

## EVALUATION AND MITIGATION OF OXIDATION REACTION HAZARDS

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### ABSTRACT

Process safety groups in the pharmaceutical industry are important components of active pharmaceutical ingredient (API) development through its life cycle from discovery to commercial scale. The pharmaceutical process safety laboratory staff conduct a series of tests to identify chemically unstable reagents, intermediates and solvents, and mixtures to ensure that the proposed operating conditions provide a sufficient safety margin from the onset of undesired and potentially catastrophic thermal decomposition. Across several pharmaceutical companies, the methods used for these assessments and how results and conclusions are made are widespread. A working group was created with members from several pharmaceutical companies within the International Consortium for Innovation and Quality in Pharmaceutical Development (IQ), with the goal of precompetitive collaboration and to understand each of the participating companies' procedures and assessment

regarding process safety. Each company was invited to provide input using a blind survey format. This was done in the interest of making this knowledge accessible for the participating companies and the wider community of other pharma and chemical companies and even academic institutions

in the India and throughout the world. This article provides the results of this in-depth survey of the members of the IQ Consortium thermal hazard working group. Various tools are being used for tech transfer of process safety data/information from development to manufacturing were addressed. A snapshot of how various assessment strategies are employed as a function of stage of development (early, mid, and late) and also oxidation reaction hazards

## 1.1 INTRODUCTION:

In Most large pharmaceutical companies have a process safety laboratory (PSL) group that is accountable for the understanding of the thermal hazards associated with reagents, chemicals, and reactions at hand.<sup>1,2</sup> Their work focuses on minimizing risks associated with handling hazardous chemicals, waste streams, and running hazardous reactions. A lack of understanding of chemical hazards can potentially expose these reagents and/or mixtures to conditions, temperatures, and/or mechanical stress that can trigger unsafe conditions such as fire, deflagrations, and explosions, which will lead to significant material loss, delay, supply chain disruptions, injuries, and/or loss of life. Process safety groups conduct a series of tests to identify chemically unstable intermediates and reaction mixtures and ensure that the proposed operating conditions provide a sufficient safety margin from the onset of undesired and potentially catastrophic thermal decompositions. There are several illustrations available in the literature where pharmaceutical process safety groups successfully managed to avert catastrophic incidents by stopping dangerous chemistry from being scaled-up.<sup>4,5</sup> For example, potential safety hazards associated with the violent thermal decomposition of dimethyl sulfoxide in the presence of an acid were identified and mitigated prior to scale-up.<sup>6</sup> Other examples include the use of continuous operation that was

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championed by their PSL staff to enable their respective companies to run potentially hazardous chemistry such as ozonolysis.

Drug development is an iterative process that requires many years to complete. During the journey of a drug from the bench to the market, different phases of development require increasingly larger amounts of material for clinical assessment, and the scales at which manufacturing processes are executed

may increase from milligrams of the limiting reagent in a Round-bottom flask to metric tons of the limiting reagent in 7570 liters equipment. The hazards of operating with flammable solvents and energetic materials/reactions drastically increase with the increase in scale. Therefore, most pharmaceutical companies have a PSL. PSL staff are tasked with the assessment of thermal and reaction hazards in order to ensure the safety of the personnel handling these materials in the lab and plant operators who will be executing the process. The most seasoned practitioners of process chemistry and engineering would agree that safety is of paramount importance in running on scale and cannot take a back seat production

The U.S. Chemical Safety Board conducted a study in the year 2002 that identified 167 industrial process safety incidents that involved runaway reactions between the years, 1985 and 2001 in an exothermic process, when the rate at which heat is released

exceeds the rate at which heat is being removed, a runaway reaction develops. Commercial reactors behave like adiabatic vessels (negligible heat losses to surroundings due to large surface to volume ratios) and therefore, the temperature inside the reactor rises at a rapid rate and eventually, leads to an explosion if appropriate measures are not taken.

Risk is often defined as a product of consequence and frequency. In the event of a runaway, the time period between the onset of the runaway reaction or self-heating of the reaction mixture and the point at which the rate of heat production is maximum is called the 'Time to Maximum Rate under Adiabatic Conditions' or the TMRad. The resulting rise in temperature is called the 'Adiabatic Temperature Rise',  $\Delta T_{ad}$ . While the TMRad is a measure of likelihood of occurrence of a runaway, the  $\Delta T_{ad}$  is a measure of consequence of the runaway reaction. The Stoessel Criticality Index classifies exothermic processes with a TMRad of 24 hours or greater as low risk scenarios.<sup>2</sup> The TMRad is a function of the temperature at which the process is being held. From a safety standpoint, the temperature at which the TMRad is equal to 24 hours is therefore, important and is known as the TD24.

The TMRad and TD24 are characteristics of reactive chemical hazards that can be evaluated by analyzing data obtained from calorimetric experiments. For the purpose of thermal hazard evaluation studies, Differential Scanning

Calorimetry is the most commonly used technique. Other commonly used techniques include Accelerating Rate Calorimeter (ARC), Advanced Reactive System Screening Tool (ARSST), Dewar Calorimeter, Reaction Calorimeter (RC), and Vent Sizing Package 2 (VSP2). The main objective of this project was to analyse data obtained from experiments run on the ARSST using mathematical methods described in literature and extract information about the TMRad and the TD24.

## 1.2 PROBLEM IDENTIFICATION

During manufacturing of Active Pharma ingredient ibuprofen manufacturing Sodium di-chromate is reacted with sulphuric acid in an aqueous medium at 400C to form Jones's Reagent and cooled to less than 300C. Acetone is taken in to an oxidation reactor and Jones reagent and aldehyde are added simultaneously maintaining the Temperature not more than 300C. The mixture is distilled to recover acetone. Hexane solvent is added for extraction and the waste dichromate layer and organic layer is separated. The organic layer is water washed and activated carbon is added for filtration and the mass is sent to crystallizers. The carbon waste gets separated in filters. From the crystallizers it is sent to centrifugation where the mother liquor gets separated. The centrifuged mass is washed with chilled hexane. The product Ibuprofen is dried, milled, sieved, blended and packed.

The mother liquor is treated with caustic lye and the hexane layer and alkaline

layer is separated. The hexane layer is distilled and recovered. The residue is sent for disposal. The alkaline is neutralized with Hydrochloric acid. The aqueous layer is separated and sent for effluent treatment. The remaining Ibuprofen precipitated mass is mixed with hexane and washed with process water and is filtered after adding activated carbon. It is sent to crystallizer and then centrifuged and Ibuprofen(API) separated.

During the extensive review of the Ibuprofen manufacturing process stage IV of the process namely oxidation process is not evaluated properly for the thermal hazards presented in the reaction, in such case potential thermal hazard will be calculated to suggest the proper control measures to avoid any explosion hazards.

## 2. LITERATURE SURVEY

### Over View of Literature

In 1980, Townsend et.al, discussed in their paper, the use of an Accelerating Rate Calorimeter for thermal hazard evaluation. Concepts of 'Time to Maximum Rate' and 'Thermal Inertia' were introduced and their importance with respect to engineering considerations in order to prevent runaway reactions was briefly discussed. The paper also presented an integral equation that can be used to evaluate the TMRad based on reaction kinetics.

Keller et.al (1997) proposed a systematic procedure for the assessment

of thermal risk based on dynamic and isothermal DSC experiments. The authors also introduced a linear correlation between the onset temperature and the TD24 (referred to as the Model Based Estimation Method). In this paper, kinetic parameters were evaluated for zero-order, first-order and autocatalytic models.

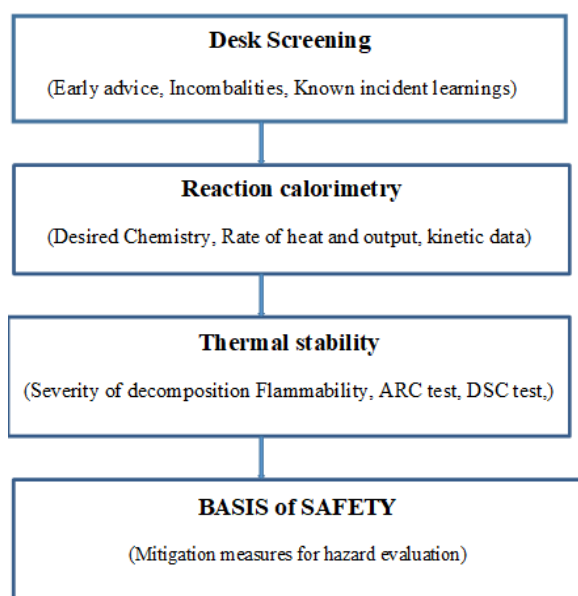
Using the concepts developed and discussed by Keller et.al in 1997 and TD24 results from 180 adiabatic experiments, Pastre et.al (2000), confirmed that the Model Based Estimation Method gave values that were more conservative than those obtained from adiabatic experiments on the Dewar Calorimeter. The paper also compares these values with the industrially used 100 K and 50 K rules. They concluded that at higher temperatures, the 100 K and 50 K rules were less conservative and at lower temperatures, they were too restrictive

Kossoy et.al (2015) compared two different approaches (referred to as the Standard Approach and the Expert Approach) used to evaluate and analyze data obtained from adiabatic experiments. The Standard Approach involves evaluation of kinetics using the Arrhenius Linearization Method, the Enhanced Fisher's Method to Reconstruct the Self-Heat Rate Curve and the Frank-Kamenetskii Method to calculate the TMRad and the TD24. The Expert Approach on the other hand, uses non-linear optimization and integral methods to calculate the kinetics and simulate adiabatic

conditions. Typically, these calculations are performed by a commercially available software package. While the Standard Approach is easy to use, the Expert Approach is more reliable in situations where the reactions are complex (multi-stage) and/or non-autocatalytic. They concluded that for simple (single-stage) non-autocatalytic reactions and initial screening studies, the Standard Approach is a more practical option

Ayman D. Allian, \* Nisha P. Shah, Antonio C. Ferretti, Derek B. Brown, Stanley P. Kolis, And Jeffrey B. Sperry have discussed the process safety in pharmaceutical industries, thermal and reaction hazard evaluation processes techniques and have clearly discussed about the evaluating the criticality of reaction using stoessel criticality index

### 3. METHODOLOGY



**Fig 3.1 Methodology.**

### 4. RESULT AND CONCLUSION

**Raw materials:** No major thermal stability issues have been identified with respect to any of the key process raw materials

**Formation of Jones' reagent:** Addition of concentrated sulphuric acid to water is known to be strongly exothermic and will result in a significant temperature rise. The addition should be done slowly and under careful control to ensure that the batch temperature is maintained within pre-specified limits. The addition of sodium dichromate was found to be moderately endothermic, with an effective adiabatic temperature drop of 10.3°C at a minimum rate of 281 watts below baseline using a 1.5-minute addition time. The material dissolved readily in the acid and the heat flow baseline had returned to baseline almost immediately after the addition was complete, indicating no significant accumulation. However, the instantaneous heat flow did drop significantly due to the relatively rapid addition rate and it is recommended that on plant scale the dosing be carried out over a much longer time scale to minimize such effects.

The thermal stability of the Jones' reagent was examined by both DSC and ARC, with both showing some minor exothermic activity. The DSC tests showed a number of small Exotherm from around 128°C and under more adiabatic conditions in the ARC this onset dropped to 104.3°C. The ARC confirmed that the Exotherm was of a relatively small magnitude, at 55.6Jg-1, and there was no significant pressure activity associated with the event.

Consequently, the Jones' reagent is not expected to create a major thermal hazard under the intended operating conditions.

**Thermal stability of Jones' reagent mixed with Acetone:** As acetone is used as the solvent for the dual addition, it was decided that additional thermal stability tests were required on a mixture of Jones' reagent and acetone. As the Jones' reagent is a strong oxidizing agent, it was thought to be possible that contact with acetone has the potential to result in the formation of acetone peroxide. Acetone peroxide is a dangerously reactive substance and is shock-sensitive and detonable and therefore its presence in the reaction mixture would represent a significant hazard.

A mixture of the two materials was tested by both DSC and ARC. The DSC test showed a small Exotherm from a temperature of around 43.0°C but under the more adiabatic conditions of the ARC this Exotherm was found to occur from ambient temperatures. The onset temperature in the ARC was 39.7°C, although exothermic activity occurred immediately on mixing at ambient temperature, but again the event appeared to be of a relatively small magnitude with no significant pressure activity.

This suggests that there is the potential for a significant exothermic reaction to occur between the Jones' reagent and acetone. Consequently, there would be an increased thermal instability hazard if there was either an overcharge of the

Jones' reagent or an undercharge of the aldehyde.

**Dual addition:** The dual addition of Jones' reagent and acetone was found to be strongly exothermic, with an effective adiabatic temperature rise of 219.1°C at a maximum rate of 24.2 watts above baseline using a 4-hour addition time. Each portion produced an immediate rise in heat output and there was no evidence of any significant reagent accumulation, although it should be noted that stall potential is likely to increase if the reaction is carried out at a lower temperature and this may affect the batch thermal stability profile.

During the addition, a viscous slurry of green material formed at the bottom of the vessel and this was assumed to be chromium salts which had formed during the oxidation. This had the effect of producing an unusually low heat capacity measurement for the batch, as a result of which the adiabatic temperature rise figure is very high. However, instantaneous heat flow levels were considered to be manageable and the addition is not expected to lead to a thermal hazard providing the rates are controlled carefully to ensure that the heat generation rate does not become excessive.

Samples were taken during the course of the dual addition and tested by DSC to establish if there was an increase in thermal instability during the oxidation reaction. All samples showed a small Exotherm in the range 55 – 60°C but this is felt to be of a sufficiently small

magnitude to avoid being a thermal hazard during the course of normal processing.

**Water quench:** The water addition was found to be mildly exothermic, with an effective adiabatic temperature rise of 2.3°C at a maximum rate of 2.2 watts above baseline using a 1-hour addition time. Instantaneous heat flow levels were relatively low and the pattern of heat release appeared to be fast and addition-rate-controlled. Providing the addition rate is controlled during plant scale operation, this is not expected to generate a thermal hazard. After the water addition and subsequent separation, both layers were tested by DSC. Although a number of small Exotherm was seen, these are not expected to lead to a significant thermal hazard under the intended operating conditions

## 5.CONCLUSION

By the study of the oxidation reaction with various tests some of the mitigation measures are suggest are as follows.

1. The desired reaction contains sufficient heat to cause the batch temperature to reach its boiling point.
2. All addition rates to be slow and controlled.
3. The quantity and identity of all charges should be carefully checked before use.
4. Drum tests may be required on any materials to be stored in drums.
5. No major thermal stability issues

were identified with respect to the key process raw materials.

6. Addition of dichromate to sulphuric acid was endothermic,  $\Delta TAD = -10.30^\circ\text{C}$ . Addition of sulphuric acid to water will be strongly exothermic and must be controlled.
7. The Jones' reagent was found to be thermally stable up to temperatures of around 104.3°C (phi-corrected ARC onset). The resultant Exotherm had a relatively small magnitude and there was no associated pressure activity.
8. Acetone will react exothermically with Jones' reagent immediately on mixing, even at room temperature. Again, the Exotherm is relatively small with no pressure activity.
9. Dual addition was strongly exothermic,  $\Delta TAD = 219.1^\circ\text{C}$ . Addition needs to be slow and controlled to minimize heat flow levels and prevent an excessive cooling demand.
8. Samples taken during the dual addition and tested by DSC indicate no major increase in thermal instability as the reaction progresses.
10. Water quench was mildly exothermic,  $\Delta TAD = 2.3^\circ\text{C}$ , with relatively low heat output using a 1-hour addition time.
11. Both layers were tested by DSC after the separation and neither showed any major exothermic activity at temperatures thought likely to cause thermal hazard.

12. Hazard Evaluation Group should be informed of any changes to the process which may impact upon its safety.

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