ENABLING TECHNOLOGIES IN API PROCESS DEVELOPMENT : GREEN CHEMISTRY METRICS

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(DR REDDYS LABORATORIES)

CONTENT

1. API / DS development cycle in API
    a. Introduction & challenges

2. PATs - Enabling technology & Green chemistry metric

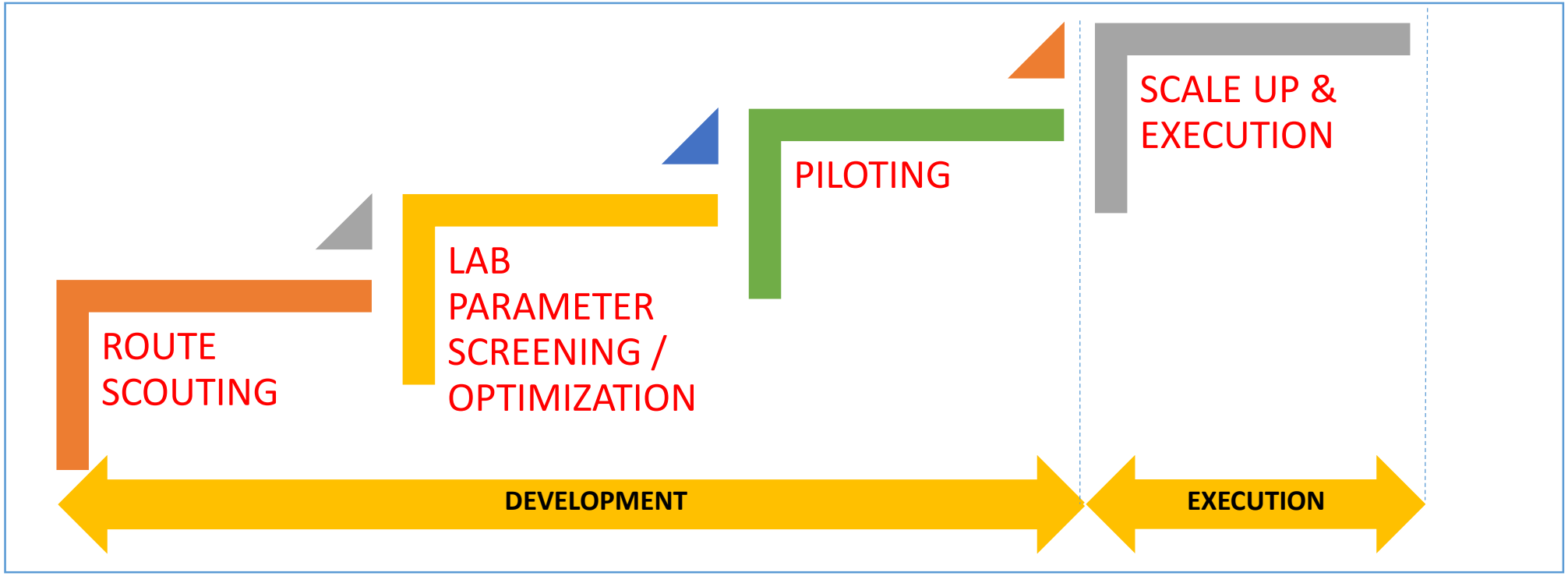
3. PATs - API industry
    a. FBRM
    b. Spectroscopic tools – ReactIR & NIR

4. PAT – Crystallization – IR & FBRM
    a. Introduction
    b. Examples

5. PAT – Reaction Monitoring - Spectroscopic tools
    a. Introduction
    b. Data analysis technique – Chemometrics
    c. Examples

6. Summary

Drug Substance development in pharmaceutical industry



DEVELOPMENT PHASE (Route scouting & Lab parameter optimization) is critical for speedy execution

Development phase challenges:

- ***Multiple reagents screening***
- ***Mechanistic understanding***
- ***Parameter optimization to improve quality & yields***
- ***Analytical method development – impurity detection and quantification***

Process Analytical Tools (PATs) – API Development

❑ PATs

- Process sensors : e.g. purity, pH, temperature, particle size, flow rate etc.
- Spectroscopy based tools (Infrared, UV-Vis, Raman etc.), chromatography etc.

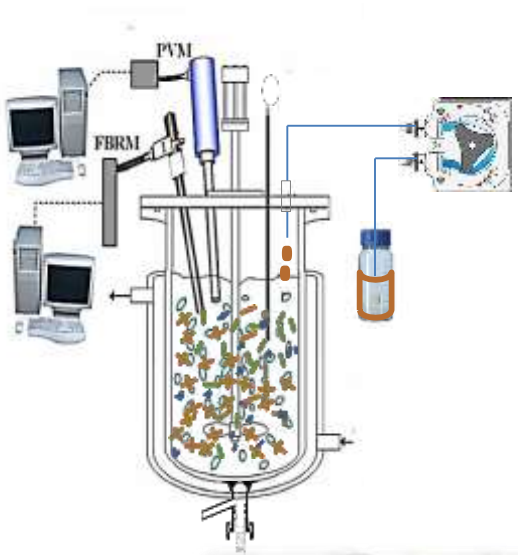
❑ Application

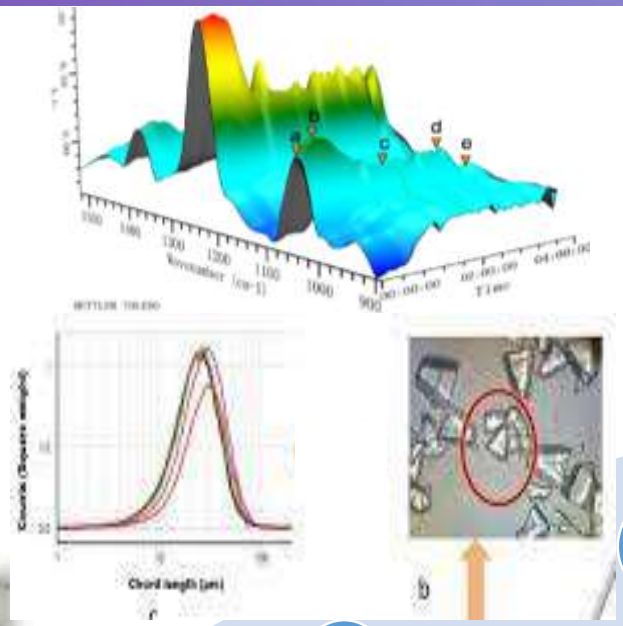
- Faster and real-time process understanding during reaction and unit operations monitoring
- Reduce number of experimentation
- Quick qualitative and quantitative analysis
- Useful in process control by incorporating as an integrated system with feedback control loop

❑ Process Chemometrics

- All analytical instrumentation encode info. about their samples → need to decode to relevant process parameters
- Multi Curve Resolution, multivariate regression etc.
- Spectral treatment enables robust performance of PAT data

PAT - API development





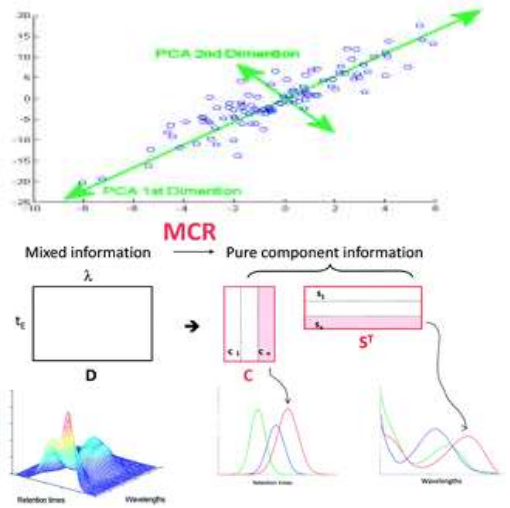
Feasibility/pre-DOE process

Inline PAT tools

Spectral / PAT information

Multivariate statistical analysis

Optimized process

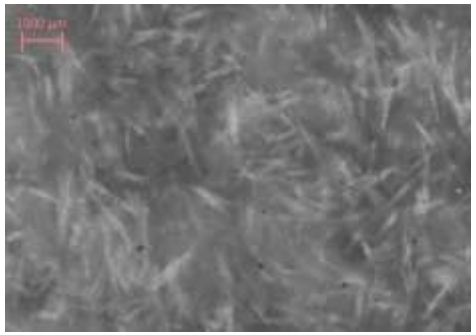


PAT - CRYSTALLIZATION

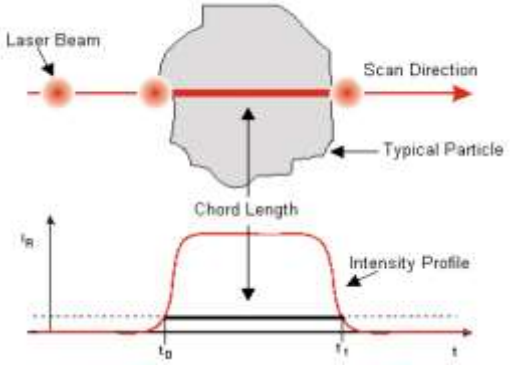
PAT tools to understand crystallization : PVM, FBRM

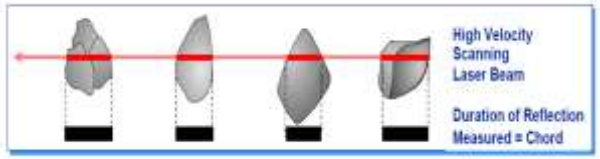
- Particle size
- Particle shape
- Particle count
- Realtime monitoring

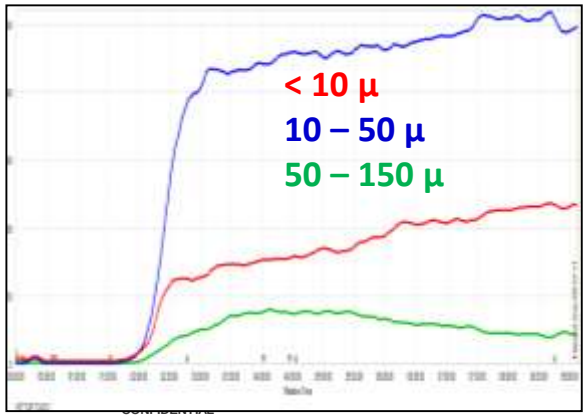
PVM- Particle Vision Microscope

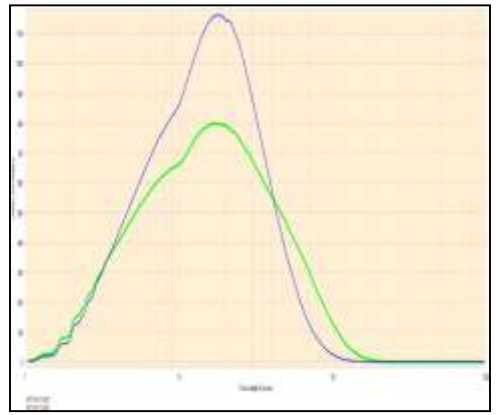


Focused Beam Reflectance Measurement

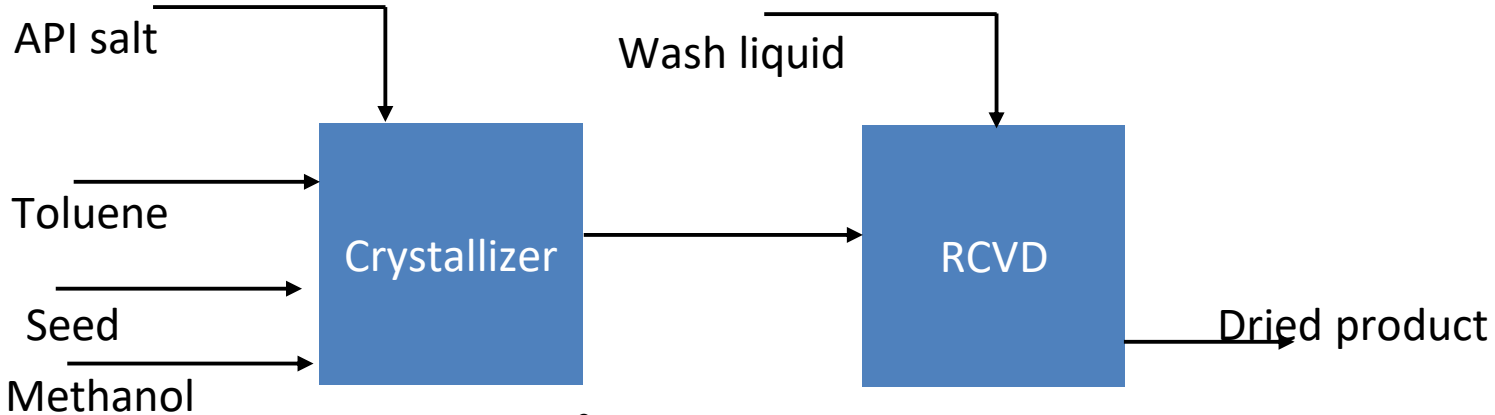


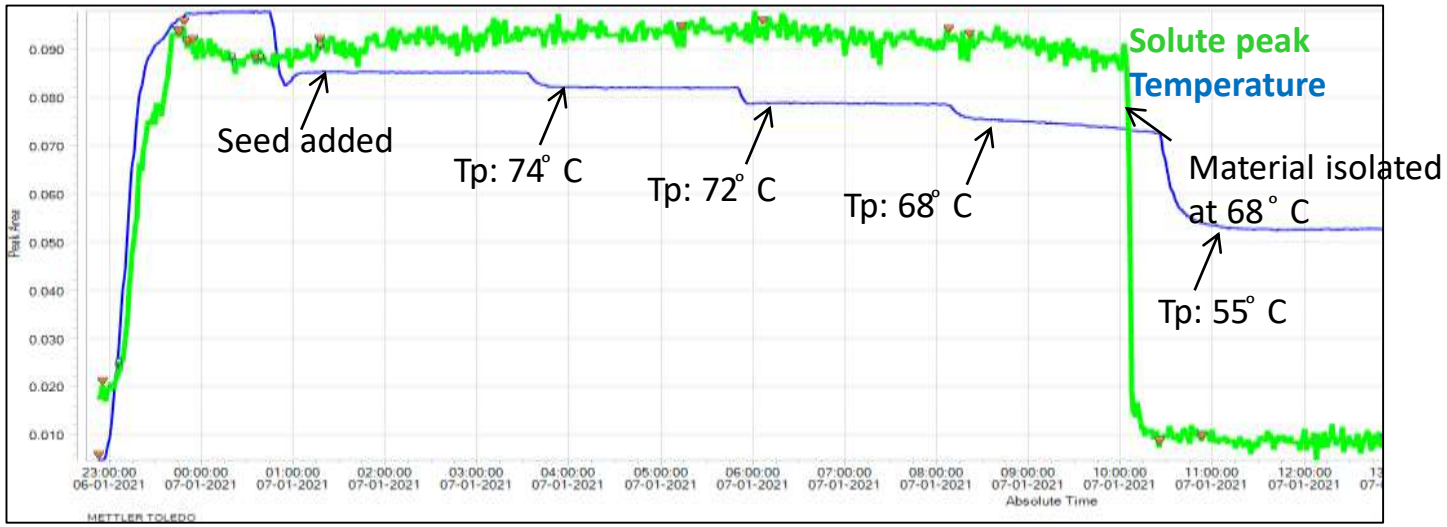






CASE-1 : IMPURITY PURGING





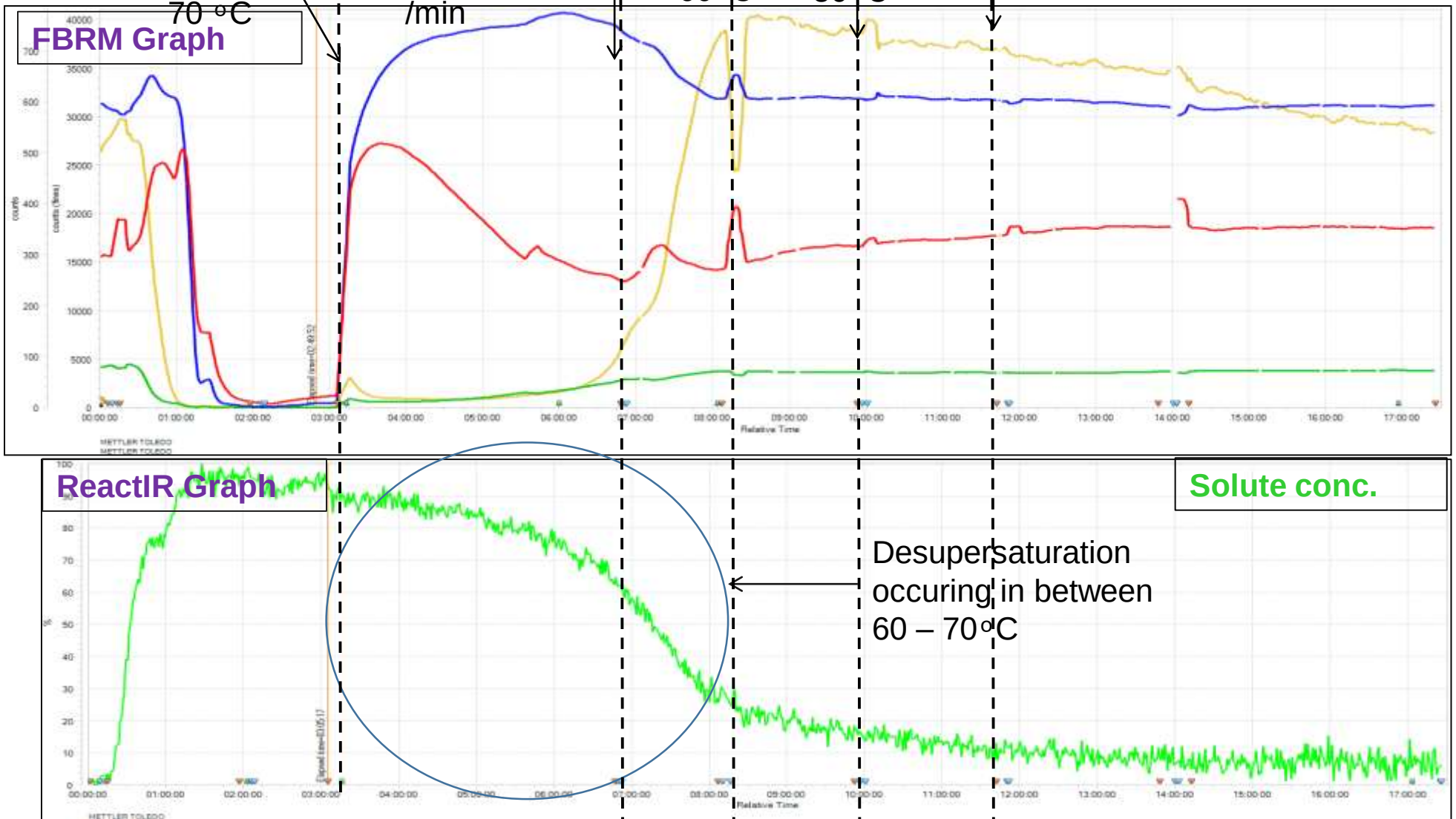
❑ Challenges

- Low filtration flux: 8-10 L/m^2.min
- Salt formation followed by 4 recrystallization to wash the impurity
- Mixture of solvents making the solvent recovery complex

Methodology:

1. Determine the optimum seeding temperature
2. Identify the growth regime during cooling crystallization
3. Enhance crystals growth - different cooling profiles

FBRM & IR PLOTS : SLOW COOLING RATE



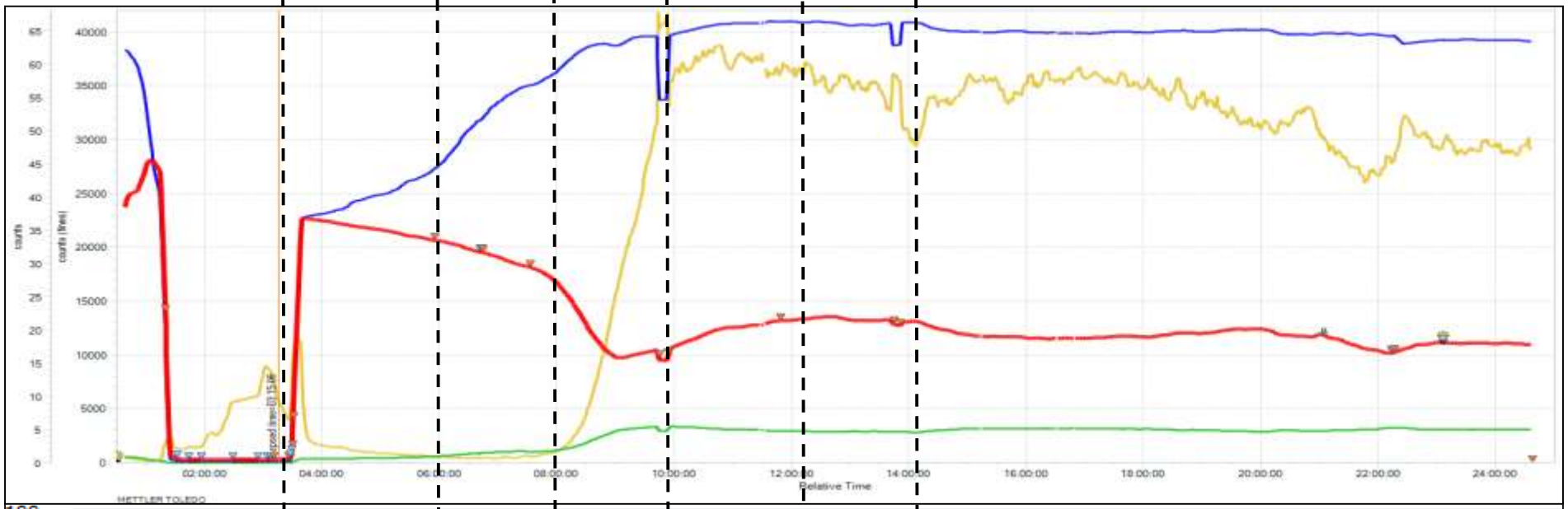
< 10 µ counts (fines)
10 – 50 µ counts (fines)
50 – 150 µ counts (fines)
150 – 300 µ counts

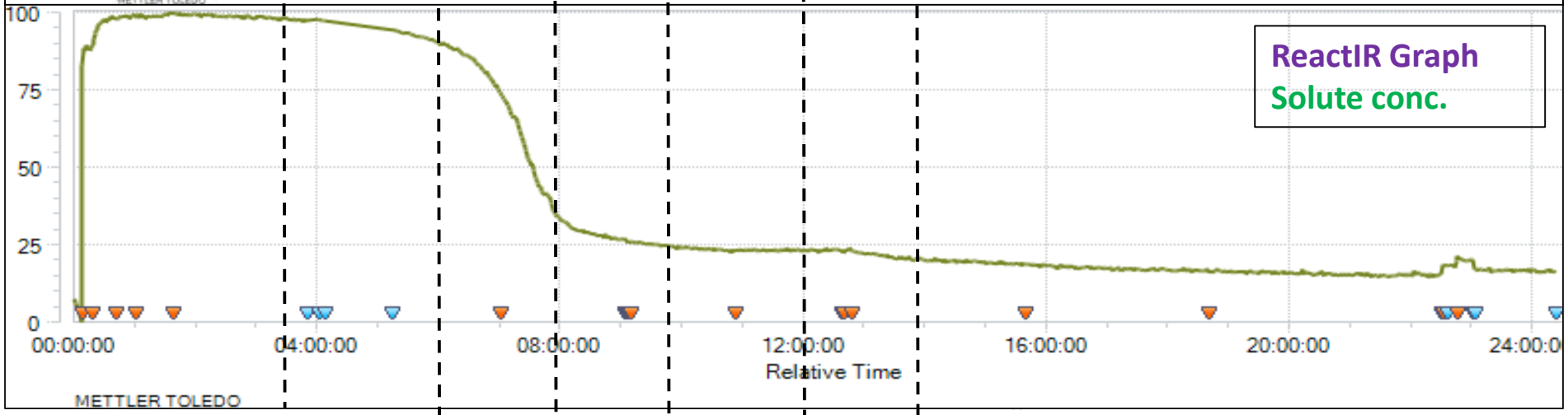
1. Seeding temperature: 70°C
2. 4h maintenance at 70°C
3. Ramp cooling to 30°C at a rate of 0.1°C/min

Filtration flux improved from 10 to 30 L/m².min

FBRM & IR PLOTS : STEP WISE COOLING

Seed charged at 72˚ C | RM cooled to 68˚ C | RM cooled to 63˚ C | RM cooled to 30˚ C





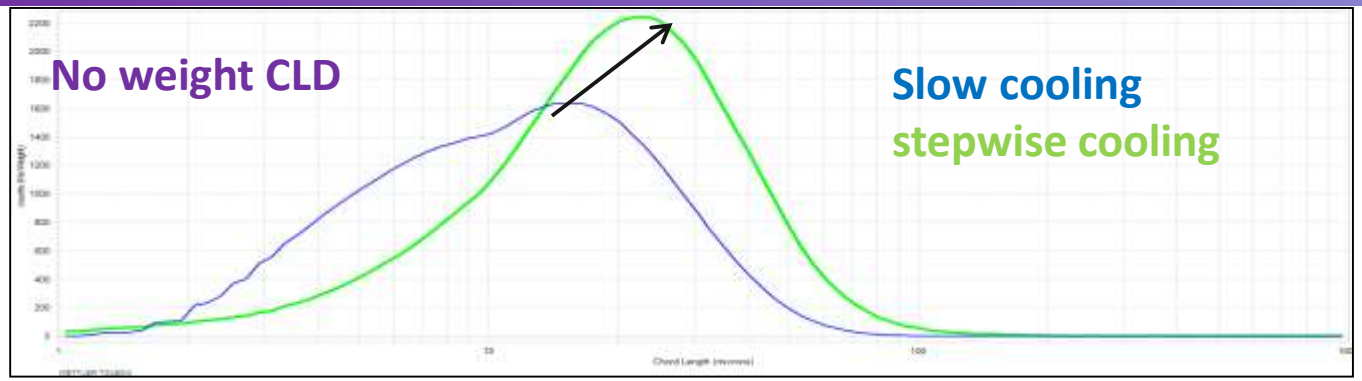
< 10 µ counts (fines)
10 – 50 µ counts (fines)
50 – 150 µ counts (fines)
150 – 300 µ counts

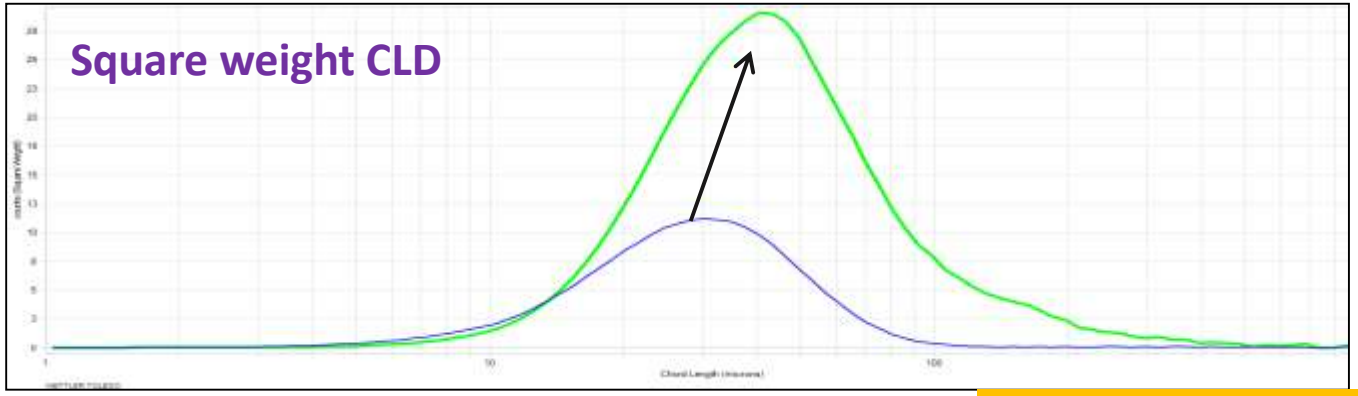
1. Seeding temperature: 72C
2. Stepwise slow cooling followed by maintenance

Step	Ramp cooling	Time, h
1	72 - 68	2
2	68	2
3	68 - 63	2
4	63	2
5	63-30	8

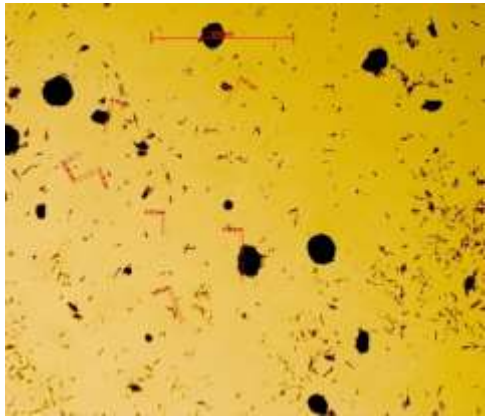
Filtration flux improved to 90 L/m².min

CHORD LENGTH DISTRIBUTION





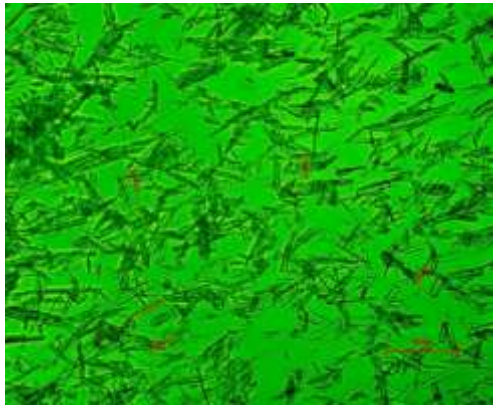
Comparing both the CLDs indicate particle growth during the cooling crystallization



Poor filtration batch: Fines resulted in agglomeration

Expt. No.	Parameter	Filtration flux
1	Slow cooling Rate	30 L/m2.min
2	Stepwise cooling rate	90 L/m2.min

- ✓ **No. of purification steps:** 2 (Previously 4)
- ✓ **Removed methanol washing step (for washing of styrene impurity) because of enhanced impurity washing. Avoided solvent mixture**



Good filtration batch: Well grown needles

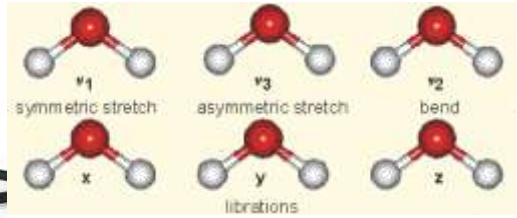
PAT – REACTION MONITORING

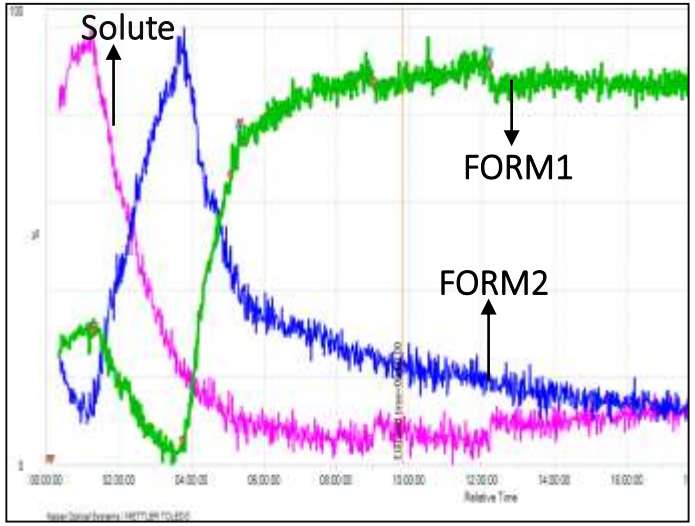
PAT tools to understand reaction and crystallization : Raman, FTIR

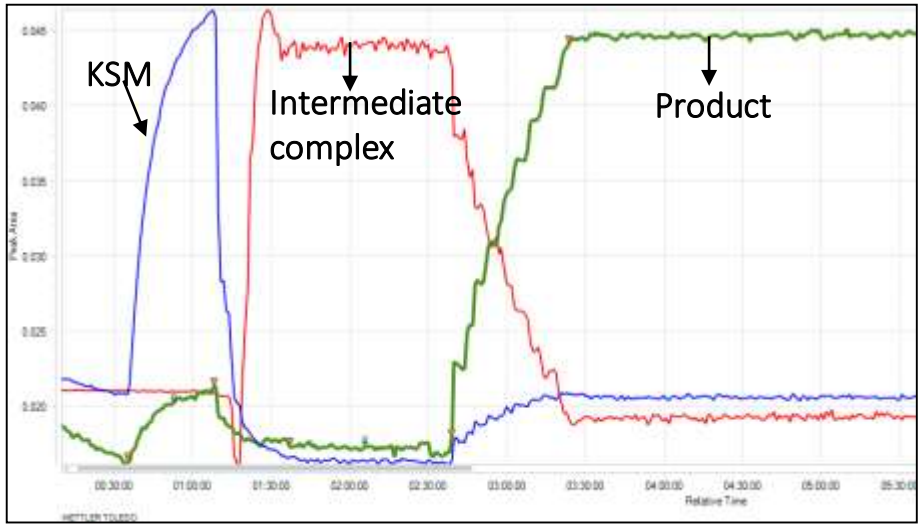
RAMAN

- Reaction mechanism
- Polymorph transformation
- Reactants / Product concentration

INFRARED (NIR & MIR)

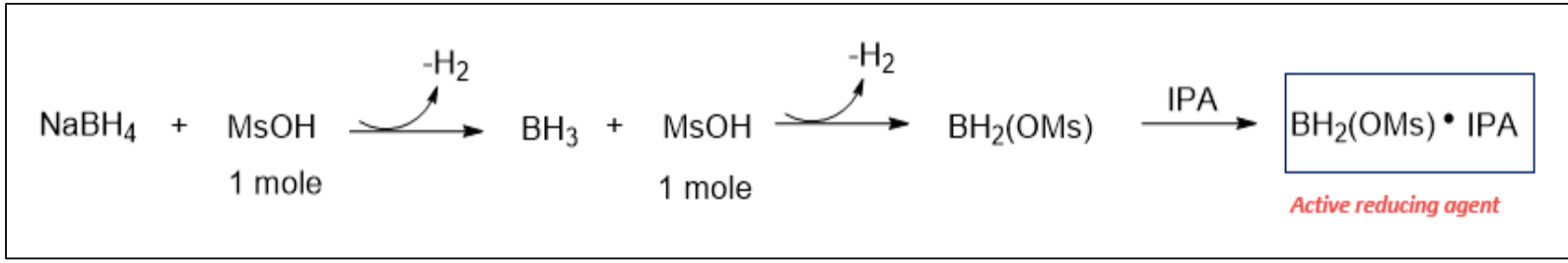


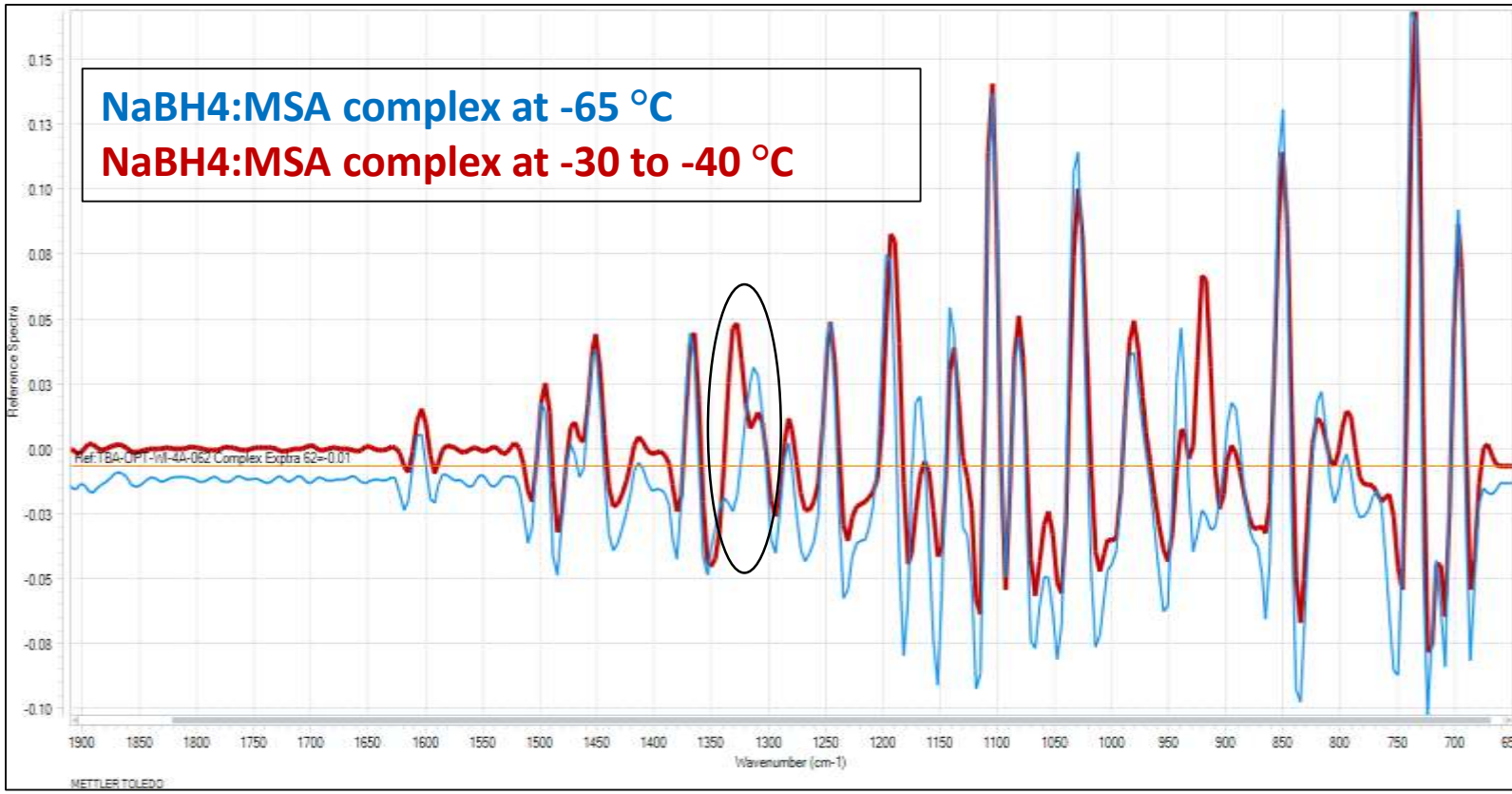




MULTIVARIATE ANALYSIS - REDUCTION

Univariate analysis	Multivariate Analysis
Single Peak is considered	Entire Data will be used
Loss of information	Multiple Data sets can be analyzed at once
Only Qualitative trends	Impurities with highly overlapping peaks can be tracked
	Predictive Quantitative Models can be built



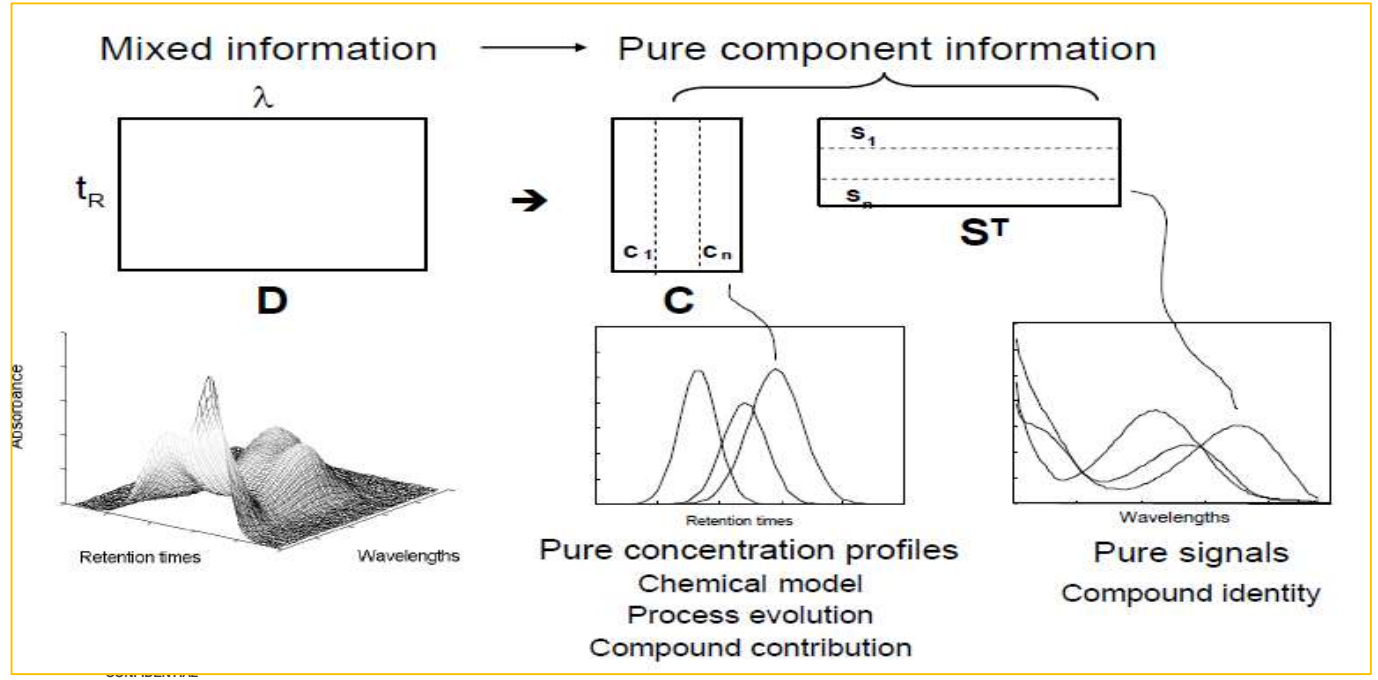


Spectra's, at two different temperatures, does not show distinct differences

CHEMOMETRICS : SPECTRAL DATA ANALYSIS TECHNIQUE

- ✓ **Chemometrics** is the science of extracting information from chemical systems by data-driven means
- ✓ It's applied to solve both qualitative and quantitative prediction problems in experimental sciences
- ✓ In both cases, the datasets are often large and complex, involving hundreds to thousands of variables

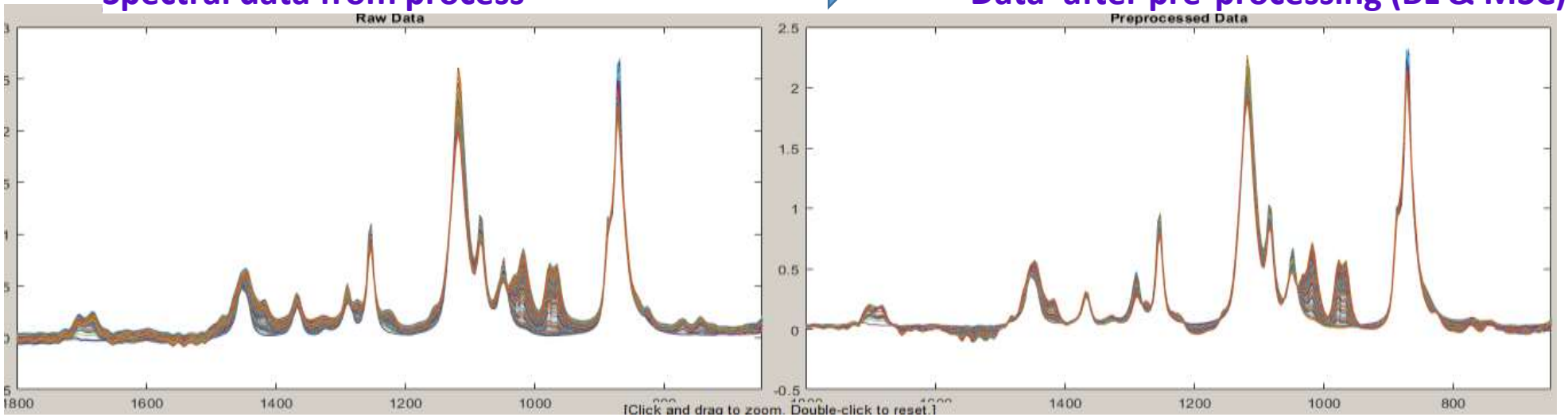
- **Multivariate curve resolution (MCR)**
  - ✓ Used to solve mixture data analysis problems & provides the information related to pure component contributions in mixed measurements



SPECTROSCOPIC DATA ANALYSIS

Spectral data from process

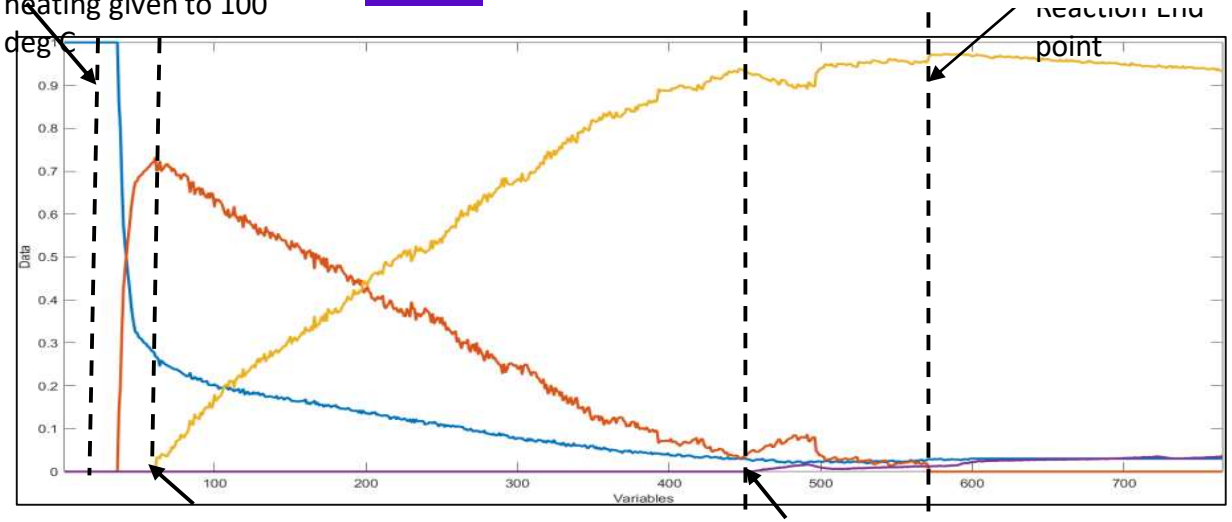
Data after pre-processing (BL & MSC)



Tends

DMEDA charged and heating given to 100 deg C

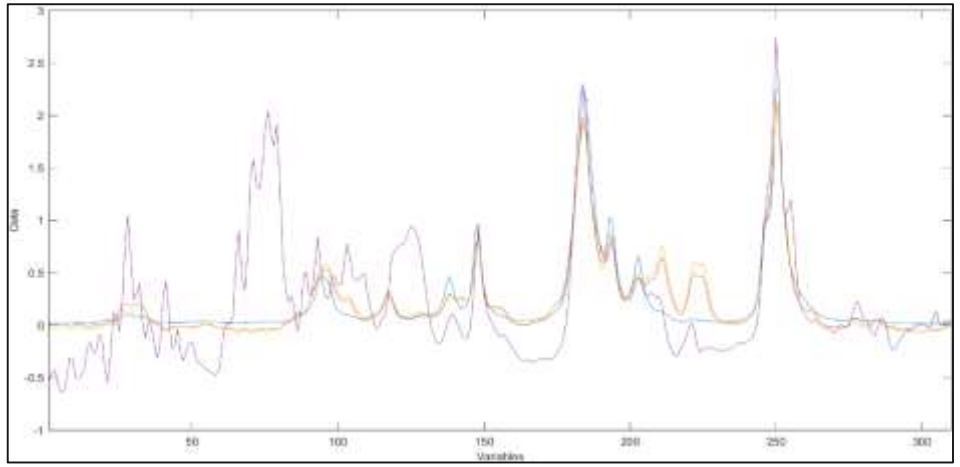
Reaction End point



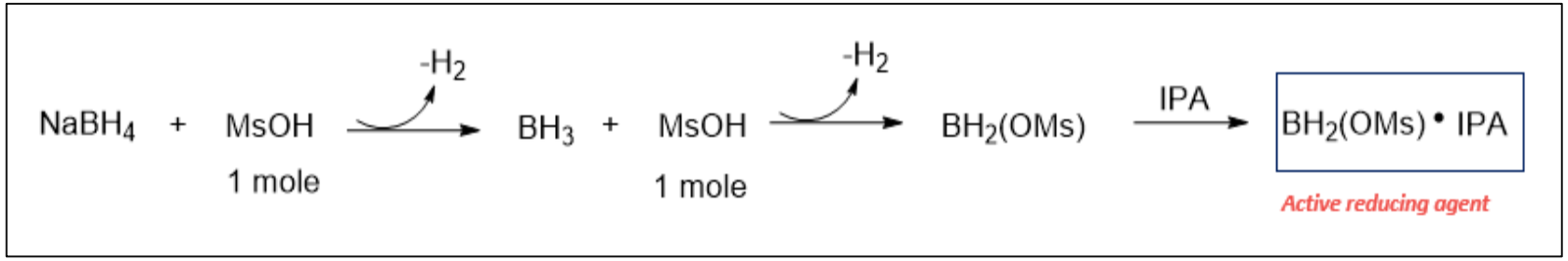
RM attained 100 deg C

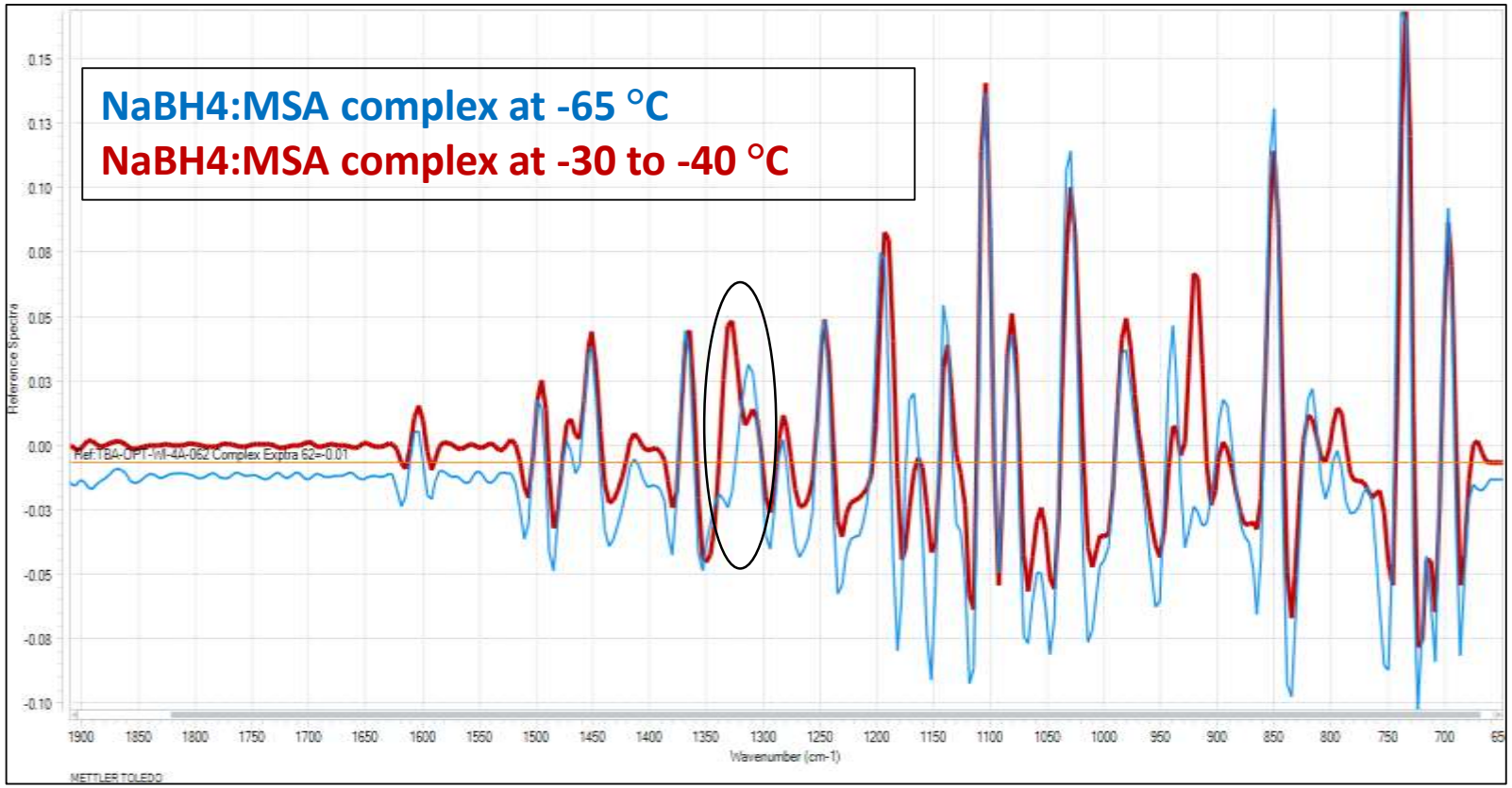
Imp 0.56 RRT formation initiated

Pure Component Spectras



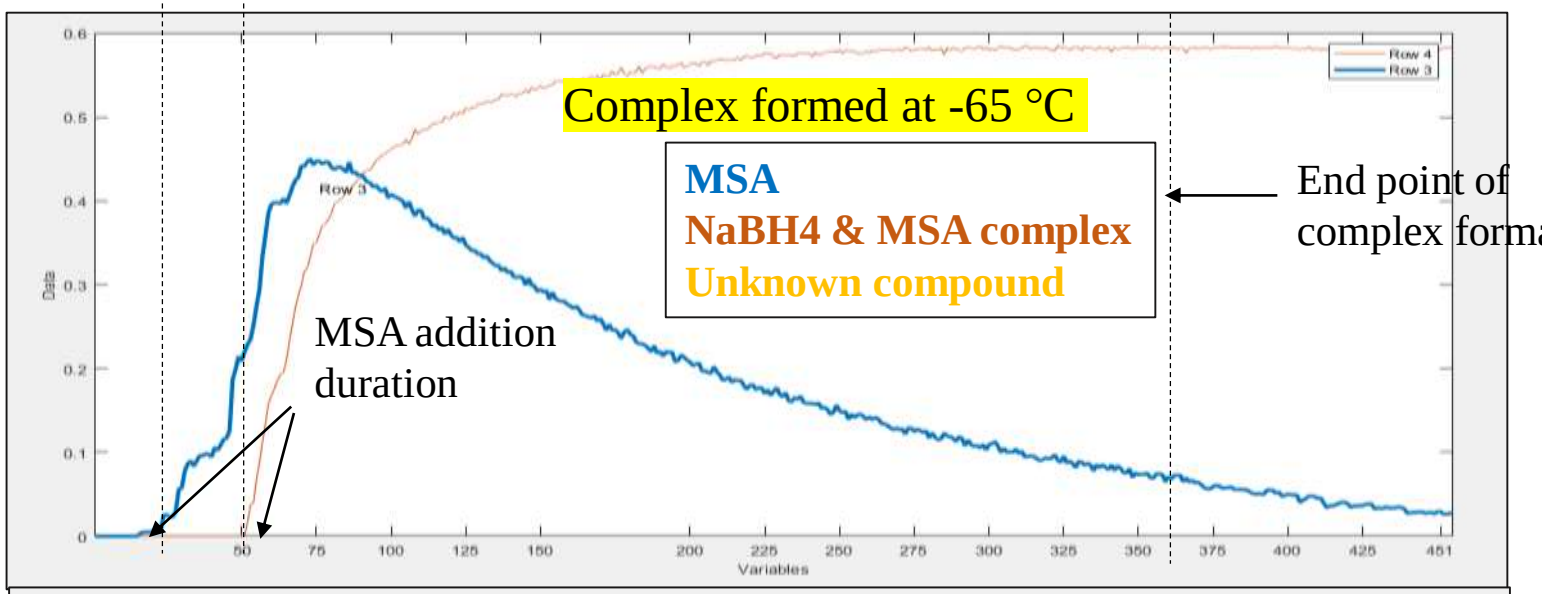
MULTIVARIATE ANALYSIS - REDUCTION

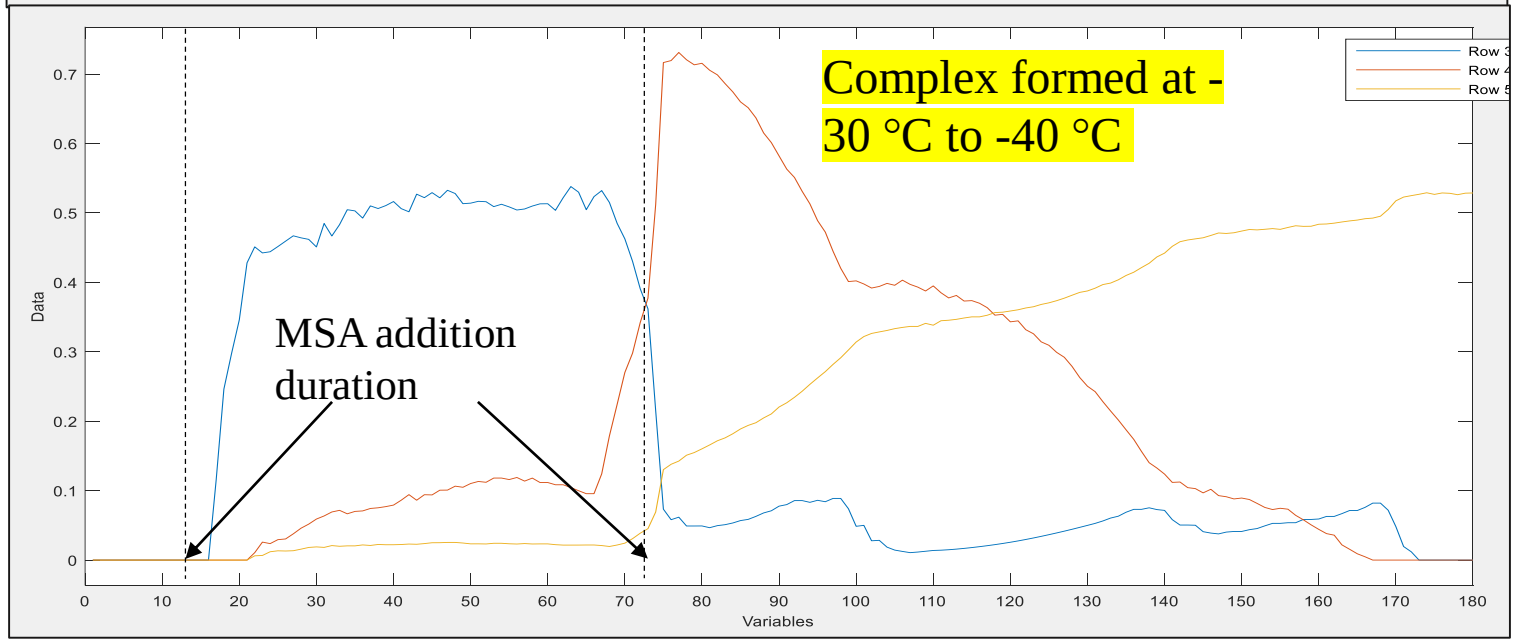




Spectra's, at two different temperatures, does not show distinct differences

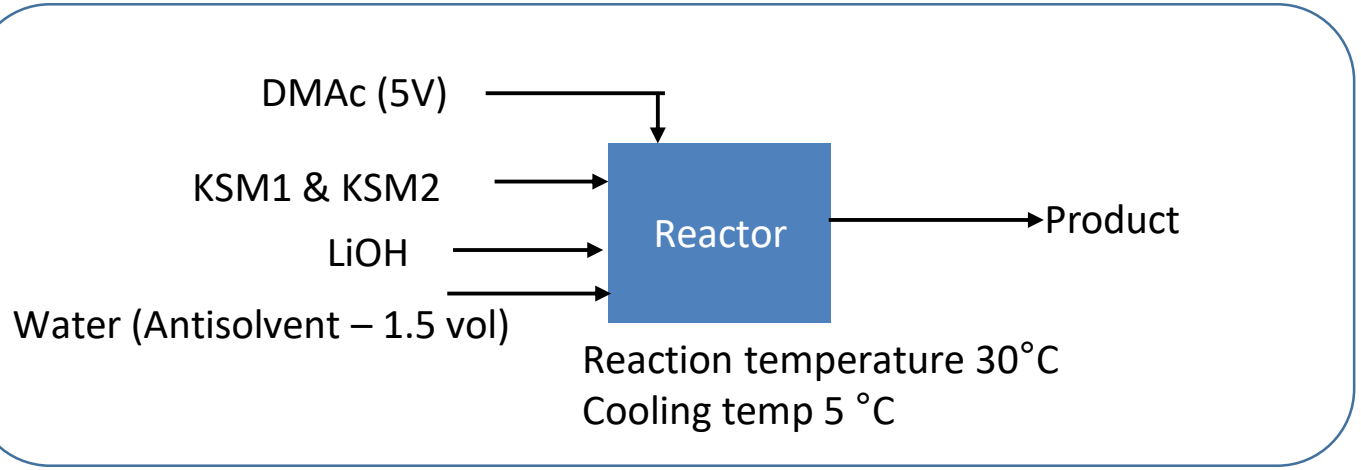
Multivariate curve resolution (MCR)

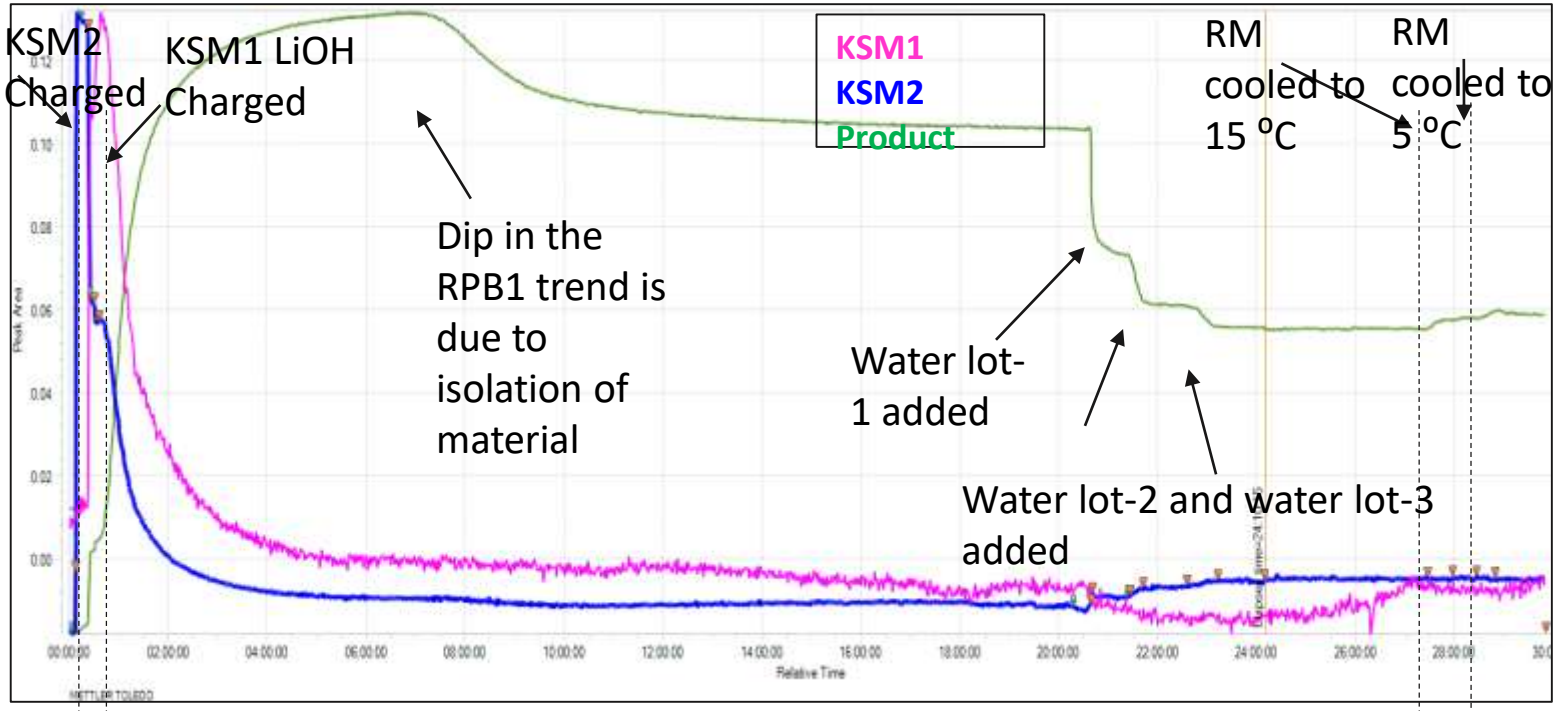




- Inline analysis and trending of reactants and intermediates which are temperature sensitive
- Optimizing the process conditions during development phase
- Validation (250 kg) completed with the process controls in place

CASE-2 : QUANTIFICATION USING PAT





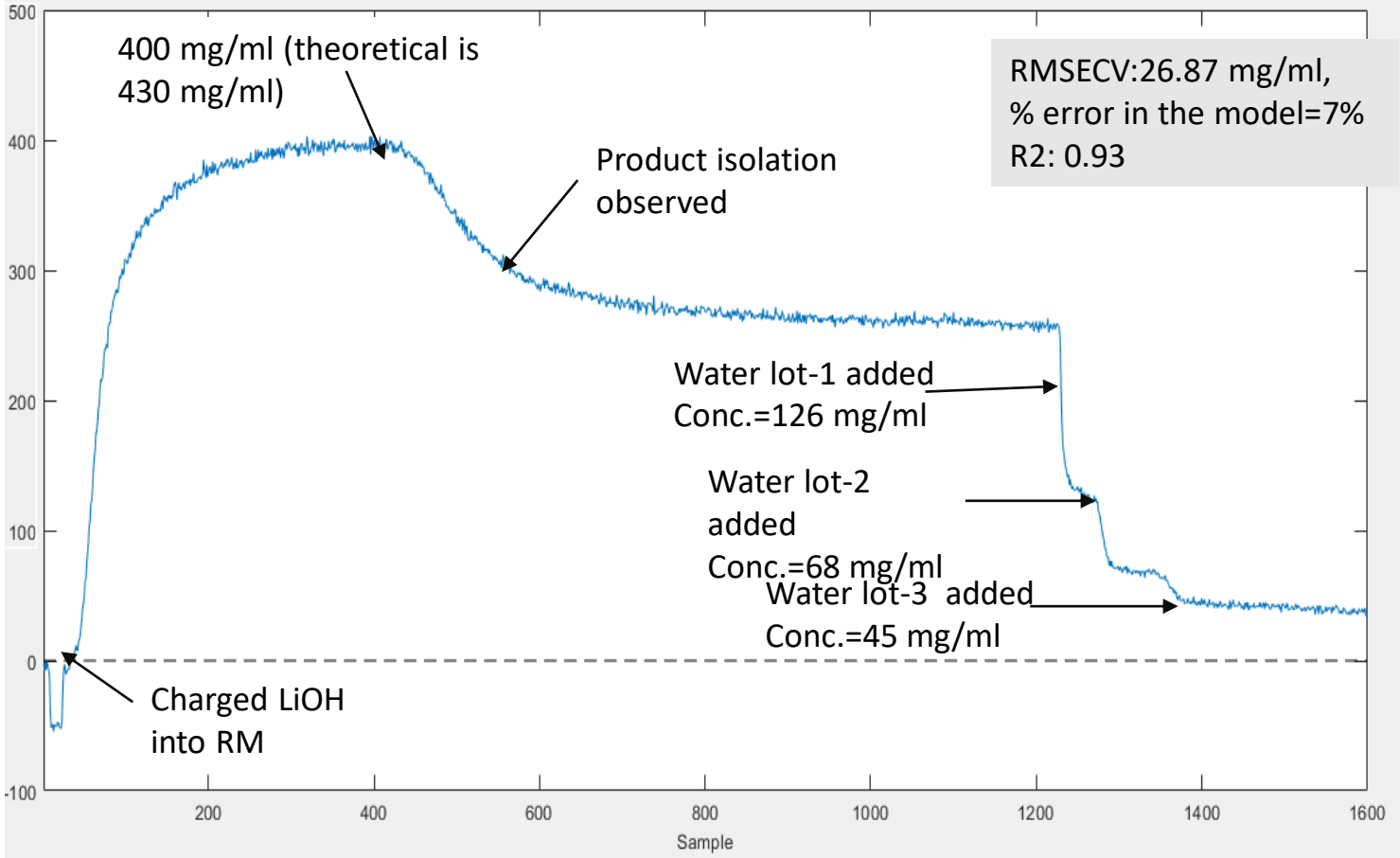
➢ Challenges:

- Yield loss in crystallization
- Theoretical yield not in accordance with solubility data
- Non availability of analytical (quantification) method to determine the solute (reagents & product) concentration in MLs

PLS - QUANTITATIVE MODELLING

Challenge with quantitative model building:

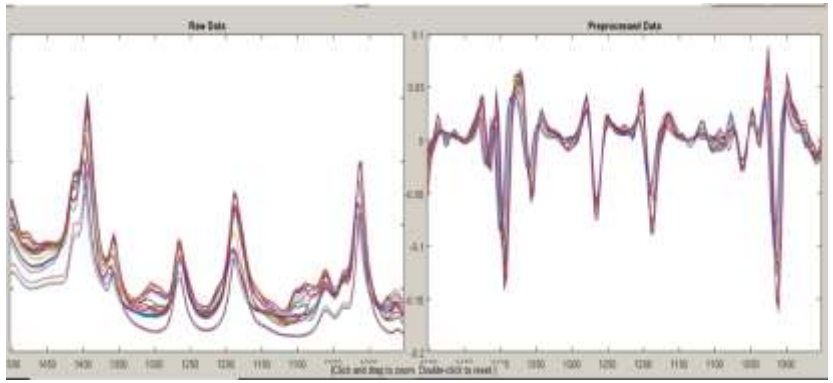
Calibration samples to include KSM1, KSM2, Product, Solvent and antisolvent.



Design of calibration dataset:

Chemical	Conc. range
Product	0- 300 mg/ml
KSM1	0-80 mg/ml
KSM2	0 – 80 mg/ml
DMAc : water ratio	5:0, 5:1, 5:2

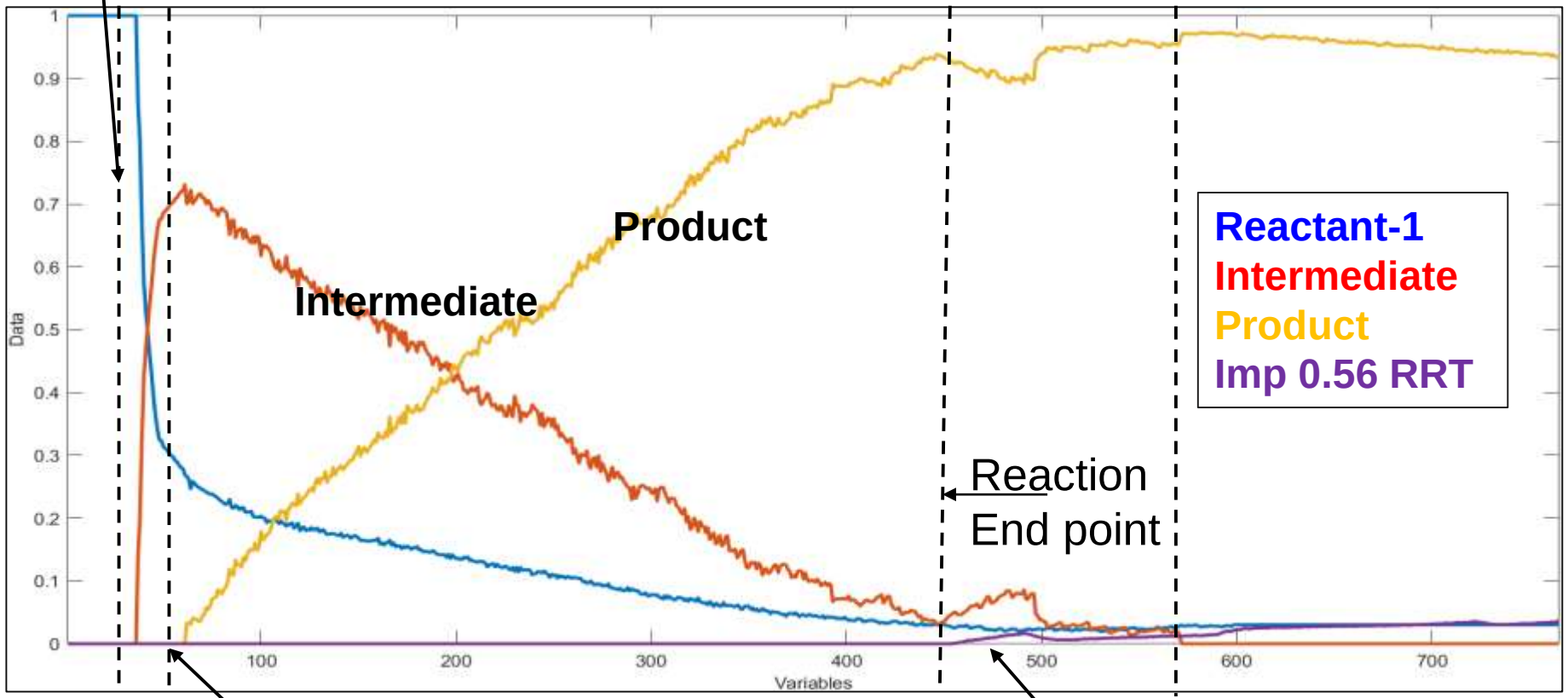
- Spectral Range:1500-950 cm-1
  Pre-processing used: Second Derivative



- **Yield is improved from 87 to 91% by changing water volumes from**

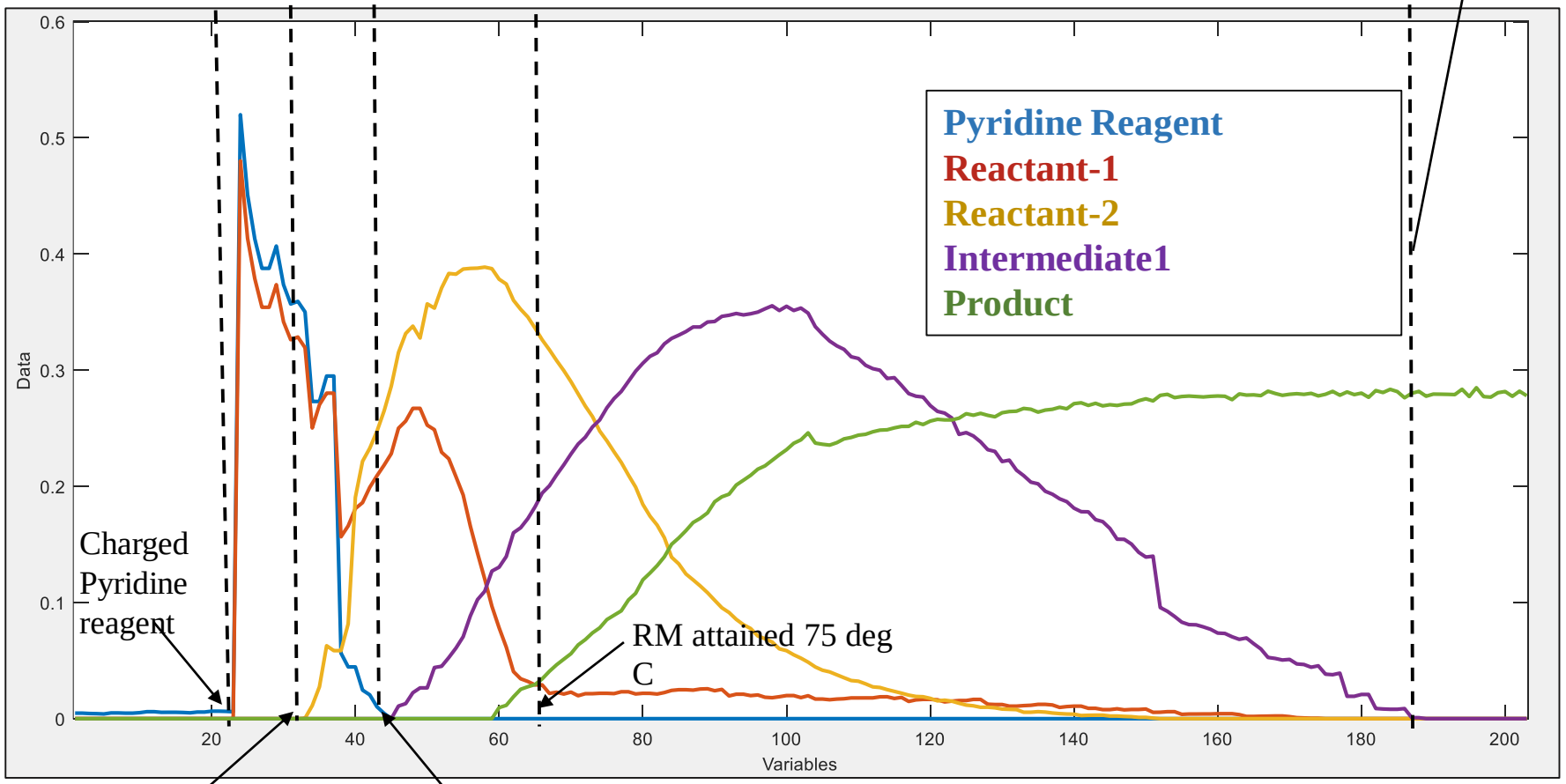
CASE-3 : IMPURITY & INTERMEDIATE DETECTION

1. Reactant-1, K2CO3, CuI and 1,4 dioxane are taken into reactor.
2. DMEDA charged into the RM and heating given to 100 °C



- Trending of intermediates which are not detected in HPLC
- Optimizing the process conditions during development phase

CASE-4 : INTERMEDIATE DETECTION



- Peak region:1800 cm^{-1} to 800 cm^{-1}

- Intermediate formation observed after increasing the temperature >70°C
- Followed by formation of product
- Multivariate analysis revealed the formation of intermediate followed by product at higher temperature
- Intermediate structure revealed based on pure spectra obtained from chemometric analysis

SUMMARY

PAT usage help in early stages of development aids the process understanding and improvement in terms of yield and quality

PAT SPECTROSCOPIC DATA ANALYSIS – QUALITATIVE *(MCR)*

- Spectral data analysis using Chemometric tools divulge more information from complex data sets
- Resolution of components present in reaction mixture
- Concentration and pure spectra resolutions supports in identification of components like reactants, intermediates, impurities etc.
- Application in Reaction and crystallization

PAT SPECTROSCOPIC DATA ANALYSIS - QUANTITATIVE *(PLS)*

- Quantification requires minimal number of calibration and validation samples
- Concentration profile of different components with time can be tracked

Thanks to IGCW & DRL team members (Srividya R, Suhas Jawalekar, Bairi Sai Vasistha)