IR Monitoring for API Process Understanding and Control

Charles A. Goss
GlaxoSmithKline
RTP, NC, USA
API Development and Manufacturing Challenges

- Need to **sample material** for analytical testing
  - Sampling not suitable in some situations:
    - Fast reactions
    - Unstable intermediates
    - Difficult to sample, e.g. vacuum distillation
    - Hazard materials, safety concerns
- Limited process understanding
- Lack of real time process control

➢ Process analytical techniques (PAT) deliver real time solutions, can eliminate or minimize sampling
Outline

• IR monitoring of a **multi-stage reaction** that cannot be sampled
• IR, UV, HPLC monitoring of a **hydrogenation** reaction
• IR monitoring of a **coupling reaction** and **distillation** for crystallization control
  • Method development
  • Transfer from Lab to plant: challenges, learning
• Benefits of PAT methods
Multi-Step Reaction Monitoring

Kirby Amponsah-Manager
Matthew Salmons
Greg Gervasio
Bob Cooley
Hawthorne Graddy
Multi-Step Reaction Monitoring

- Two-step reaction converts **AH** to product **A-CO₂⁻ Li⁺**

![Chemical Reaction Diagram]

**Difficult to monitor reaction by HPLC**
- Butyllithium difficult to handle
- Intermediate unstable
- Sensitivity to oxygen

**PAT Measurement Goals**
- Reaction initiation
- Intermediate formation
- Reaction progression
- Reaction endpoint (ensuring consistent desired parameters)
Multi-Step Reaction Monitoring

**Lab development**

**Instrumentation:**

**ReactIR ic10**
- DiComp probe
- LN$_2$ cooled MCT detector
- 650-2000 cm$^{-1}$
- 8 cm$^{-1}$ resolution

**Goal** - Develop and test monitoring method on lab system then transfer method to plant equivalent for in-process control of API manufacturing
Reference Spectra

Step 1

THF, Hep, AH
All plus BuLi

Step 2

Before CO₂ addition
After CO₂ addition

- Identified peaks appropriately processed
- Processed peaks used to follow constituents of interest during reaction

Starting materials:
- AH
- THF
- Heptane
Method Development & Application on ReactIR iC10

Part 1: Formation of lithium anion

BuLi addition (stepwise)

Part 2: Formation of final product

CO₂ addition

Product precipitates
IR Monitoring of a Multi-Step Reaction

Instrumentation for Plant: ReactIR 247

- Requires only **power** and **communication connectivity**.
- Directly coupled to reaction vessel
- Ideal for limited space
- Can also be used with conduit attachments
### From Laboratory to the Plant

<table>
<thead>
<tr>
<th>ReactIR ic10 (MCT detector)</th>
<th>ReactIR 247 (DTGS detector)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Large spectral range</td>
<td>No detector cooling</td>
</tr>
<tr>
<td>High quantum efficiency</td>
<td>Smaller, less bulky</td>
</tr>
<tr>
<td>Detector cooling required</td>
<td>Small spectral range</td>
</tr>
<tr>
<td>Logistical concern for field use</td>
<td>Low resolution and image quality</td>
</tr>
</tbody>
</table>

Extra data treatment to compensate for detector response
Monitoring of a Pilot Plant Process using ReactIR 247

- ReactIR 247 successfully reproduced reaction profiles obtained at small scale using ReactIR iC10
- Used as an in-process-control for pivotal manufacturing campaign
Multi-Step Reaction Monitoring Summary

- IR method successful at lab and pilot plant scales using different instruments (iC10, 247)
- Provides vital process understanding because reactions are difficult/impossible to sample
- Also monitors product crystallization
Hydrogenation Reaction Monitoring by IR, UV-Vis and HPLC

Brian Crump

+ Large Supporting Cast
IR and UV-Vis for Hydrogenation Reaction Monitoring

Key Issues

- Want kinetic profiles to optimize reaction process and develop model
- Need to limit impurities to low levels
- Sampling undesirable
  - Cumbersome and time-consuming
  - Causes breaks in reaction
  - Reaction sensitive to oxygen
IR and UV-Vis Hydrogenation Vessel Setup

- Mettler Toledo ReactIR 45M MultiplexIR
- Mettler Toledo LabMax Pressure Reactor
- Zeiss MSC-522 Spectrophotometer
IR Spectra from Hydrogenation Reaction

Wavenumbers (cm\(^{-1}\))
Absorbance (AU)

#1 Air Blank
Added Starting Material and Catalyst
#34 Heated to 50C
#40 After H2 Started
#151 End Reaction
#7 2B Added Ethanol
IR and HPLC from Hydrogenation Reaction

Content (%)

Time (min)

-50 0 50 100 150 200 250 300

Starting Material IR %
Product IR %
Starting Material HPLC %
Product HPLC %
Starting Material + Byproducts HPLC %
UV-Vis Hydrogenation Reaction Monitoring

- Orthogonal Project Approach (OPA)
- Multivariate curve resolution with some similarities to Iterative Target Transfer Factor Analysis (ITTFA)
- Uses OPA to obtain initial estimates,
- More flexibility with the constraints applied during the solution optimisation.
IR and UV-Vis Comparison

- Starting Material IR %
- Product IR %
- Starting Material UV %
- Product UV %

Content (%) vs. Time (min)
Example Kinetics

- Comparison of different catalysts, catalyst amounts, reaction volume, hydrogen pressure, and temperatures.
- Overall, reaction rates reflect expected results based on these factors.
**Kinetic Model for Hydrogenation**

Reaction rate is initially 0 order in [Reactant] and later 1\textsuperscript{st} order (consistent with adsorption of reactant on the catalyst).

- Reaction rate is 1\textsuperscript{st} order in [Catalyst].
- Reaction rate is independent of the hydrogen partial pressure (in kinetically controlled regime).

\[ R = \frac{k_B k_A e^{-E_A/RT}[\text{Reactant}][C_{tot}]p_{Hyd}}{1 + k_A/k_A[\text{Reactant}] + k_C/k_C[\text{Product}]} \]

\[ R = \frac{Ke^{-E_A/RT}[\text{Reactant}][C_{tot}]}{1 + k_A/k_A[\text{Reactant}] + k_C/k_C[\text{Product}]} \]
Kinetic Model at 1-L and 20-L Scales

Starting Material Reaction Profiles
20-L and 1-L Data vs Kinetic Model

Later 20-L data deviates from model due to H2 integration problem
Hydrogenation Reaction Achievements

- Reduced impurities significantly
- Eliminated subsequent recrystallization
- Successful at 1600L scale in Singapore Pilot Plant and GMS
Heterogeneous Reaction and Quantitative Distillation Monitoring

Shannon Condon
Bob Cooley
Hawthorne Graddy
Kirby Amponseh-Manager
Seán Sisk
**API Stage 1 Coupling**

**Unit Operation and Issues**

**Heterogeneous slurry**
- Reactant A dissolves as reaction progresses
- Sulfonyl Chloride and Product are soluble
- Pyridine HCl precipitates
- Low volume reaction

**Reaction Completion** – Target Reactant A <1% a/a by HPLC
Equipment Setup for Distillations

DiComp 9.5mm AgX Probe

ReactIR 4000
API Stage 1 Reaction Profile – IR

- Product - 900 to 1750
- Reactant A - 1536 to 1750
- Pyridine - 1430 to 1750
- Toluene - 1032 to 1750

Reactant dissolution
API Stage 1 Reaction Profile – IR

Product

Reactant A

Key Points
- Small amount water solubilizes Reactant and increases rxn rate
- More than 1% w/w water starts to cause problems
API Stage 1 Distillation

Distillation Endpoint – Target 42-46% w/w Product (420-460mg/g)

- Target concentration ensures acceptable crystallization
- Higher product concentration increases yield
- Temperature varies with distillation pressure
- Product precipitates if overdistill or temperature decreases
- Offline sampling not possible due to crystallization in lines
## Calibration Transfer Risks

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Potential Impact</th>
<th>Mitigation</th>
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</thead>
<tbody>
<tr>
<td>Wavenumber Reproducibility</td>
<td>Variable spectral features</td>
<td>Spectrometer Performance</td>
</tr>
<tr>
<td>Probe Pathlength</td>
<td>Absorbance differences</td>
<td>Spectral Preprocessing</td>
</tr>
<tr>
<td>Fiber Length and Connections</td>
<td>Variable transmission Baseline shifts</td>
<td>Spectral Preprocessing</td>
</tr>
<tr>
<td>Temperature</td>
<td>Variable spectral features (H bonding)</td>
<td>Vary T in calibration Control T in process</td>
</tr>
<tr>
<td>Input materials (e.g. EtOH content)</td>
<td>Variable spectral features</td>
<td>Vary composition in calibration Material specifications</td>
</tr>
</tbody>
</table>
Distillation Calibration Experiment

Equipment
- Multi-Max Reaction Vessel
- ReactIR 4000, 9mm AgX Probe with 2m fiber

Calibration Solutions
- 591 to 276mg/g Product in toluene
- Single solution prepared by adding known weights toluene

Procedure
- Hold solution at 85, 95, and 105°C
- 3 spectra at each temperature
IR Spectra - Product in Toluene

- Blue = 591mg/g
- Red = 276mg/g

Toluene 1031cm⁻¹
IR Spectra - Product in Toluene Zoom

- Blue = 591mg/g
- Red = 276mg/g

Toluene 1031cm⁻¹

Wavenumber (cm⁻¹)
IR - 2\textsuperscript{nd} Derivative

- Blue = 591mg/g
- Red = 276mg/g
IR - 2nd Derivative

- Toluene 1031 cm⁻¹
- Blue = 591 mg/g
- Red = 276 mg/g

Wavenumber (cm⁻¹)
## Example PLS Models Evaluated

<table>
<thead>
<tr>
<th>Univariate</th>
<th>Multivariate</th>
<th>Multivariate</th>
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</thead>
<tbody>
<tr>
<td>❖ Peak Height 1173 cm-1</td>
<td>❖ 1200-800 cm-1,</td>
<td>❖ 1200-800 cm-1,</td>
</tr>
<tr>
<td>❖ Baseline 1031 cm-1</td>
<td>❖ Baseline 1750 cm-1</td>
<td>❖ Baseline 1031 cm-1</td>
</tr>
<tr>
<td></td>
<td>❖ Mean center</td>
<td>❖ 2nd derivative</td>
</tr>
<tr>
<td></td>
<td>❖ 4 Factors</td>
<td>❖ Mean center</td>
</tr>
<tr>
<td></td>
<td></td>
<td>❖ 4 Factors</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Also tried 1st derivative</td>
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</tbody>
</table>
Example Calibration
IR Equipment Summary

- **4 Instruments**
- **3 Probes**
- **All distillations used different instrument from calibration**

**IR Instrument:** Mettler Toledo ReactIR 4000 with MCT Detector

**Software:** Mettler Toledo iCIR v4.0.636.0 or v4.0.641.0

<table>
<thead>
<tr>
<th>Serial Number</th>
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</tr>
</thead>
<tbody>
<tr>
<td>R4K-B4332, iCIR v4.0.641.0</td>
<td>EE453055</td>
</tr>
<tr>
<td>R4K-B4385, iCIR v4.0.641.0</td>
<td>EE448739, EE451433, EE480917, EE490149</td>
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<tr>
<td>R4K-B4362, iCIR v4.0.636.0</td>
<td>EE438971, EE441063, EE444453</td>
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<tr>
<td>ReactIR iC10, RIC-1615, iCIR v2.0.150.2</td>
<td>EE493203</td>
</tr>
</tbody>
</table>

**Probe:** DiComp (Diamond) probe connected via AgX 9.5mm x 2m Fiber (Silver Halide)

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<tr>
<td>SHFP-9-457-2-6284</td>
<td>EE448739, EE451433, EE438971, EE441063, EE444453, EE480917</td>
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<tr>
<td>SHFP-9-431-2-6286</td>
<td>EE453055, EE490149</td>
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<tr>
<td>SHFP-9-457-2-6772</td>
<td>EE493203</td>
</tr>
</tbody>
</table>

**Acquisition Parameters:** Sampling 2000 to 650 at 8 wavenumber resolution; Scan option: 128

**Background:** Taken in air, typically with 256 scans
Example API Stage 1 Distillation – IR

Key Points
- Profiles vary significantly with method
- Errors not uniform across distillation
Key Points

- Preprocessing significantly effects accuracy
- HPLC = 451-460mg/g, agrees with best IR method
Effect of Moving Fiber

Key Points

- Preprocessing eliminated sensitivity to fiber movement

Product Concentration (mg/g)

Time

- Multivariate 1190-1140 to Baseline@1031
- Univariate 1140-1190 Peak to Baseline@1031
- Univariate 1173 to Baseline@1031
- Multivariate 1190-798 1st Deriv to Baseline@1190
- Multivariate 1200-800 2nd Deriv to Baseline@1031
Final PLS Model Calibration Results

Model Details

- Multivariate 1200-800 cm⁻¹,
- Baseline at 1031 cm⁻¹
- 2nd derivative, mean center
- 4 Factors

Actual vs. Predicted

RMSEC vs. #Factors

4 factors

Predicted - 322A Conc

Actual - 322A Conc

250 300 325 350 375 400 425 450 475 500 525 550 575 600

2 4 6 8 10 12 14 16 18 20

Factor

RMSEC vs. #Factors

0.0 1.0 2.0 3.0 4.0 5.0 6.0 7.0

Value - 322A Conc

0.0 1.0 2.0 3.0 4.0 5.0 6.0 7.0

Factor

METTLER TOLEDO
IR and HPLC Summary

- IR and HPLC results similar across various equipment

HPLC measured after diluting from ~4.12 vol to ~5.12 vol
Conclusions

Quantitative IR Method Calibration Transfer can work!

Calibration
- Cover expected concentration ranges
- Account for temperature differences

Equipment Transfer Effects
- Baseline shifts
- Absorbance / Pathlength differences
- Fiber effects

Chemometric Model
- Baseline selection is critical
- Preprocessing is critical
- 2\textsuperscript{nd} derivative worked best here
IR Process Monitoring Summary

IR successful at lab and pilot plant scales
Reduces or eliminates offline testing

Benefits Provided

Process Understanding
- Evaluates entire process, process kinetics

Control
- Consistent process endpoints
- Continuous improvement

Safety
- Reduces exposure risk
- Controlled outside of containment area
Acknowledgments

GSK Pilot Plant Staff in UP, Jurong and Cork

Mettler Toledo Autochem for the opportunity to present

Thanks for your attention!

Questions?