An Introduction to Reaction Calorimetry



Syrris – A brief history

Driven by "Productizing Science"

- Founded in 2001 to address the challenges faced by the pharmaceutical industry
- Syrris is the longest established flow chemistry company
- Our customers include all of the top 20 pharmaceutical companies and most leading academic institutions
- Headquartered in Royston (UK), with over 125 people globally over 8 offices









Part of the Blacktrace Group

- <u>Syrris</u> Advanced technology for chemists & chemical engineers
- <u>Dolomite Microfluidics</u> Cutting-edge products for microfluidics
- <u>Glass Solutions</u> High-quality precision scientific glassware
- <u>Particle Works</u> Precision engineered nano- and micro- materials
- <u>Dolomite Bio</u> Innovative products for high throughput single cell research



10/12/2018

- Introduction
- Process safety fundamentals
- Calorimetry and heat measurement
- Reaction calorimetry first principles and overview
- Examples
- Summary
- Live Q&A session

Quick poll:

What level of experience do you have?







Process development and safety of chemical reactions









Process development timeline

Simplified workflow of the process development



The challenges of process development

- Identifying the product
 - What do we want produce?
- Finding the synthesis path of desired product
 - What are the steps to get desired product?
 - What are the properties of the materials used? Are they stable?
 - What are the kinetics of the process?
- Optimisation
 - How can we run the process efficiently and safely?
 - What are the process control parameters?
 - What are optimal temp ramps, dosing profiles?
- Scaling up

- Is it possible to increase the scale safely?
- Is it possible to keep control of the process at higher scale?
- Failure scenarios, are we able to minimise risks?
- Production
 - Standard operation procedures
 - Changes to process
 - Quality control



Process development timeline

Simplified workflow of the process development





Chemical Production Safety Precautions in History

Alfred Nobel, Nitroglycerin production (1864)

- Large scale production of NG for dynamite use
- Very dangerous process by its nature. AN lost his brother to explosion during manufacture
- Adding fuming nitric acid and sulphuric acid to glycerine, at temperature of 25 °C
- Operator controlled dosing to keep temperature in acceptable range to prevent runaway
- Implemented first failsafe One-legged stool
- In case of thermal runaway, the whole reactor volume was supposed to be dumped into drown-out tank, initiated by operator in case the temperature couldn't be controlled anymore



What can go wrong?

We'll have a look into accident, that was caused by poor understanding of the thermochemistry leading to major damages to people, property and environment.

Jacksonville FL, USA (2007)



Oppau (Germany) 1921

Flixborough (UK) 1974





Reported Incidents

Jacksonville, FL, USA 2007

Runaway reaction caused by cooling failure

Production of methylcyclopentadienyl (Batch process)

- 2,500 gallon production scale reactor (initiated by melting solid sodium metal (98.9 °C). Afterwards, heating was turned off at 150 °C., as the process was self-sustaining
- At 182 °C, operator tried to start cooling, but T continued to increase
- After 10 minutes, the ongoing decomposition reaction in the reactor increased pressure beyond capability of the PRV system
- "Jet engine-like" sound heard, just before vessel ruptured
- Explosion yield of 750 kg of TNT





Reported incidents

Jacksonville, FL, USA 2007

The Causes

- Direct scale-up from one-litre reactor
- Poor reactor vessel design too many single point failure points on cooling systems
- Inadequate reactor pressure venting burst too late
- Poor understanding the thermochemistry the secondary reaction was way more energetic than anticipated

Aftermath

- 4 dead, 32 injured, massive damages to property
- AIChE introduced mandatory reactive hazard awareness to chemical curriculum





So, why is it important to perform calorimetric studies?

- To fully understand the kinetics whole process
- To make sure process can be run safely under all circumstances
- To understand what can go wrong, and make sure the risks are minimised, and implement risk reducing measures
- Optimising processes that are already run on production scale
- Understanding even the non-reaction side of the process (safe storage, shelf life etc.)





Calorimetry overview











Heat measurements, and its challenges

- Heat cannot be directly measured
- Heat can not be contained
- Heat losses are localised
- Heat losses depend on the heat transfer properties
- Heat transfer may change over time (and usually non-linearly)

Different calorimetry solution utilize the above facts to their advantages





Calorimetry - history

Joseph Black (1728-1799)

- considered the founder of calorimetry
- First to recognize difference between heat and temperature

Antoine Lavoisier (1743-1794)

- Built first device for measuring heat exchange with his colleague
 Pierre-Simon Laplace, the Calorimeter
- The design was based on calculations and discoveries of Joseph Black, and allowed measurement of heat involved in various chemical changes - relied on the heat required to melt ice to water to measure the heat released from chemical reactions
- First used the heat from the guinea pig's respiration to melt snow in his apparatus, showing that respiratory gas exchange is combustion, similar to a candle burning
- Experiments with the device laid foundation of modern understanding of energy, and was fundamental for definition of First law of Thermodynamics

But why there are so many different types calorimeters?















Bomb Calorimeters

Used mainly for determination of heat of combustion – for example the energy contained in fuels.

Micro Calorimeters

Differential Scanning calorimeters - simple and effective technique to asses stability and properties of substances

Adiabatic calorimeters

Used to asses decomposition and undesired reactions – thermal runaways.

Reaction calorimeters

Used to simulate plant conditions, used for determination of heat of reaction, optimisations etc.



Micro Calorimeters

Differential Scanning Calorimeters

By far, the most used screening method

- 2 crucibles, one loaded with sample, other blank
- Ideal tool for screening studies
- Quantitative energy data, small sample size required (mg), very quick, provides kinetic data to some extent
- The result is energy fingerprint of the compound/mixture, which can be used to predict the behaviour of such
- However, the samples are not stirred, no pressure monitoring, dosing is not possible





Adiabatic Calorimeters

Undesired reactions understood

- Specialised instruments, allowing assessing the most dangerous scenarios
- The heat sensors calculate heat produced in the vessel, and heat up the vessel in way that adiabatic conditions are kept
- Need to be able to cope with rapid increase of temperatures (up to 2000 K/min) and pressures, to investigate chemical runaways
- Invaluable tool for designing safety systems of production scale reactors pressure relief systems
- Heat Wait Search
- Compared to DSC it provides more detailed data mainly pressure profiles, and ability to stir and dose into the cell





Reaction Calorimeters

Simulating the plant operation

- Designed in way to mimic the actual plant as close as possible
- Designed to allow controlled addition of reactants
- Higher volumes (typically 0.25 2 L)
- Allow for capturing thermal data usable not only for process safety, but identifying reaction kinetics, allowing for further optimisation of the process
- Generally used to investigate the desired reaction, in comparison with DSC/ARC, which are mostly used for undesired ones





Process development timeline

Sufficient calorimetric studies should be done before performing scale-up of the process.

It provides essential data to run desired reaction safely and effectively.



Reaction Calorimetry and its Place in the Process Development











Process safety development evolution

Reaction calorimeters – the paradigm shift

The commercial availability of reaction calorimeters changed the situation considerably from the mid 1980s

It has allowed for staged process development with easy means of finding energy involved as the process grows, and develop methods to keep process under control at most situations.

Using calorimeters, it is not only possible to confirm hypotheses, it allows for prediction of even undesired thermal events.

Last not least, allows for further optimisation of the process, reducing costs and increasing yields!





Reaction Calorimetry

What is it?

 Original concept by Willy Regenass in 1970 for safety studies, however found its way very fast into process optimization and development

Allows performing kinetic and thermal analysis of chemical reactions

- IN SMALL SCALE
- UNDER REALISTIC PROCESS CONDITIONS



From W. Regenass' patent (1976) - Apparatus for the determination of the thermal efficiency of chemical reactions

Reaction calorimetry topics:

• Applications of reaction calorimetry

• When should it be performed

• What data can we get

• Interpretation of data - examples

Applications of Reaction calorimetry

Where does it work?

- Mostly, semi-batch reactions only
 - Batch and continuous can be studied under some circumstances
- Liquid (mobile) media only
 - Solids, highly viscous media are very difficult to assess
- Reflux & distillation
 - To maximize efficiency, many processes are run under reflux
- Elevated pressures
 - Elevated pressures to raise boiling points



Techniques utilised in Reaction Calorimetry

As heat can't be directly measured

- Measurement of secondary heat transfer
 - Heat Flow Calorimetry
 - True Heat Flow Calorimetry
 - Heat Balance Calorimetry
- Power compensation calorimetry
 - Measurement of electrical power needed to maintain temperature
- Process can be run under different conditions (as plant would):
 - Isothermal
 - Isoperibolic





What data can we obtain with RC?

- Heat of reaction
- Heat capacity
- Reactant accumulation
- Adiabatic temperature rise
- Power output
- Describe physical characteristics and their changes
- Gas generation
- Species formation



Heat of reaction (ΔH_r), enthalpy change

Definition

• Amount of energy released/absorbed by chemical reaction.

Units

- Molar enthalpy ΔH_r (kJ mol⁻¹)
- Specific heat of reaction Q'_r (kJ kg⁻¹)

Notes

- Specific enthalpy is most practical for scale-up purposes, as it is easily used at process scale
- By convention, exothermic reactions have negative enthalpy, endothermic positive
 - HOWEVER, calorimeters report all effects that increase temperature as positive
- Theoretical enthalpy can be obtained from enthalpies of formation, however it is advisable to measure heat of reaction under realistic conditions if possible

 $\Delta H = H_f - H_i$



Heat Capacity (C_p)

Definition

• Amount of energy needed to raise samples temperature by 1 K.

Units

• Heat capacity C_p (J K⁻¹), specific heat capacity C'_p (kJ kg⁻¹ K⁻¹)

Notes

- Specific heat capacity more widely used, as it is directly scalable
- Typically increases with rising temperature (ie: water at 293K 4.18, at 373K it is 4.22 kJ kg⁻¹ K⁻¹), however, this phenomenon has negligible effect
- Allows calculation of vital safety parameters adiabatic temperature rise

Adiabatic temperature rise (ΔT_{ad})

Definition

- Temperature rise when conditions change to adiabatic
- All energy released is used to increase system's temperature
- Typical example is reactor cooling failure

Calculation

• Calculated from specific heat of reaction and specific heat capacity of reaction mixture

•
$$\Delta T_{ad} = \frac{Q'r}{c'r}$$

Notes

- One of the major indicators about the criticality of the process
- Measurable wholly by RC

Reactant Accumulation

- Very important value, especially for semi-batch processes
- Usually expressed in %
- Gives instantaneous percentage of non-converted reactants

Fast Reactions

- Reactant immediately converted
- Ideal situation as the temperature can be directly controlled by controlling feed
- Rate of reaction is limited by rate of addition

Slow reactions

- Slow reaction rate leads to accumulation
- To reach appreciable rate of reaction, the amount of reagent has to reach certain level
- Processes with high level of accumulation are more hazardous, as even when feed is closed there can be significant amount of reagent present



Reactant Accumulation Diagram



Time



What data can we obtain with RC?

- Heat of reaction
- Heat capacity
- Reactant accumulation
- Adiabatic temperature rise
- Power output
- Describe physical characteristics and their changes
- Gas generation
- Species formation



What can we do with the data?

Decisions can be made, to make sure the potential of the reaction mass doesn't reach:

- Boiling conditions
- Secondary/decomposition reaction onset

Power output

• provides cooling requirement for the plant

Accumulation data

- Optimising dosing feeds
- Running at higher temperatures
- Use of catalysts

The efficiency of the process can be fine tuned using RC data EVEN FOR DEVELOPED PROCESSES



However, it is not all

Advances in sensors allow for advanced methods to be implemented:

- In-situ FTIR
- Raman IR spectroscopy
- Particle sizing/distribution
- pH
- Realtime sampling
- GCMS analysis of headspace gases online





The process deviations





Criticality assessment by Francis Stoessel

- Any process can be put into criticality group, depending on the parameters that are found using calorimetric methods
- Depending on the criticality group, there are guidelines that help minimise risks
- Four values need to be known to successfully assess the process
 - Decomposition temperature (Orange)
 - Boiling point (Blue)
 - Process temperature (Red)
 - Maximum temperature of the synthesis reaction (MTSR) (TOP+Tad; Green))





Potential process deviations

- Wrong Reactants
- Wrong Catalyst
- Wrong dosing order
- Impurities in starting materials
- Reaction of Reactants with Equipment
- Incompatibilities in plant construction
- Corrosion
- Too much/too little reactants

- Too much/too little solvent
- Unexpected product
- Flow rate of reactants too fast/slow
- Addition at wrong temperature
- Addition of wrong temperature
- System failures





Example 1

Reduction using solid metal hydrides

Facts:

• Semi-batch process, heterogenous reaction

Things to consider:

- Solid reagent addition agitation of slurry
- Batch temperature critical initiation
 - T too low, no initiation, high level of accumulation, leading to runaway when reaction initiates

Findings

• No deviations found during process dev



Example 1 – LiAlH₄

Proceed to Scale-up

- Scaled-up to 100 L reactor, thermal runaway occurred!
- Why, as it didn't show in preliminary tests?

Back to Reaction Calorimetry, simulated the runaway with information from 100 L reactor

- Simple fix found, raise the batch temperature by 10 K
- The reaction initiated immediately upon addition of hydride, leading to no accumulation of reactants, keeping the batch temperature at acceptable levels

USE REACTION CALORIMETRY TO UNDERSTAND AND REDESIGN!

Example 2 – NaBH₄

Similar reaction, sodium borohydride added as reduction agent

- Heterogenous reaction (solid added)
 - Similar challenges as in previous example

Process ran for 20th time in Pilot lab, without problems

• Decision made not to sample and analyse the reactor contents

Decision to proceed with another step – quench by aqueous sulphuric acid

• The plant was immediately filled with smell of rotten eggs after quenching

WHAT WENT WRONG?

Example 2 – NaBH₄

After venting:

- Agitator head corroded and fell of the shaft due to corrosion
- Tachometer still indicated correct speed, as the shaft was intact
- Lack of stirring lead to high level of accumulation of NaBH₄
- After quenching, the accumulated reactant reduced water from the quench to hydrogen gas, that subsequently reacted with sulphuric acid, forming hydrogen sulphide

Confirmed in Reaction Calorimeter

The reduction of water is preferred path – so it is essential to make sure all NaBH₄ is spent before quench

$NaBH_4$ + 2 $H_2O \rightarrow NaBO_2$ + 4 H_2

 $H_2 + H_2SO_4 \rightarrow H_2S \uparrow + H_2O$



Conclusions

Is it really necessary?

 Reaction calorimetry can provide you all necessary data to understand of desired reaction in your process SYRRIS

- Should be used at every suspected step of the process, where doubts exist
- Use it for simulation of "what if" scenarios
- Use it for worst case scenario (wrong reagents, wrong order, etc.)
- Scaling-up without such knowledge can lead to potentially hazardous situations

Summary:

- Process development/safety fundamentals
- Calorimetry and heat measurement
- Reaction calorimetry first principles and overview
- Application examples



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QUESTION TIME

View the questions we were asked – and their answers – at <u>syrris.com</u>









