Thermal Hazards Evaluation for Flow Processes

Sai Sathanapally
Process Safety, Process Development
P2SAC Spring 2024 Conference

Introduction

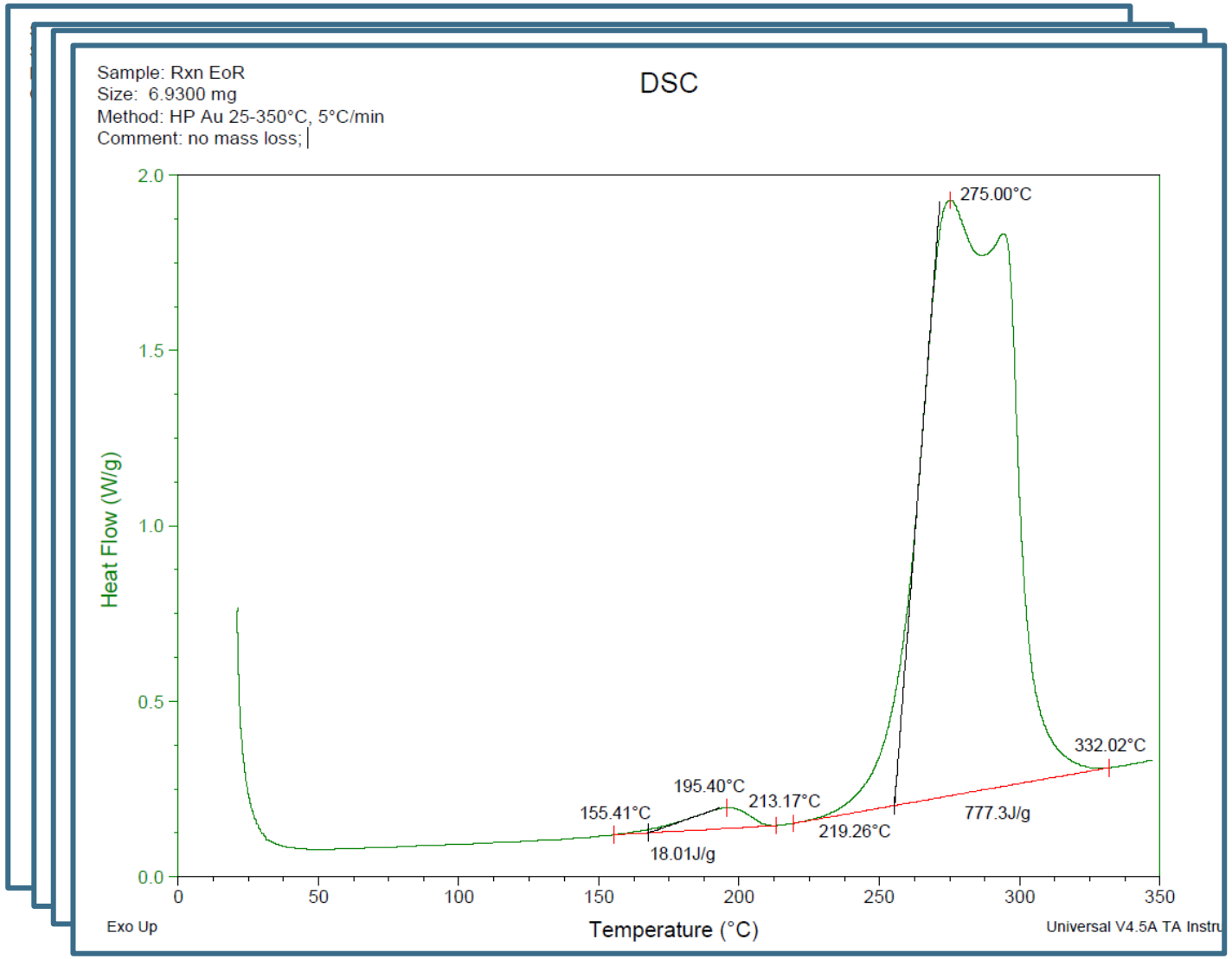
- Biopharmaceutical company based in Foster City, CA
- Process Safety within the Process Chemistry Department
- Developing safe and economic processes to manufacture Active Pharmaceutical Ingredients (APIs)

Problem Statement

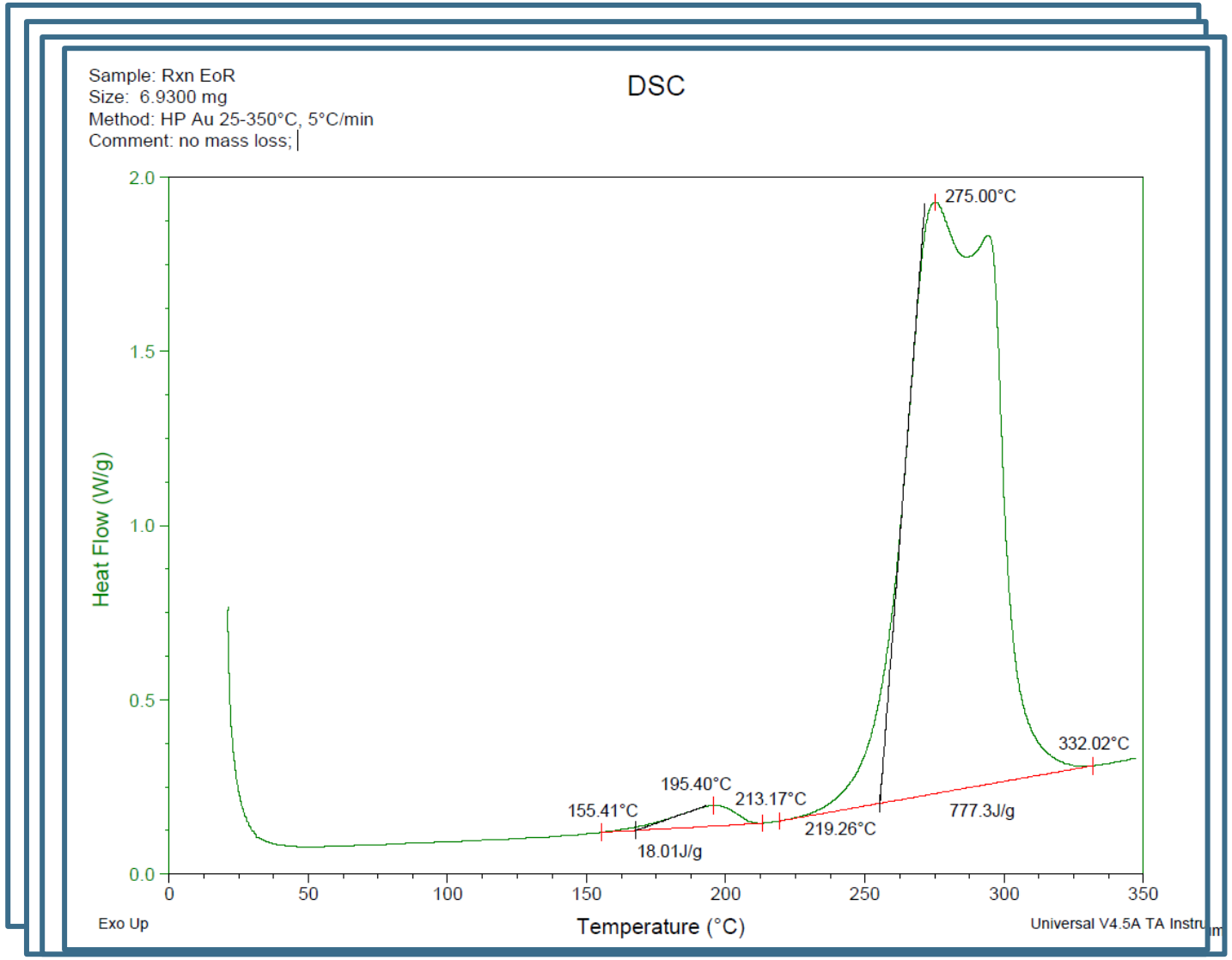
- Process Chemistry team was working on establishing ‘proof-of-concept’ for an alternate route for one of our early-stage oncology programs.
- They were developing a high-temperature SNAr (nucleophilic aromatic substitution) reaction using DMSO (dimethyl sulfoxide) and base (TBD-triazabicyclodecene). Process Safety was contacted for hazard evaluation ahead of scale-up.
- Potential explosion hazards associated with thermal decomposition of DMSO are well-documented.
- Studies also show that the presence of certain substances can significantly lower the onset temperature of DMSO decomposition and potentially increase the severity of the decomposition reaction through autocatalytic behavior.

Differential Scanning Calorimetry

- DSC tests were conducted on samples of the substrate, product, start of reaction (SoR) and end of reaction (EoR)
- **SoR and EoR samples had very similar thermograms by DSC**



DMSO-TBD Incompatibility



- Thermal decomposition likely due to DMSO-TBD combined with substrate and/or product
- **Maximum Recommended Processing Temperature is 140°C**
- **Chemist's intended reaction temperature is 180°C**
- Consider alternatives to DMSO

DMI: 1,3 Dimethyl-2-Imidazolidinone

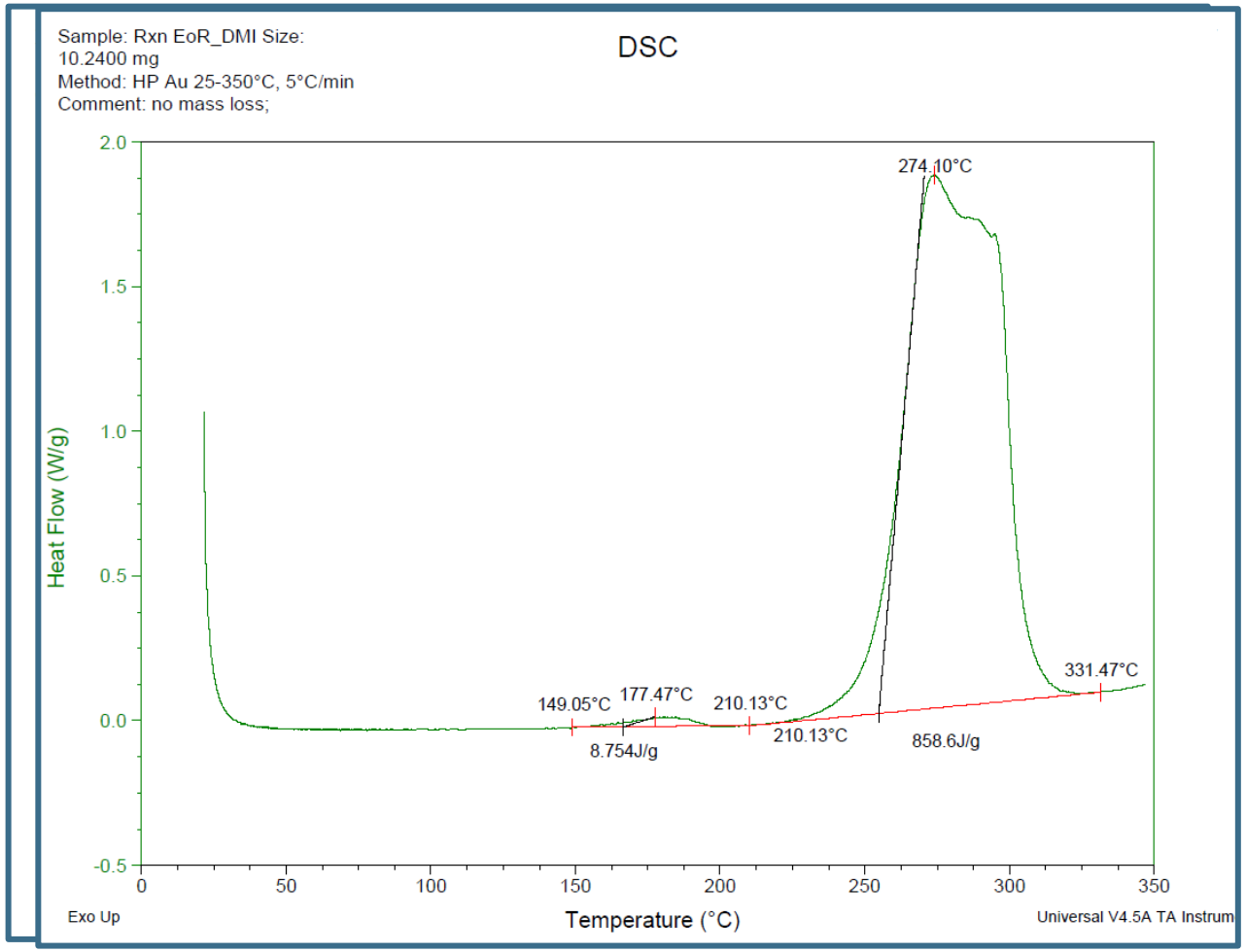
DMI has a high boiling point, high thermal stability and doesn't produce azeotrope, therefore it can be used commercially as a solvent in processes such as liquid-liquid extraction, counter current distribution, extractive distillation and counter current washing process.

mitsui chemicals america, inc.
https://us.mitsuichemicals.com › ... › Product List

DMI™ 1,3 Dimethyl-2-Imidazolidinone

- DSC of EoR in DMI showed an almost identical decomposition thermogram
- No advantage from a safety perspective
- Lower purity compared to DMSO

Can we run this reaction in DMSO in flow at 180°C?



TMRad and TD24

- **TMRad** is the ‘time to maximum rate’ of heat production under adiabatic conditions and is a measure of the probability of occurrence of a thermal runaway.

- **TD24** is the temperature at which the TMRad is 24 hours.

Literature

A Continuous Process for Manufacturing Apremilast. Part I: Process Development and Intensification by Utilizing Flow Chemistry Principles

Hsiao-Wu Hsieh, Carolyn M. Cohen, Daniel J. Griffin, Padmini Ananthoji, Nadide Hazal Avci, Derek B. Brown, Ari Ericson, James D. Fostinis, Muhammad Irfan, Neil Langille, Michael A. Lovette, James I. Murray, Simone Spada, Oliver R. Thiel, Frankie Aiello, Joseph Daou, Nicole Goudas-Salomon, Ende Pan, Nandini Sarkar, Rasangi Wimalasinghe, Zufan Steven Wu, Alicia Zeng, and Matthew G. Beaver

Organic Process Research & Development Article ASAP DOI: 10.1021/acs.oprd.3c00400

Thermal Hazard Evaluation

- Chemistry run in DMSO in the presence of acid at 130°C with a mean residence time of 25 min
- Accelerating rate calorimetry (ARC) data showed a thermal decomposition with an onset temperature of 149°C
- The phi-corrected TD24 based on the ARC data was calculated to be 108°C
- The time-to-maximum-decomposition-rate was estimated to be just under 5 hours

Literature

A Continuous Process for Manufacturing Apremilast. Part I: Process Development and Intensification by Utilizing Flow Chemistry Principles

Hsiao-Wu Hsieh, Carolyn M. Cohen, Daniel J. Griffin, Padmini Ananthoji, Nadide Hazal Avci, Derek B. Brown, Ari Ericson, James D. Fostinis, Muhammad Irfan, Neil Langille, Michael A. Lovette, James I. Murray, Simone Spada, Oliver R. Thiel, Frankie Aiello, Joseph Daou, Nicole Goudas-Salomon, Ende Pan, Nandini Sarkar, Rasangi Wimalasinghe, Zufan Steven Wu, Alicia Zeng, and Matthew G. Beaver

Organic Process Research & Development Article ASAP DOI: 10.1021/acs.oprd.3c00400

Basis of Safety

- Temperature monitoring of the reaction mixture inside the plug flow reactor
- Avoid accidental prolonged exposure to elevated temperatures

AKTS Modeling of Decomposition

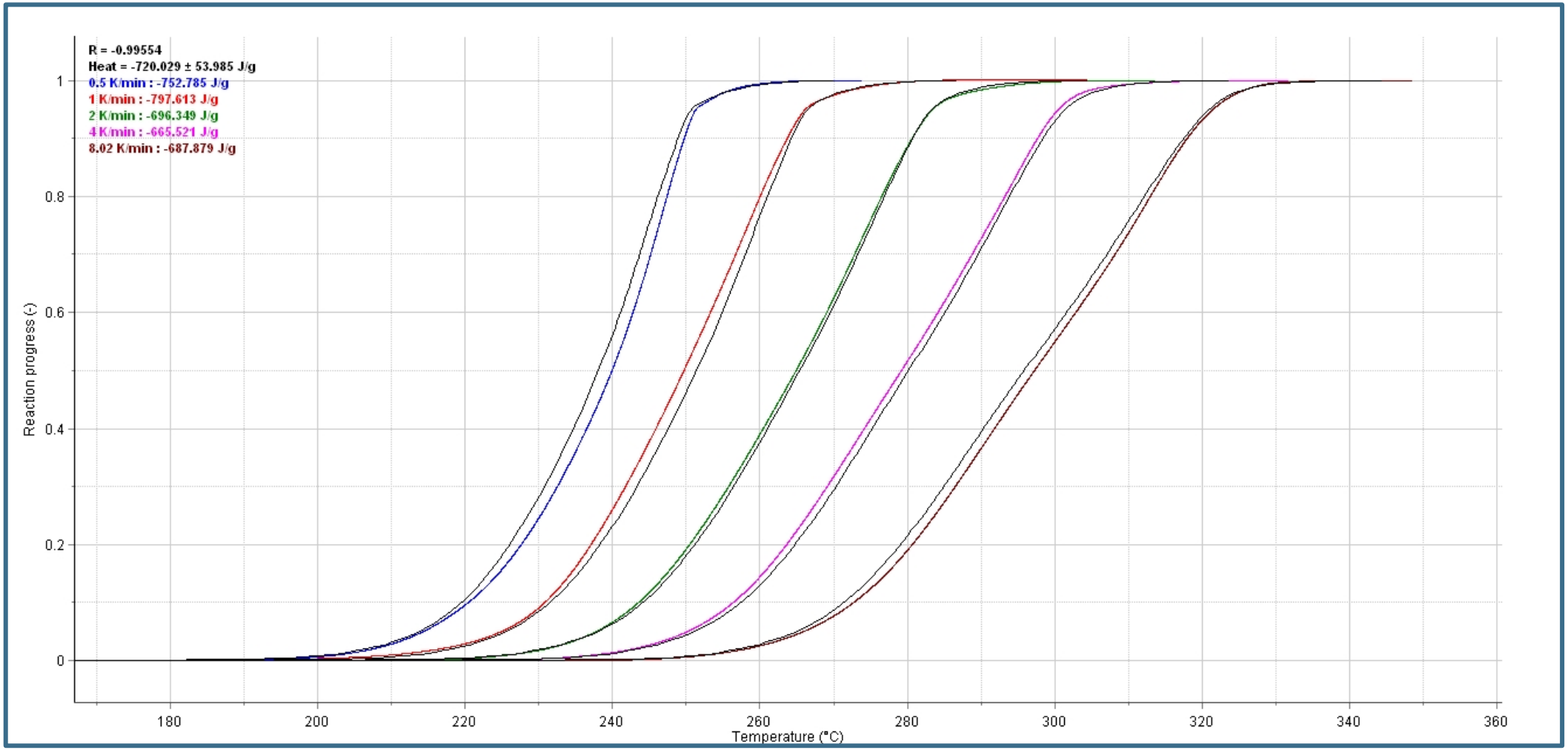
- **Advanced Kinetics and Technology Solutions -** Kinetics of the reaction are evaluated using experimental DSC data by assuming the differential iso-conversional approach

- Samples of the reaction mixture were tested by differential scanning calorimetry (DSC) in high pressure gold-plated crucibles at multiple different heating rates: 0.5, 1, 2, 4, and 8 K/min

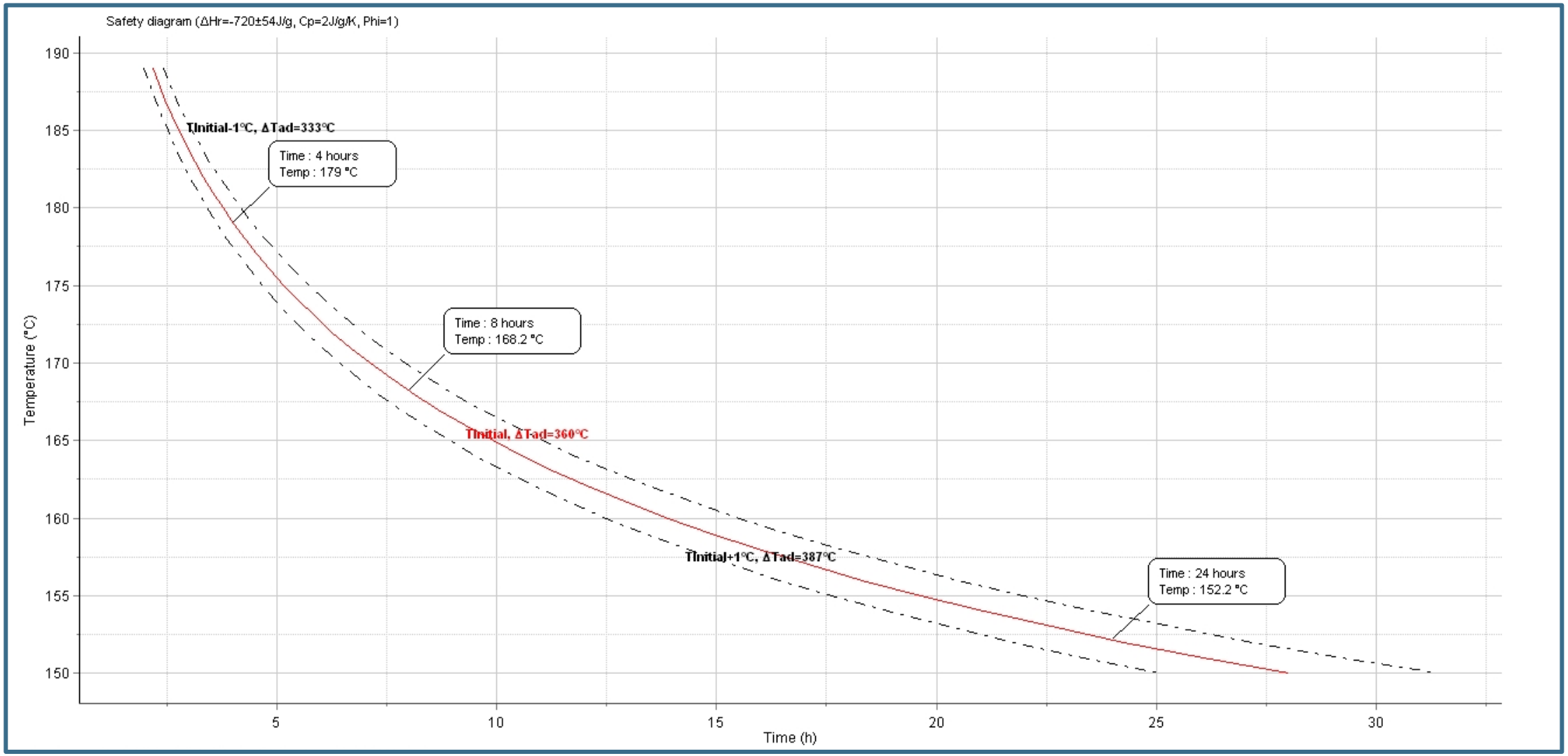
- **The TD24 (temperature at which time to maximum rate of decomposition) for the reaction was estimated at 150°C**

- **The TMR (time to maximum rate of decomposition) at 180°C was estimated to be 4 hours**

AKTS Modeling of Decomposition



AKTS Modeling of Decomposition



Basis of Safety on Lab Scale

- The TMR (time to maximum rate of decomposition) at 180 °C was estimated to be 4 hours. The intended residence time for the reaction was 7-10 minutes.

- **Avoid accidental prolonged exposure to elevated temperatures** – instrument shuts off automatically in the event of a clog. Chemist will be present to monitor all the experimental runs in lab.

Thermal Risk for Flow Processes

- Flow chemistry can offer unique safety benefits over batch processing due to lower reaction volumes, better temperature control, and the ability to accommodate higher pressures.

- The 50 K and 100 K rules, which are widely used to establish safe operating limits for batch processes, may sometimes be overly conservative for flow processes.

- Evaluating decomposition kinetics, understanding the chemistry and failure modes of equipment being used is necessary to establish safety protocols along with input from SMEs.

Challenges/Open Discussion

- TMRad, TD24 validation experiments with limited material.
- Given that the RT was really small compared to the estimated TMRad, we were comfortable running this using the equipment we have (on a small scale) with the appropriate safety measures in place.
- How do we approach risk assessment if this was to be run on a pilot-plant or manufacturing scale?

Acknowledgements

Process Safety

Process Chemistry

Flow Chemistry SME