its "MOC" compatibility with sample to be tested.
2. Weigh the empty test bomb using balance and tare the weight reading. Remove the test bomb from balance and insert 6 gm material/sample into the test bomb.
3. Check the weight of the test bomb with sample and use the value in the software for analysis. Handle reaction mass and hygroscopic materials nitrogen atmosphere in fume hood for sample preparation.
4. Different type of MOC test cells is available like Titanium, Hastelloy, Glass and SS
5. The three test cells available are standard side clip as i.e., reaction mass monitoring sensor connected to the test cell on the side clip.
6. During the analysis the heat capacities are to be given and they are: HC22: 0.42J/gK, Titanium: 0.52J/gK, SS0.42J/gK.
7. HC22, Titanium and SS round test cells/bombs are in 10ml volume and can with stand upon 200 bar pressure.
8. Test cell/bomb has to be selected as per "MOC "compatibility.

Preliminary observations:

1. Ensure that all electrical connections are secured.
2. Ensure the test bomb outer surface is cleaned after charging sample into it and is fitted properly to lid section.

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3. Ensure all cables inside the ARC instrument are connected.
4. Ensure the sample thermocouple is placed properly to the test bomb

Parameters:

1. Sample Name: Distilled Residue
2. Sample Mass (g): 6.00
3. Sample Heat Capacity (kJ/kg K): 2.00
4. Test-cell Information: (Hastelloy)
5. Test-cell Mass (g): 14.50
6. Test Mode: Heat-wait-seek

Startup Operation:

1) Switch on the power supply and switch on the CPU and monitor.
2) Double click this icon to run the ARC software.
3) Software starts to run and below window displays.
4) Always ensure the system settings as shown in window and click on the Test setup for new experiment.

Figure 11: High Pressure Bomb

Figure 12: Set Up Of Accelerating Rate Calorimeter

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RESULTS AND DISCUSSIONS

Result for Rapid screening device

Table 1: Values for RSD

TIME (min)	TEMPERATURE (°C)	PRESSURE (bar)	TEMPERATURE RATE (°C/min)
22.5	90	4	4
25	100	4.5	4
27.5	110	4.75	4
30	120	5	4
32.5	130	5	5
35	140	6	5
37.5	150	7	7
40	213	57.5	25

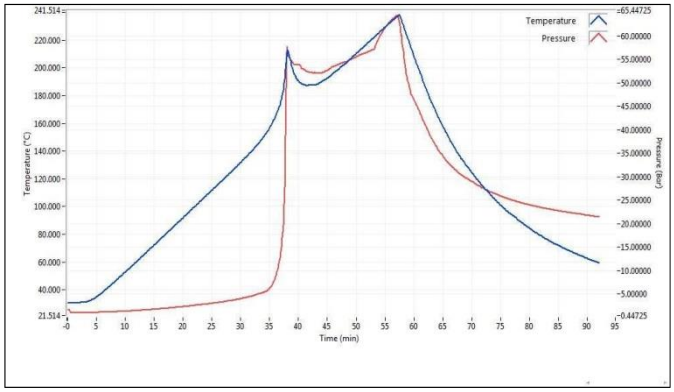

Figure 13: RSD Temperature, Pressure vs time trends for Distilled Residue

The heat of reaction is also known as **Reaction Enthalpy**. The difference in the enthalpy of a specific chemical reaction is obtained at a constant pressure. It is the thermodynamic unit of measurement applied in measuring the total amount of energy per mole either produced or released in a reaction.

Heat of reaction = m cp ΔT

= 6*2*(213-132)

=6*2*(81)

=972kJ

Heat evolution =Heat of reaction/mass

=972/6

=162 KJ/g

Adiabatic temperature raise= Heat evolution/2

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=162/2

=81 (medium severity)

1. The RSD analysis showed an exotherm onset at 132°C and ended at 213°C with heat evolution of 162J/g. The adiabatic temperature rise for the exotherm is 81°C and the severity is medium.
2. Maximum pressure attained is 65 bar at 240°C and no residual pressure at 60°C. Onset of pressure event observed at 132°C.
3. As per RSD 50°C thumb rule, the safe operating temperature based on exotherm is 82°C. The distillation process temperature is 85°C. It is recommended to perform ARC analysis to understand the thermal stability of distilled residue.

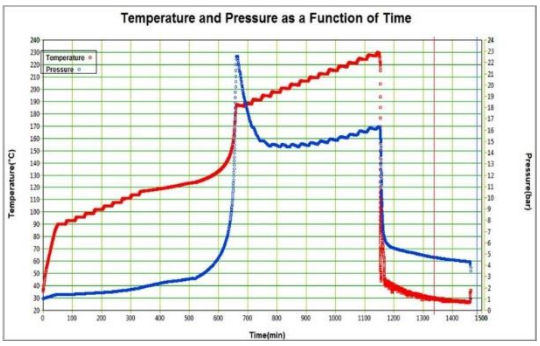
Result for accelerating rate calorimeter

TMRad (TIME TO MAXIMUM RATE): - TMRad (T0) = CpRT02/ q0E

TMRad for 8 Hours: -110.55°C TMRad for 24 Hours: - 102.48°C where

T0=initial temperature Cp=specific heat capacity R=universal gas constant E=activation energy

q0=heat release rate at initial temperature



1. The ARC analysis showed an exotherm onset at 117.4°C with heat evolution of 234.55J/g. The adiabatic temperature rise for the exotherm is 117.25°C and the severity is medium.
2. Maximum pressure attained is 22.5 bar and observed 4.5bar at 30°C residual pressure due to non-condensable gases.
3. As per ARC analysis, based on exotherm TMRad for 8h is 110.55°C and for 24h is 102.48°C.
4. The distillation process temperature at 85°C is thermally safe.

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Table 2: Severity of an Exothermic Event Based on Heat Released and the Corresponding Adiabatic Temperature Rise

Severity	Adiabatic temperature rise (°C)	Energy released J/g
high	>200	>400
medium	50–200	100–400
low	<50	<100

For example, if a reaction exhibits a Δ*T*ad of 200 °C and is operating at room temperature, 22 °C, it can potentially increase the temperature of the reactor contents to 222 °C if cooling failed. Clearly, this can be catastrophic as the temperature increase could lead to further speed up of the reaction rate, solvent evaporation, and initiate other thermal decompositions. Based on the Stoessel classification criteria Table 2, a thermal event that exhibits a Δ*T*ad of 200 °C or higher is considered a high severity event. On the other hand, a Δ*T*ad of 50 °C or less is considered low severity, while a Δ*T*ad of 50–200 °C is considered medium.

Surveyed companies were asked to express severity in terms of the energy associated with an exotherm and/or in terms of the adiabatic temperature rise (Δ*T*ad) associated with that exotherm. Figure 4a shows what is considered a low exotherm (green), a medium exotherm (yellow), or a high exotherm (red) in the 10 companies that answered this question. Figure 4a indicates that most companies consider an adiabatic temperature rise below 50 °C as a low severity exotherm, while a Δ*T*ad higher than 200 °C would be classified as a high severity exotherm which reflects the classification proposed by Stoessel. However, three companies were on the conservative side and considered Δ*T*ad higher than 50 °C as high severity.

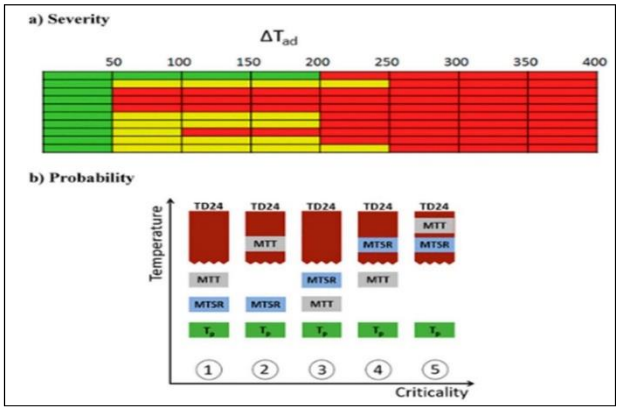

Figure 15: (a) Classification of exotherms in terms of adiabatic temperature rise as low (green), medium (yellow), high (red). Each line corresponds to the criteria given by a single company. (b) Stoessel criticality classes, used by 12 out of 15 companies

CONCLUSIONS

The IQ thermal hazards and process safety working group completed a survey of its membership to assess approaches to process safety development. Participation rates among the member companies was excellent, and the information gathered covered all phases of

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development and manufacturing. While many commonalities exist, it should not come as a surprise that each company has a different approach for gathering and developing process safety information, and these approaches are likely reflective of the individual member companies' cultures and risk tolerance. In addition, there were very few commonalities noted among the way member companies interact with CMOs and share their thermal hazard results.

The key findings from the survey in terms of engaging PSL throughout the drug development lifecycle is the following. At the early phase, some companies reported not having medicinal chemistry groups to support, whereas others are either supporting the early phase in a scaled-back manner or not at all. Most companies surveyed have a threshold that triggers an evaluation by PSL; however, that threshold varies significantly from company to company. The "mid-stage" of development (roughly corresponding to the execution of drug substance campaigns in the kilo-lab or pilot plant) is where the majority of companies surveyed are executing process safety work. Almost half of the companies' PSL are not providing process support in the late phase, which likely reflects a desire to have most process safety risks understood and discharged prior to transfer to manufacturing. Based on the thermal analysis, the defined process temperatures are thermally safe to operate at plant scale and no additional controls required.

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