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Challenges on Scaling-Up Heterogeneous Reactions

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Hovione is a science-based company providing products and services for the Pharmaceutical Industry

- Founded in 1959
- Our customers are **Biotechs**, **medium**, **speciality and large pharma**

Drug Substance | Drug product | Particle engineering

Manufacturing capacity spread over three continents

NEW JERSEY, USA
Manufacturing facilities small volume
R&D Labs, Kilo and pilot plant
Sales and marketing for North America

LOURES, PORTUGAL
Manufacturing facilities including R&D Labs, Kilo and Pilot plants

CORK, IRELAND
Manufacturing facilities

MACAU, CHINA
Manufacturing facilities

The incident

On 24th September 2021

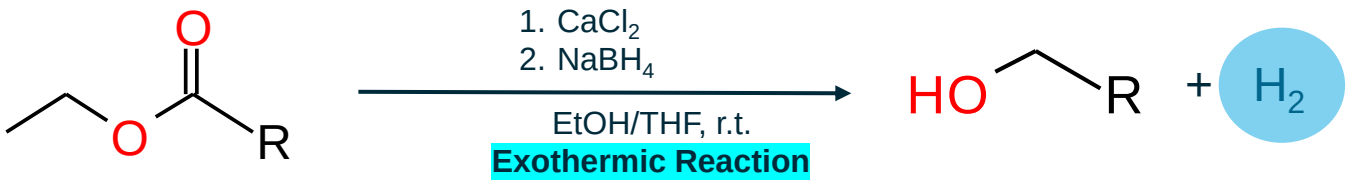
- After reagent addition, a thermal runaway event occurred from 22ºC to 46.7ºC
- H_2 off-gassing with overpressure of 0.6 bar and foaming
- 80 L of triphasic reaction mixture was ejected through the vent line
- No personal injuries and no property damage
- The affected area was isolated and properly cleaned

Process safety incident

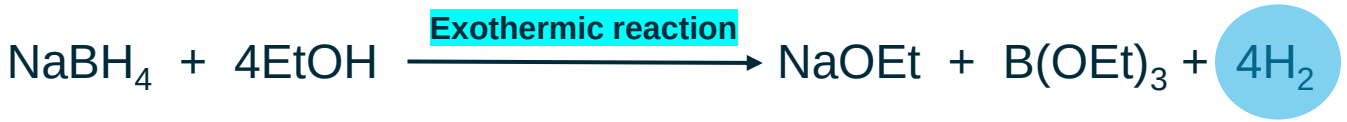
Classified as “Potential Critical” (due to severity of the thermal runaway in case of failure of preventive measures in place)

Chemical Process

Main reaction - Ester redution into an alcohol



Secondary reaction - Redution of ethanol (ethanolisis)



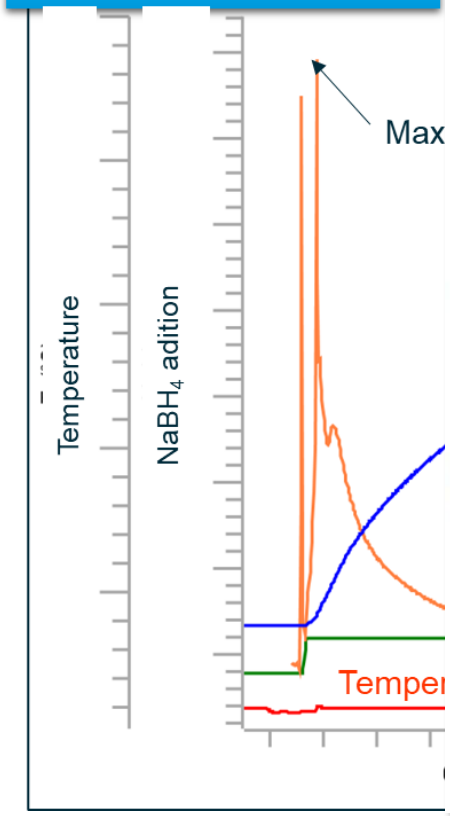
Important chemical features

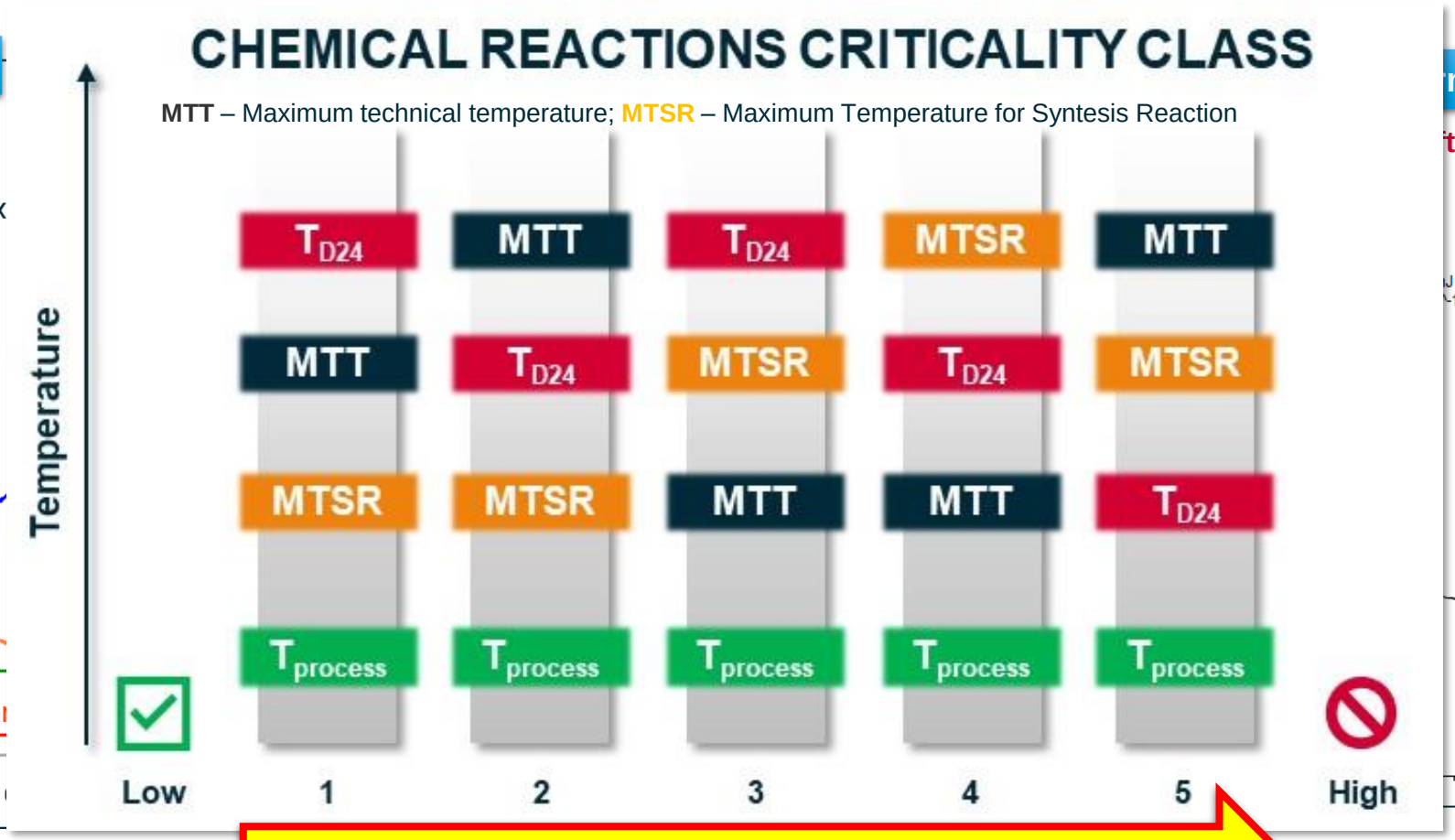
- Excess of $NaBH_4$ to increase process yield
- $CaCl_2$ act as a catalyst to activate $NaBH_4$
- Heterogeneous mixture - very low solubility of $NaBH_4$ and $CaCl_2$ in EtOH/THF
- Hydrogen off-gassing results from both main and secondary reactions

Process Safety studies

Thermal Hazard

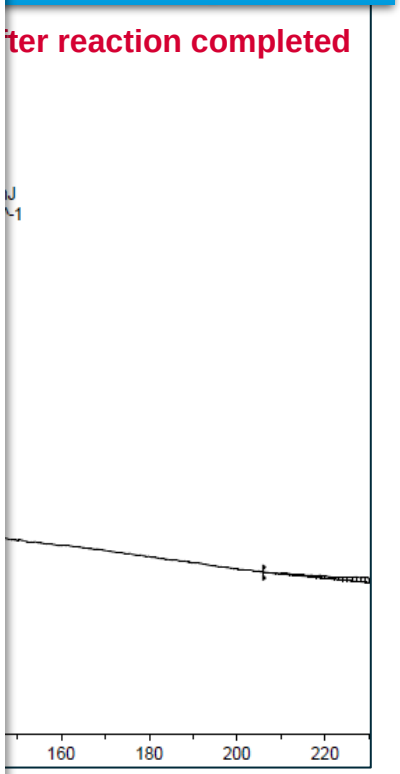
Reaction Calorimetry





mal Stability by DSC

ter reaction completed



Additional studies came out from the HAZOP

How can we decrease the heat accumulation?

Can we increase the T_{D24} , using a diferente approach?

What if SRM or $CaCl_2$ charge fails?

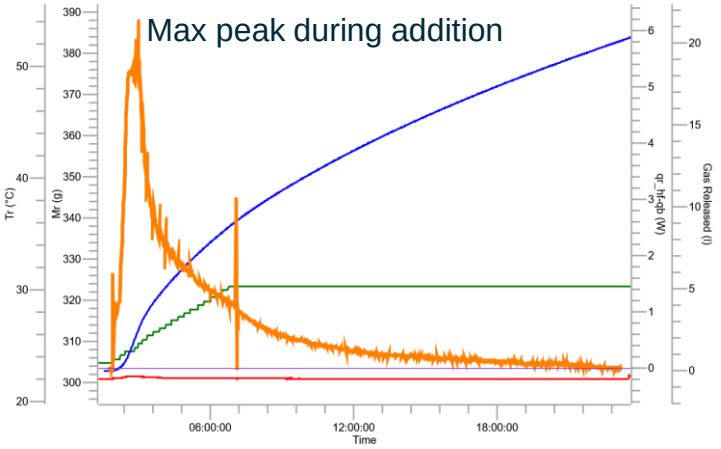
Additional studies came out from the PHA

How can we decrease the heat accumulation?

$NaBH_4$ addition stepwized in 5h reduced the accumulation from 23% to 12%

Can we increase the T_{D24}, using a diferente approach?

What if SRM or $CaCl_2$ charge fails?



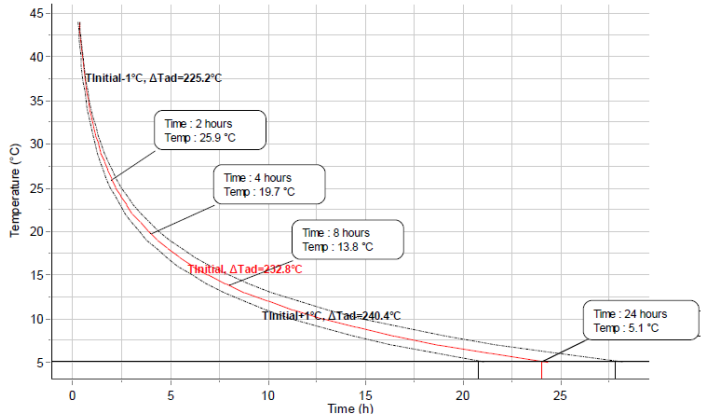
Additional studies came out from the PHA

How can we decrease the heat accumulation?

Can we increase the T_{D24} , using a diferente approach?

- New T_{D24} (from kinetic studies) is 5ºC
- The secondary reaction had more impact on the heat and gas release that the main reaction

What if SRM or $CaCl_2$ charge fails?



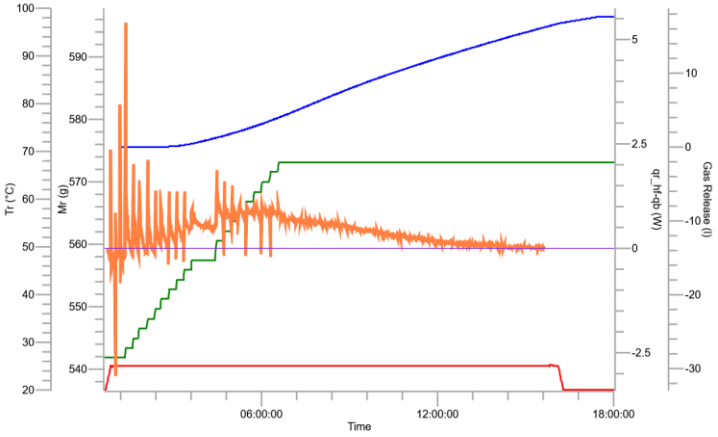
Additional studies came out from the PHA

How can we decrease the heat accumulation?

Can we increase the T_{D24} , using a diferente approach?

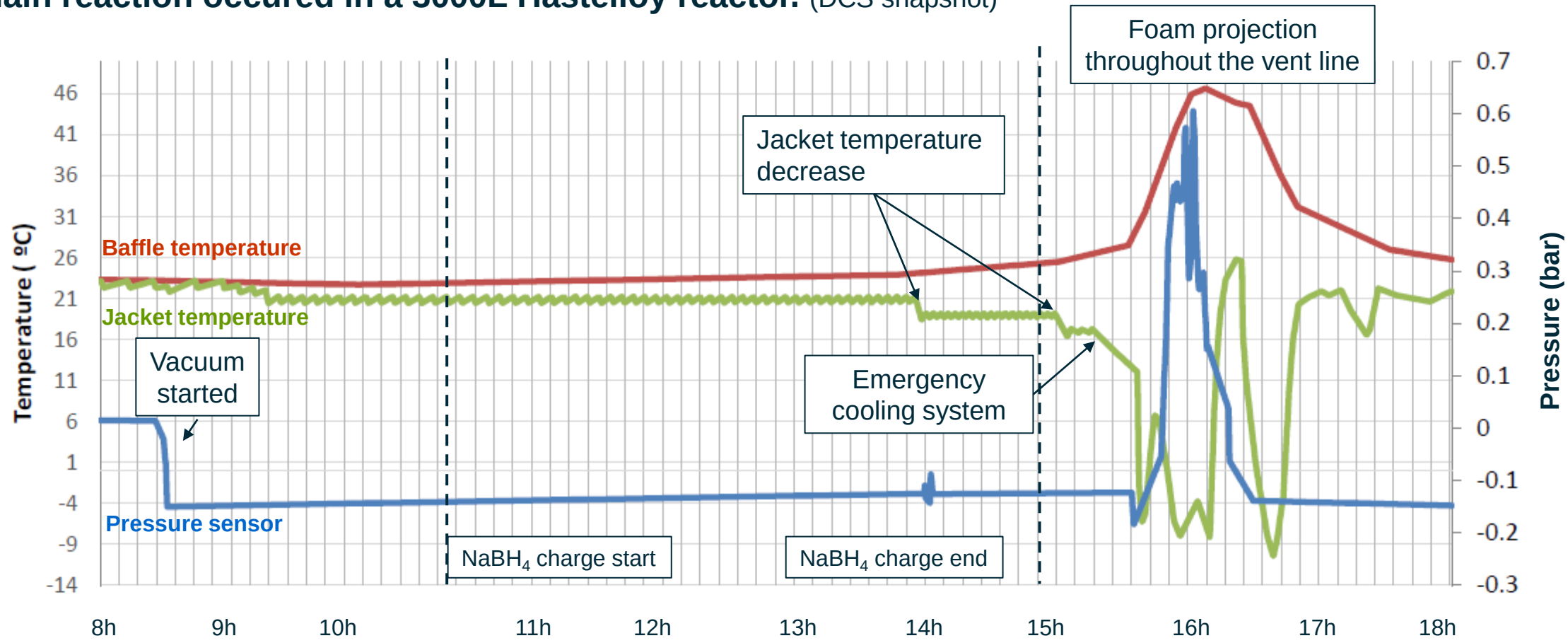
What if SRM and $CaCl_2$ charge fails?

Decrease of 74% on the heat release



The incident

Main reaction occured in a 3000L Hastelloy reactor. (DCS snapshot)

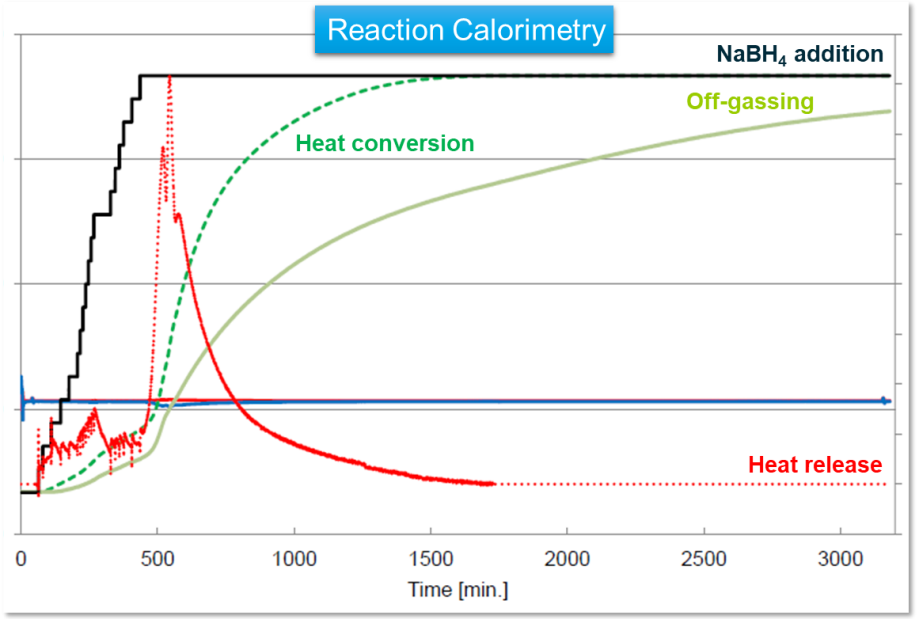


The temperature peak unexpectedly occurred 1h after the $NaBH_4$ addition

Incident investigation

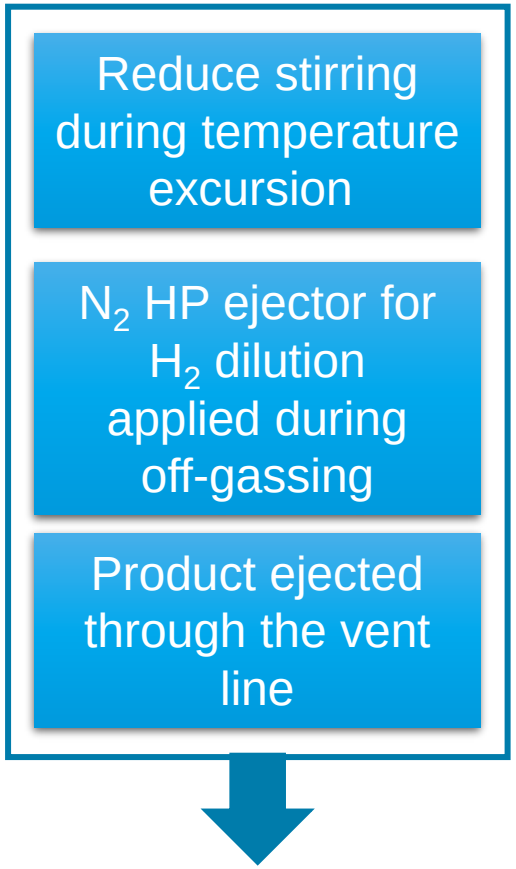
Heterogeneous nature of the reaction mixture

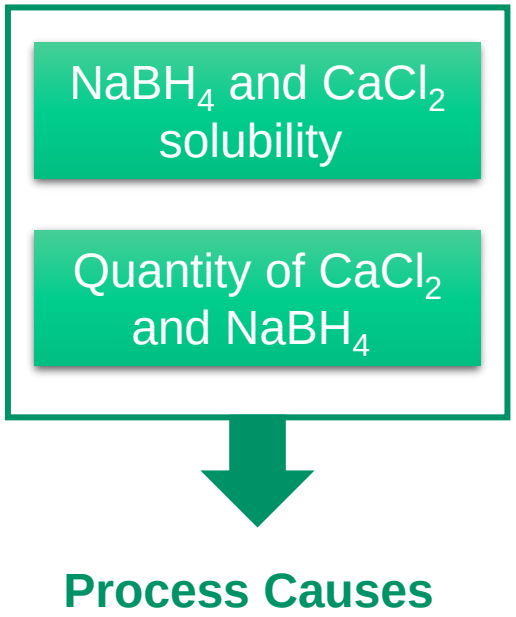
- Mixing and stirring have impact on the heat and gas release profile with high variability on the process safety data



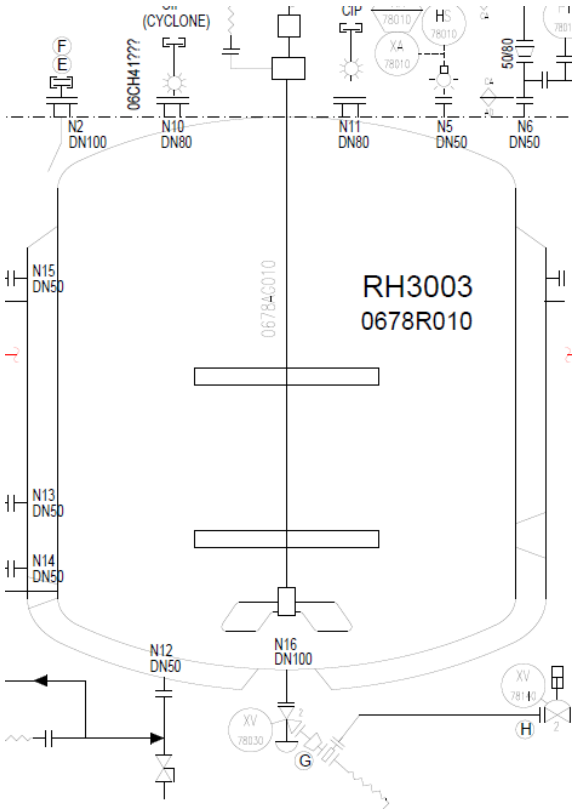
Incident investigation

Immediate Causes





ROOT CAUSE – Training and performance assurance



Decrease of stirring speed during the temperature excursion to avoid foam

Lack of awareness of side effects (heat accumulation) and pressure build up.

Inefficient temperature control by building thermal system. HAZOP identified requirement for double recirculation pump, but manual controlled system.

ROOT CAUSE – Management of Changes

Heterogenous nature of reaction mixture and lack of full knowledge of the reaction mechanism

Changes in ratio quantities of calcium chloride and sodium borohydride not fully understood.

Rate of sodium borohydride not followed – lack of temperature increase when expected.

ROOT CAUSE – Process Knowledge Management

H_2 dilution in normal vent done using N_2 ejector. High nitrogene flow produces higher vacum in Venturi system.

Release system not prepared for foam formation. Emergency vent prepared with Knock out tank but not the normal vent, only design for one phase release.

Highligts and Strategy after the incident

Worflow defined to evaluate criticality of all reactions and those classified as class 4 and 5 are subjected to HAZOP assessment

Evaluate vacum effects on reaction with high rate of gas release

Reinforce operators reaction in case of unexpected situations

Heterogenity of reaction medium must be evaluate in HAZOP assessment

Pre startup safety reviews performed prior to each campaign

Thank you
for your attention

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