EVALUATION OF RAMAN, MID-IR, AND NEAR-IR SPECTROSCOPIES FOR IN-LINE MONITORING OF AN API SYNTHESIS STEP TO REPLACE HPLC

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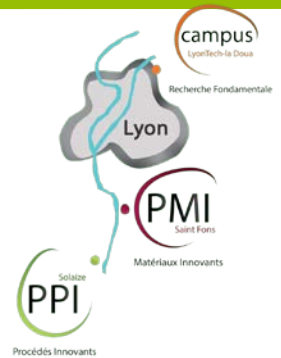
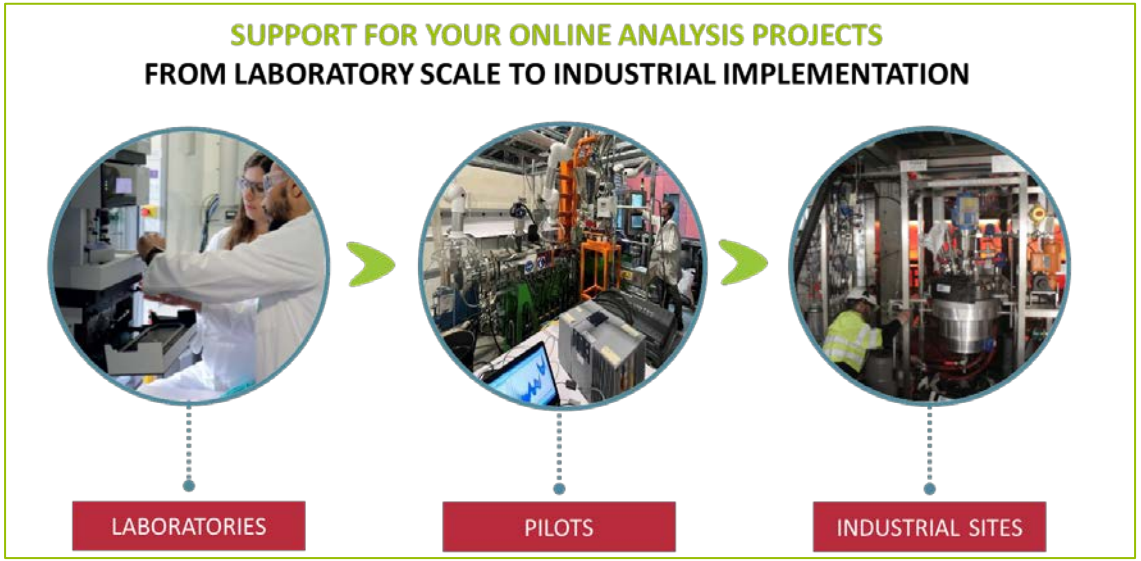
AXEL'ONE INNOVATIVE PROCESSES PLATFORM – PPI

- Axel'One is a **collaborative innovation platform** created in 2011.
- Its innovative proposals help **chemistry industries** to reduce costs, risks and environmental impact.
- It develops **innovative projects** mainly focused on:
  - Catalysis and energy efficiency,
  - Advanced and bio-sourced materials
  - Optimized intelligent processes



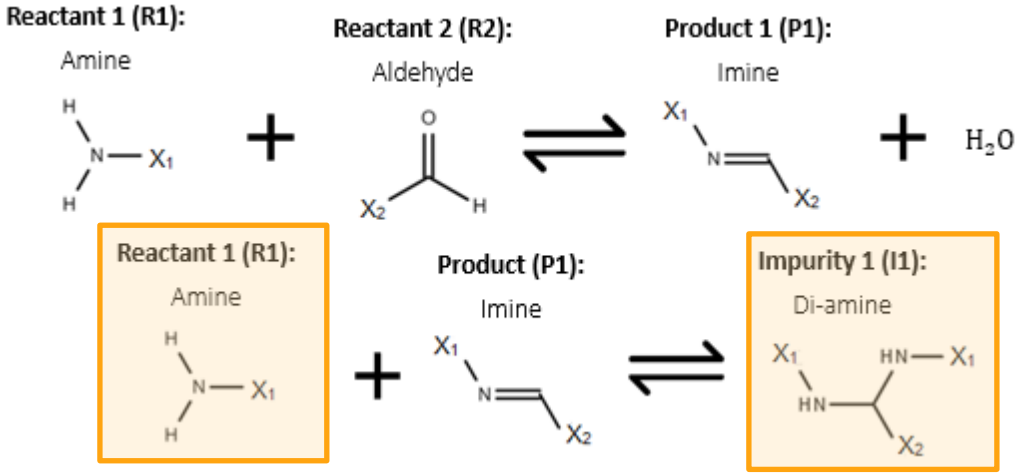
Axel'One ANALYSIS



SERVIER GROUP AND ORIL INDUSTRIE

- **Servier** is the 34th largest pharmaceutical group worldwide and the **2nd in France.**
- **Oril Industrie** manufactures almost **98% of Servier's API** (Active Principal Ingredients), with nearly 2000 tons per year.
- 60 Years of production and **20 APIs** produced and distributed.
- Oril Industrie represents **10% of French pharmaceutical chemistry** and reports a 10% investment in safety and the environment.

SYNTHESIS STEP

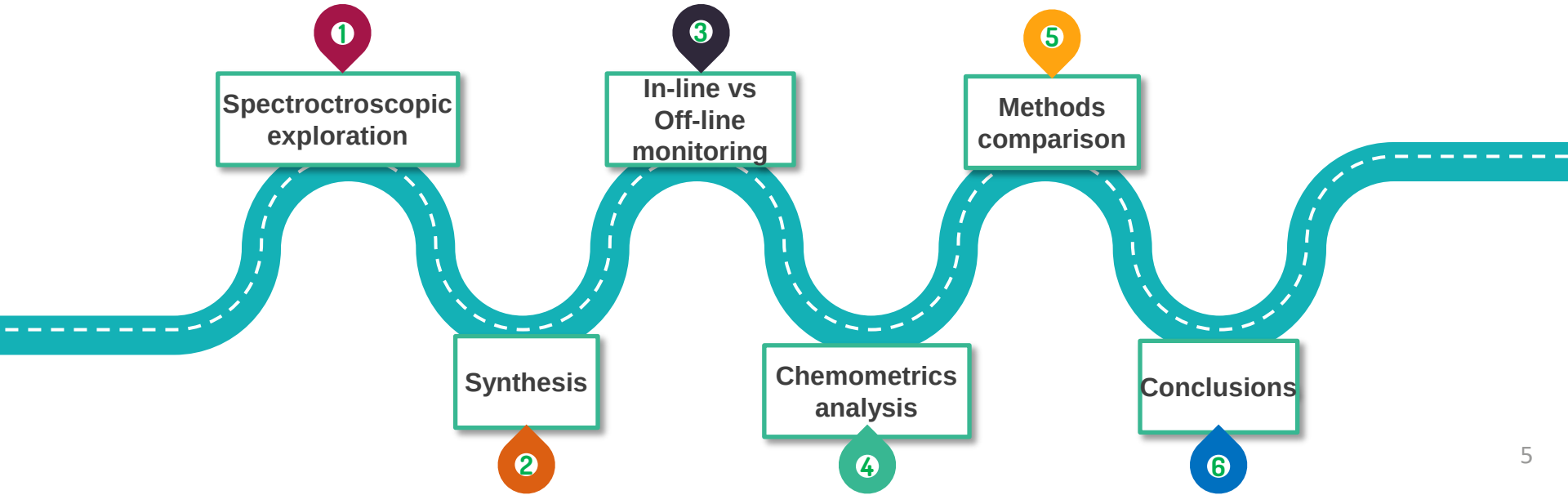


Oril Industrie reports the monitored **R1+I1%** at the end of this synthesis step

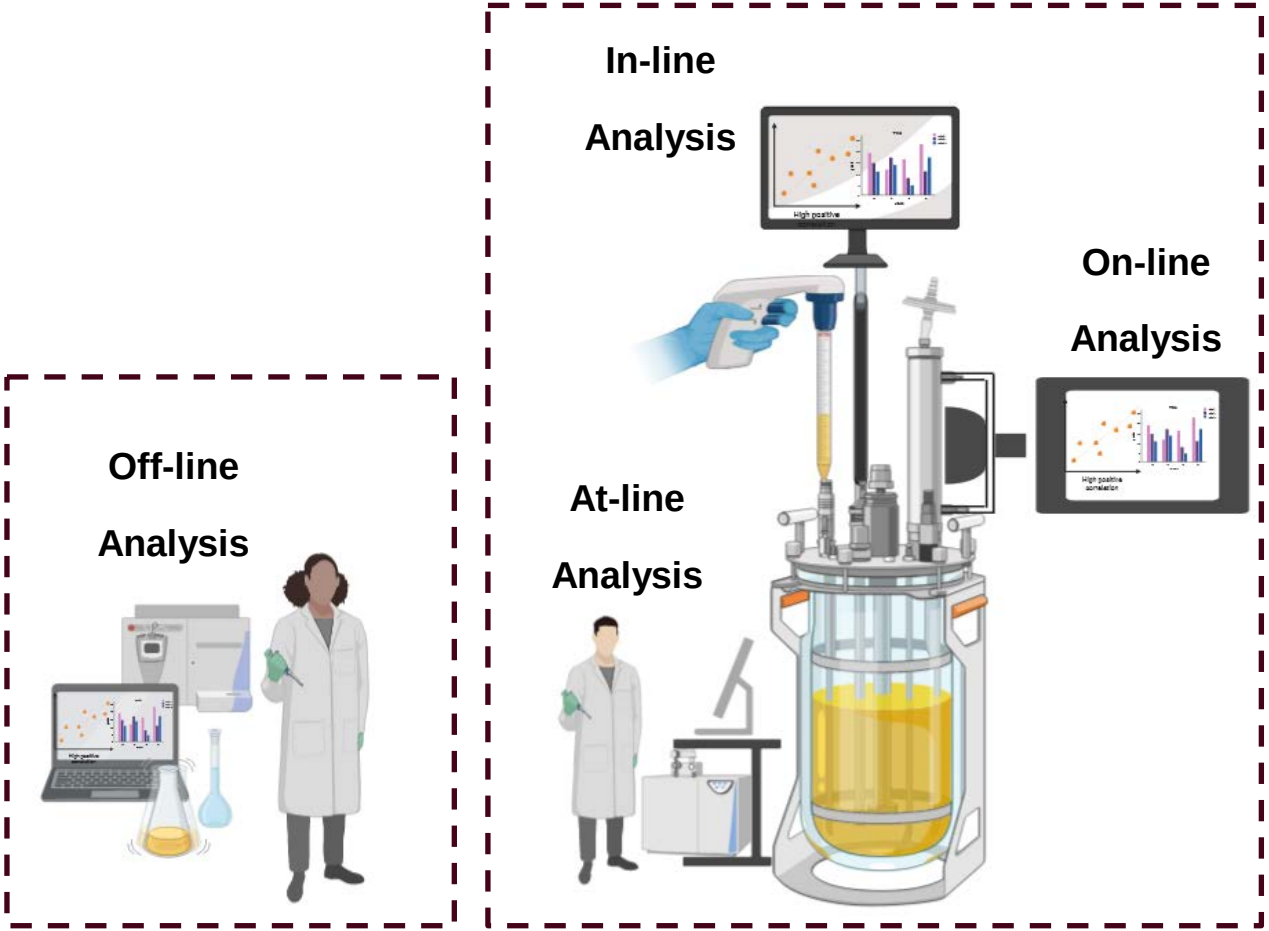
- **Spectroscopic In-line monitoring** to replace off-line HPLC.
- **Sampling** must be done between **65-85°C to avoid crystallization**.
- The sample contains components with harmful effects.

OBJECTIVE

Define between **Raman**, **MIR**, and **NIR**, **the most suitable** spectroscopic technique **to in-line monitor** that the **concentration of R1+I1 at the end of the synthesis step is lower than 2.0%**, with an expanded absolute **uncertainty lower than 0.05% (k=2)**.

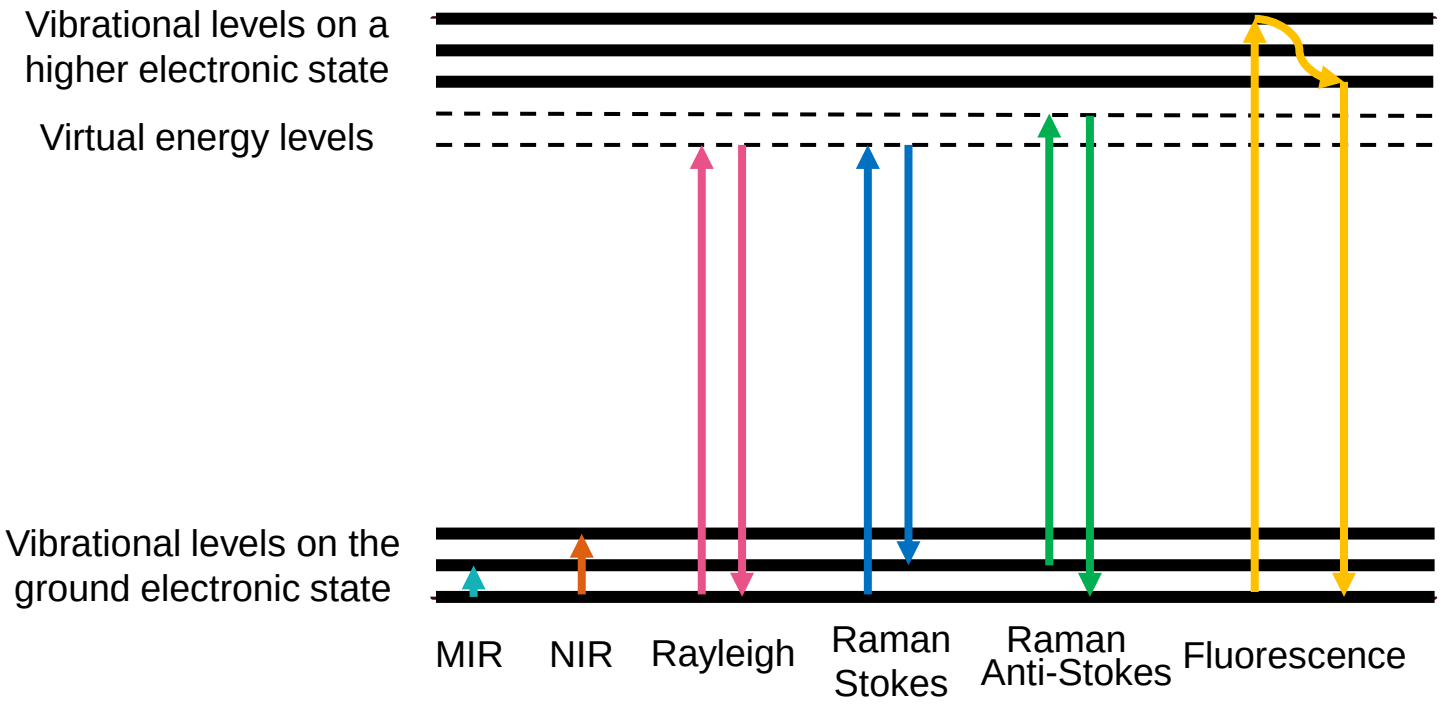


IN-REAL TIME ANALYSIS

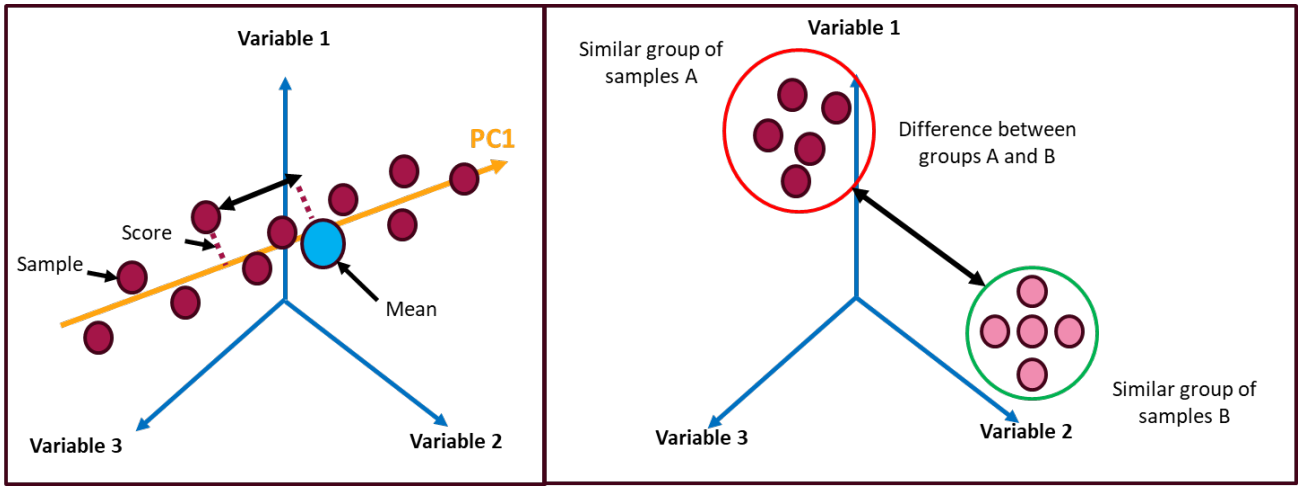


- **Optimize** the process and product quality.
- **Impact less** on the thermodynamics of the process.
- **Better representativity** in the analysis.

VIBRATIONAL SPECTROSCOPY

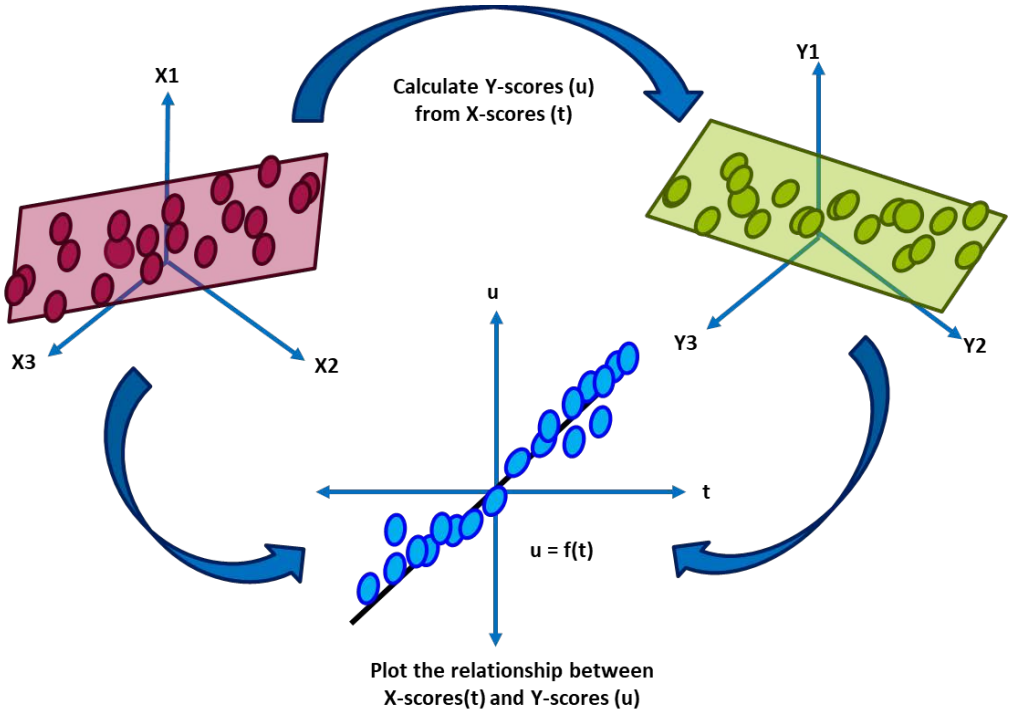


PRINCIPAL COMPONENT ANALYSIS (PCA)



- Linear combination (**projection of latent variables (PCs)**) of the information content in the initial variables about the variations between samples
- **Information about variance between samples** is condensed.
- Exploration of similitudes and differences between samples.

PARTIAL LEAST SQUARES REGRESSION (PLS)



- **Regression algorithm** that models X data according to Y data.
- Projection of variables in X that best predict Y.
- **Maximizing covariance between X and Y**.
- The RMSE represents the residual variance for individual responses.
- **RMSEP is a measure of the average uncertainty** that can be expected when predicting Y **for new samples.**

RMSE (Root Mean Square Error). RMSEC (RMSE of Calibration). RMSEV (RMSE of Validation). RMSEP (RMSE of Prediction)

METHODOLOGY

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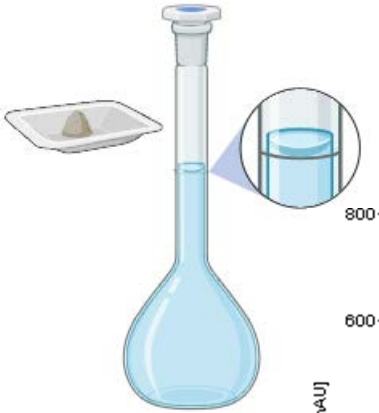
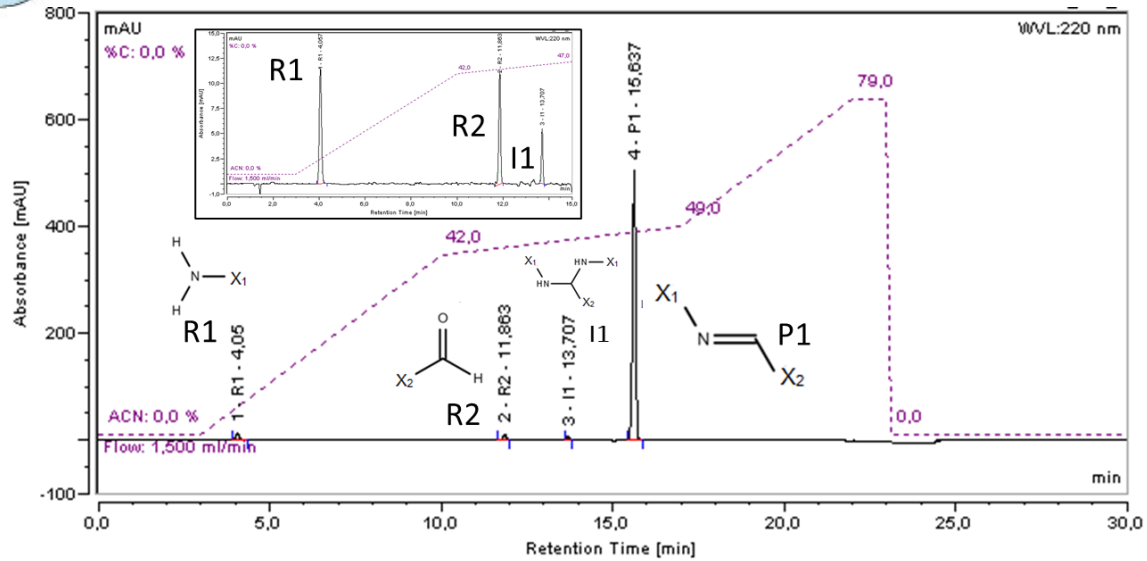
Thermo Ultimate 3000 (DAD)



Parameter	Specification
System	Reverse phase gradient
Column	RP18 (4.6x150 mm, 3.5 µm)
Mobile phase A (MPA)	Buffer/Acetonitrile 95/5
Mobile phase B (MPB)	Acetonitrile
Diluent	MPA/MPB 21/79
Analysis time	29 min

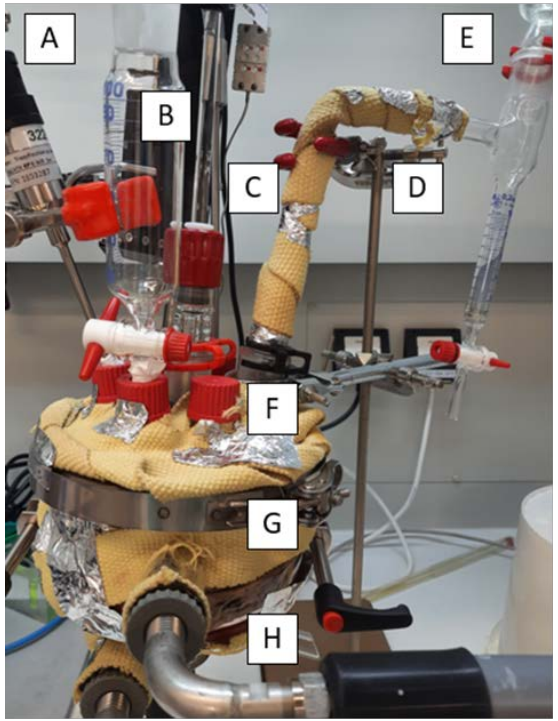


SPECTROSCOPIC IN-LINE MONITORING

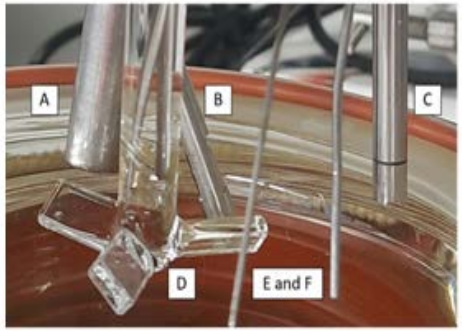
Raman (Viserion-Indatech)	MIR (MB3000-ABB)	NIR (Matrix F-Bruker)
		
300-3300 cm^{-1} (laser 785 nm, 500mW)	530-2000 cm^{-1}	4000-12000 cm^{-1}
4 cm^{-1} resolution	4 cm^{-1} resolution	4 cm^{-1} resolution
0.5 mm focal distance	ATR (diamond)	Optical path of 2 mm
Integration time 20 seconds 3 scans per spectrum	22 scans (Approx. 1 min per spectrum)	60 scans (Approx. 1 min per spectrum)

ATR (Attenuated Total Reflectance)

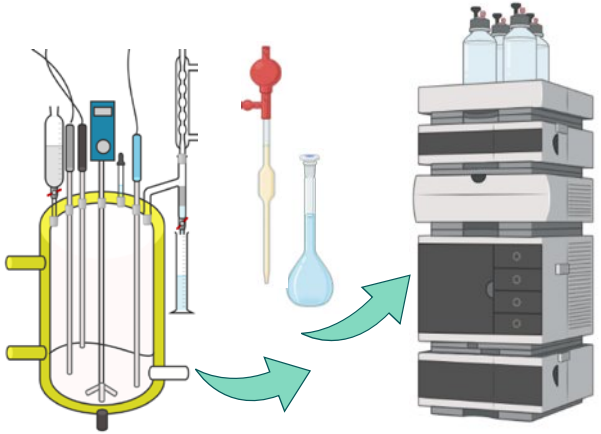
THE SET UP



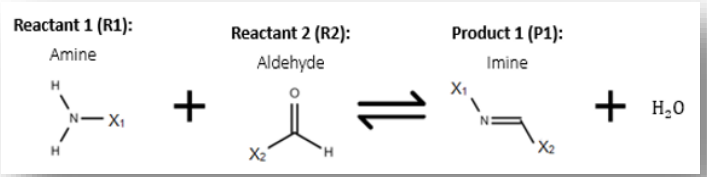
A. Probes in the rear openings
B. Dropping funnel for liquids addition
C. Agitator in the central opening
D. Dean-Stark head
E. Connection to the condensation system
F. Frontal opening for solids addition and sampling
G. Reactor
H. Connection to thermal regulation

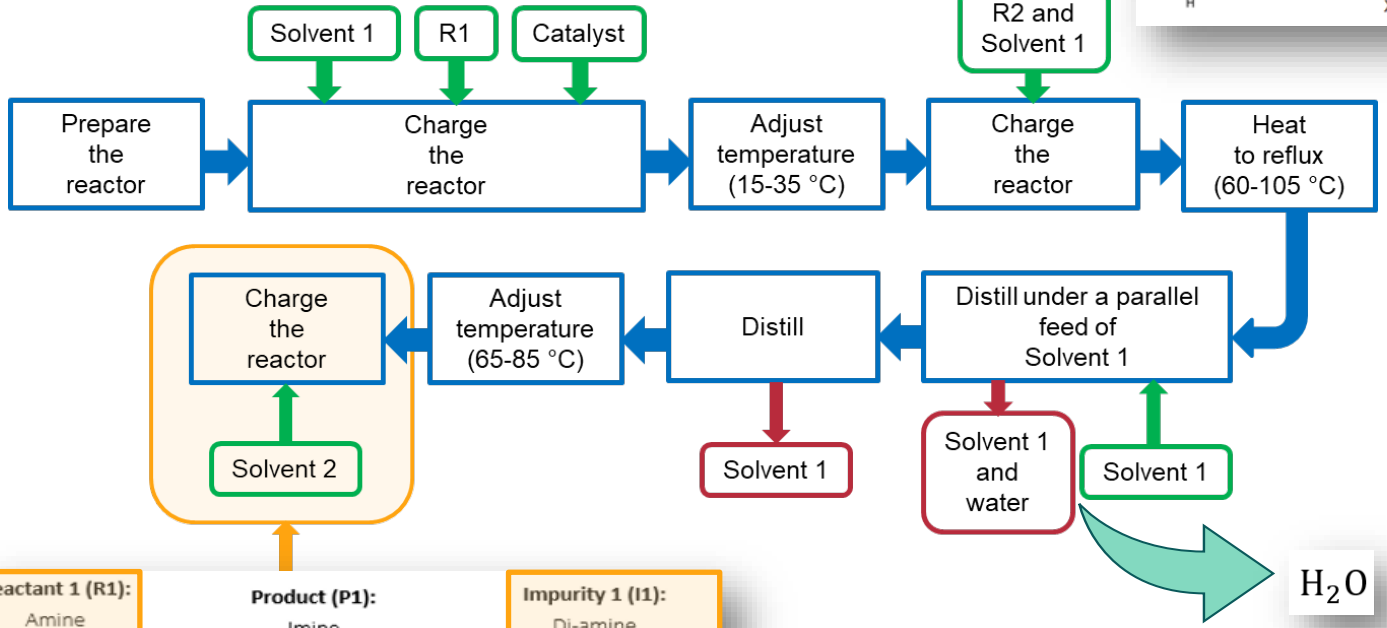


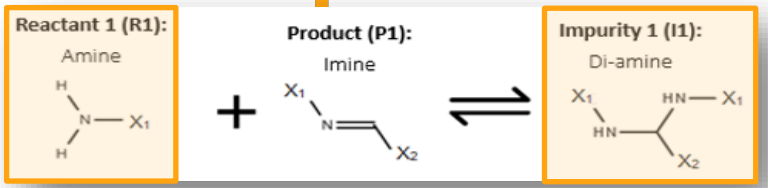
A. Raman probe
B. NIR probe
C. Agitator (150 rpm)
D. E and F temperature probes



SYNTHESIS STEP

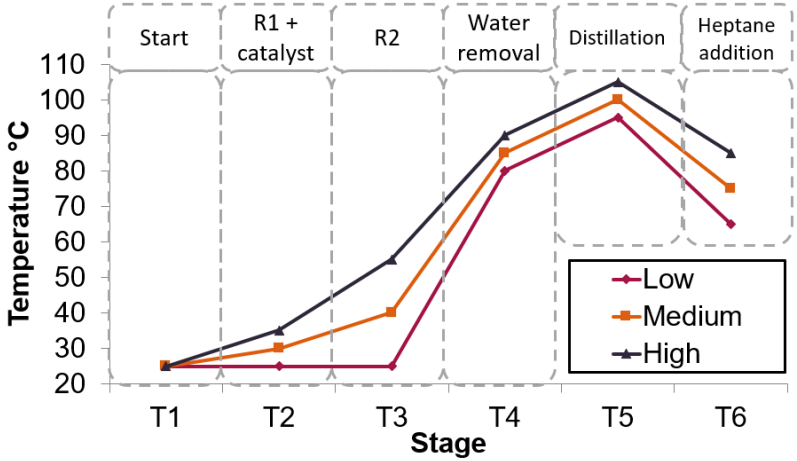






SYNTHESIS REPLICATES

Synthesis	Temperature	Reactants ratio
S01	0 – Medium	+1 – High concentration R1
S02	0 – Medium	0 – Industrial conditions
S03	+1 – High	0 – Industrial conditions
S04	-1 – Low	+1 – High concentration R1
S05	-1 – Low	0 – Industrial conditions
S06	0 – Medium	0 – Industrial conditions
S07	+1 – High	+1 – High concentration R1
S08	0 – Medium	0 – Industrial conditions



- Industrial conditions ratio:
  - R1/R2= 0.66
- High concentration R1:
  - R1/R2= 0.68 to 0.85

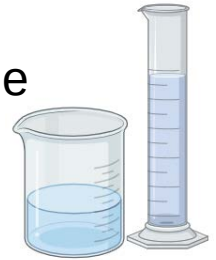
SYNTHESIS REPLICATES

Synthesis	Temperature	Reactants ratio
S01	0 – Medium	+1 – High concentration R1
S02	0 – Medium	0 – Industrial conditions
S03	+1 – High	0 – Industrial conditions
S04	-1 – Low	+1 – High concentration R1
S05	-1 – Low	0 – Industrial conditions
S06	0 – Medium	0 – Industrial conditions
S07	+1 – High	+1 – High concentration R1
S08	0 – Medium	0 – Industrial conditions

Additional experiments

- **Spiking**
  - R1
  - P1
  - Water

- **Dilution**
  - Heptane



- **Aging**
  - Minutes to hours

RESULTS

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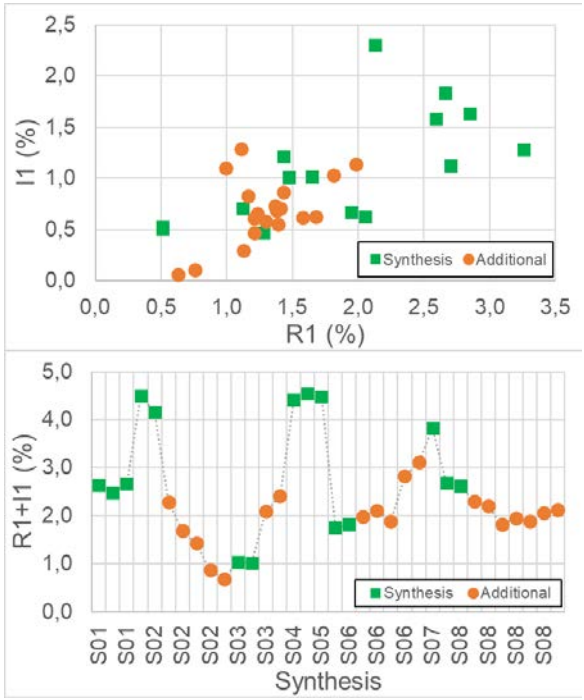
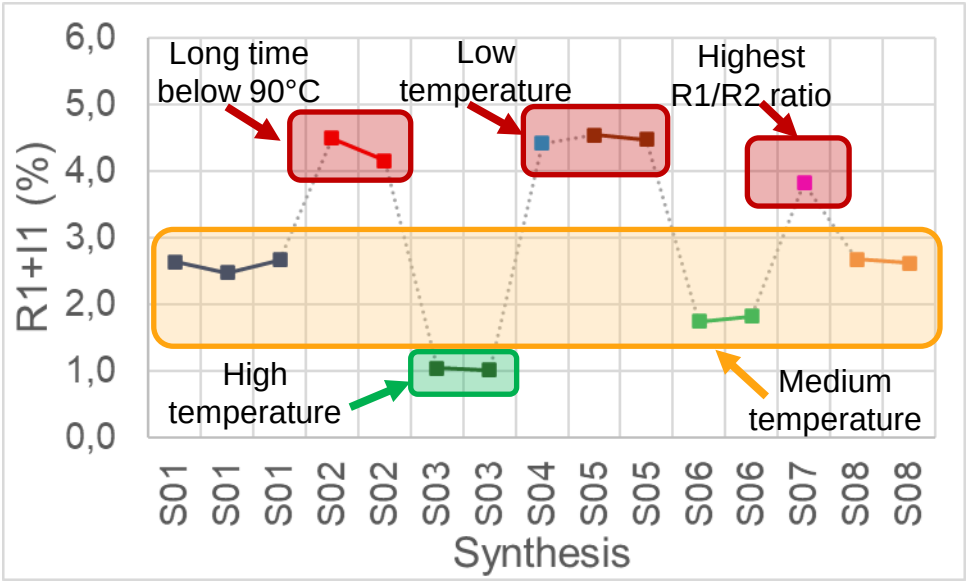
HPLC QUANTIFICATION

- **15 Samples** from the syntheses.
- **19 Samples** from additional experiments.

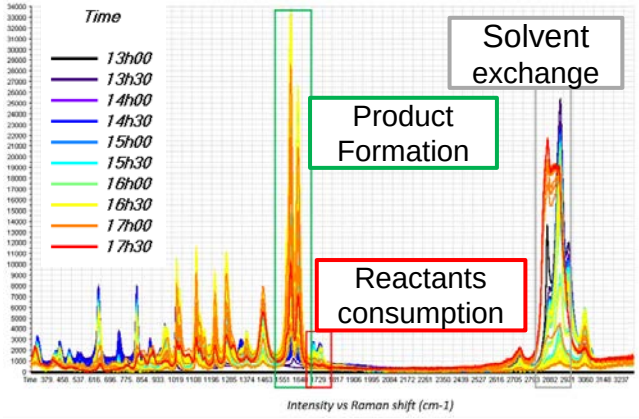




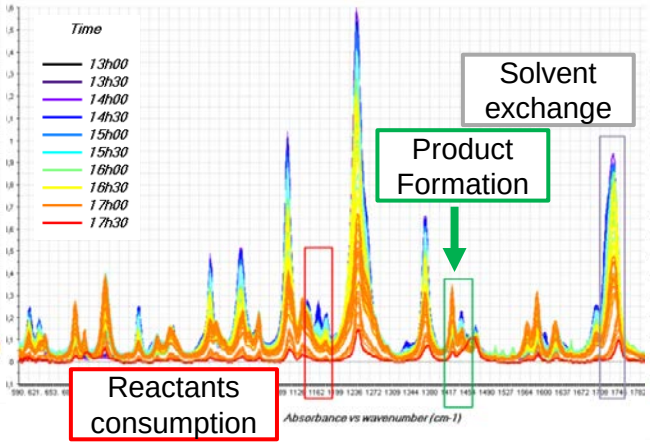
HPLC control	Number of data (n)	Mean (%)	Standard Deviation (%)	Expanded uncertainty (K=2) (%)
R1+I1	52	1.53	0.23	0.45

PROCESS MONITORING

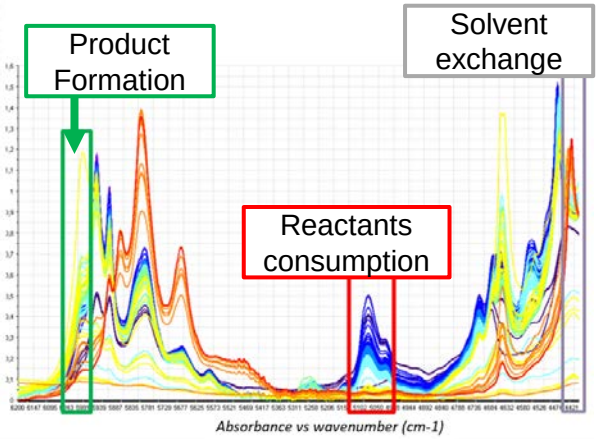
Raman

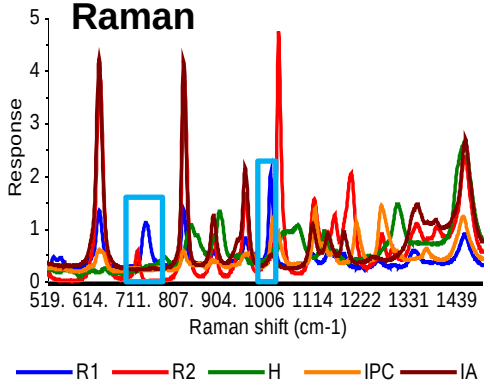


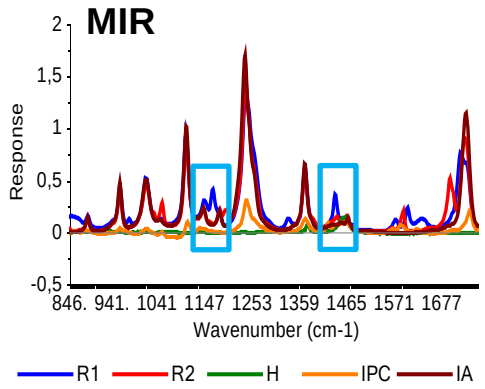
MIR

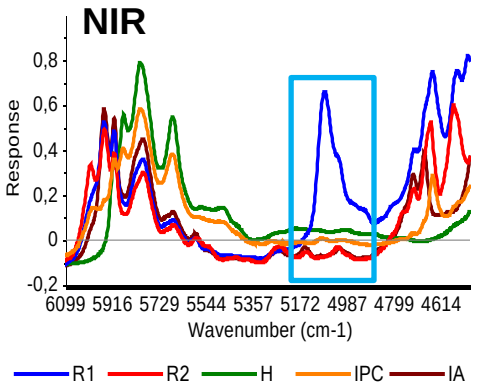


NIR

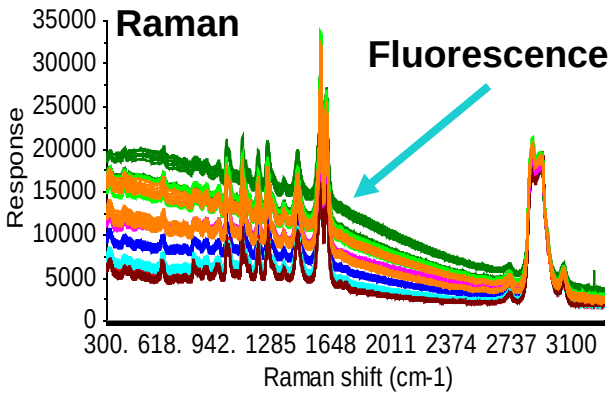


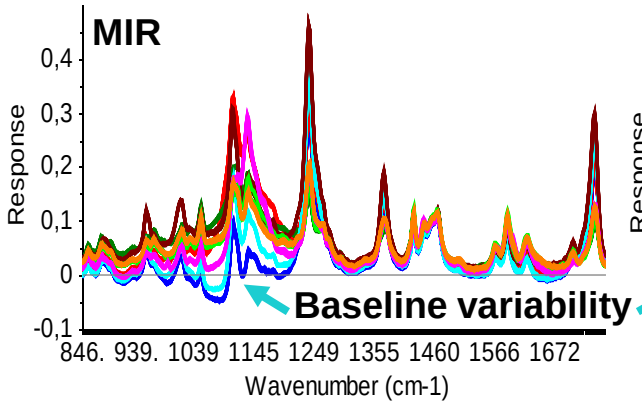


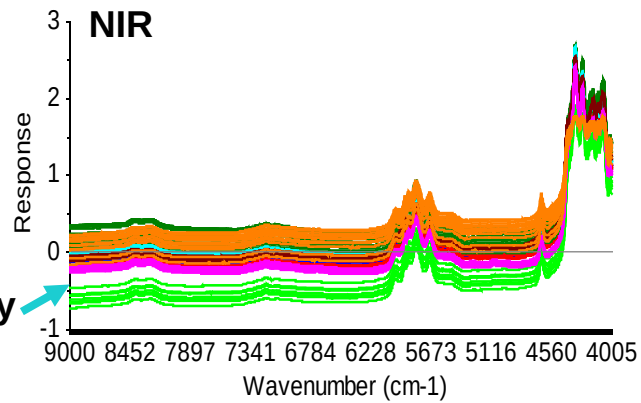


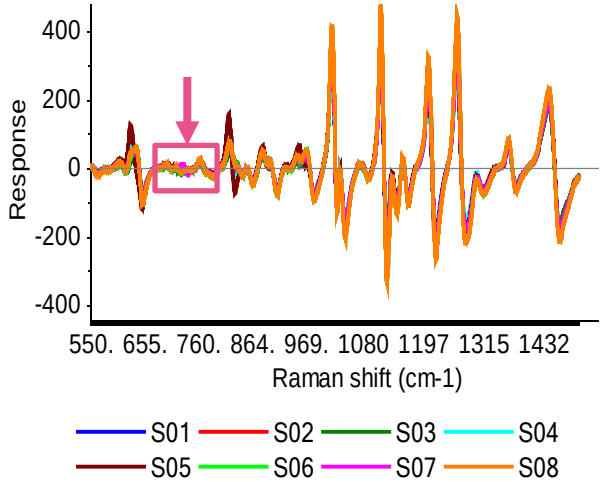


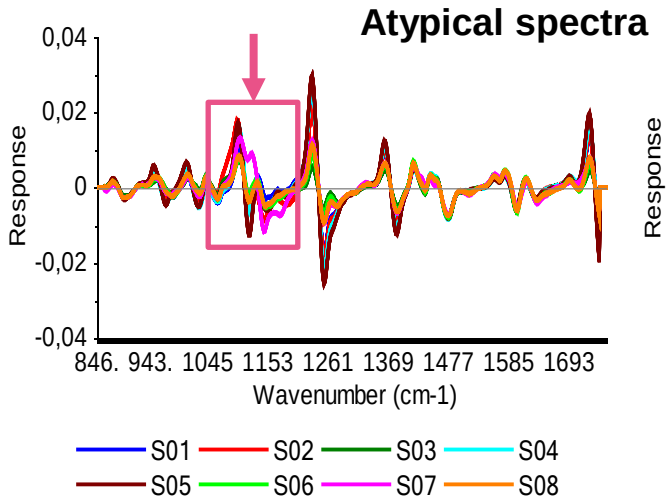
DATA PRE-TREATMENT

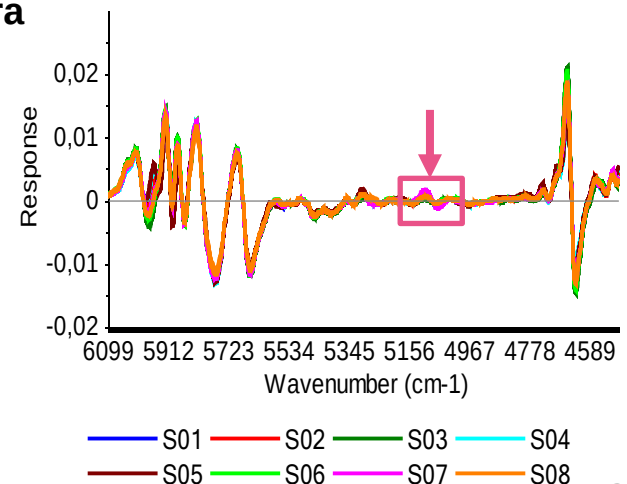






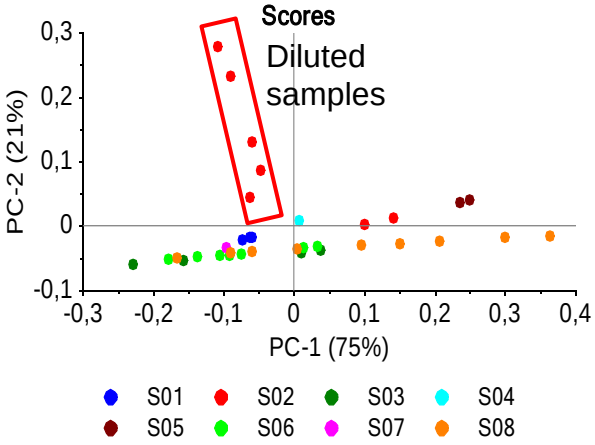




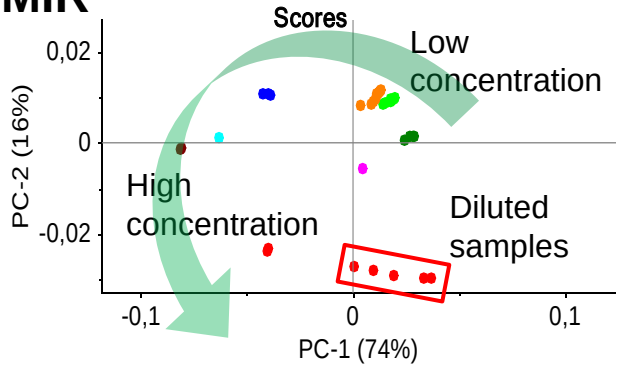


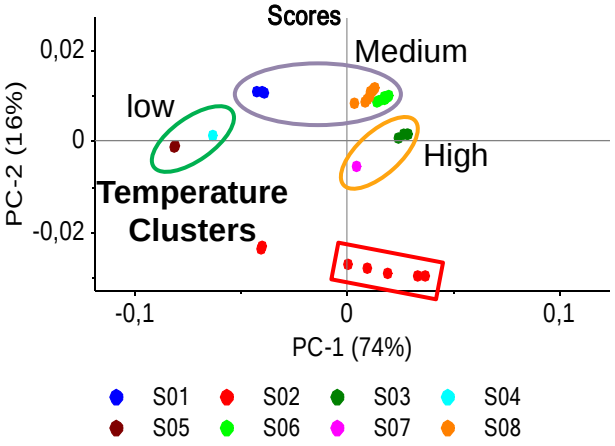
PCA EXPLORATION

Raman

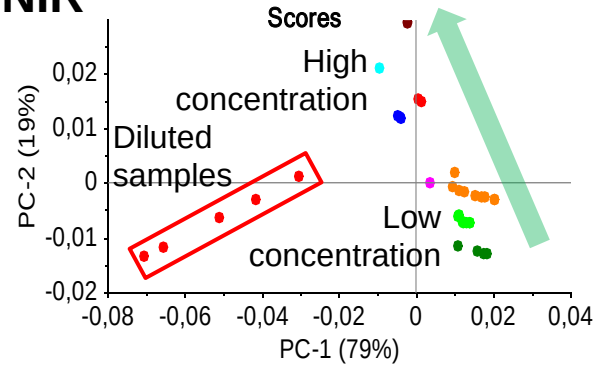


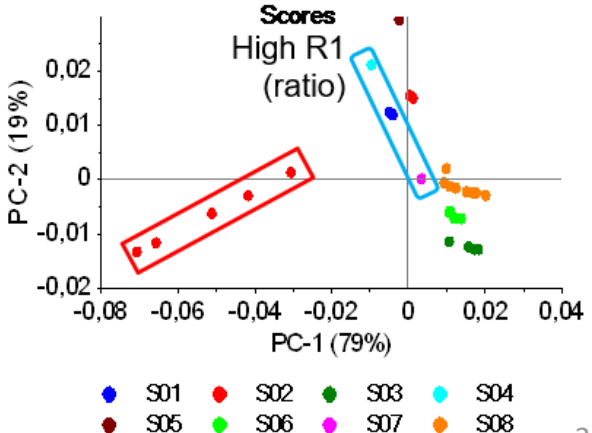
MIR





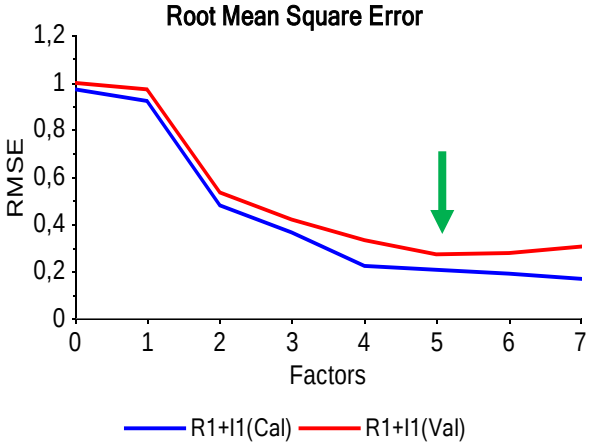
NIR

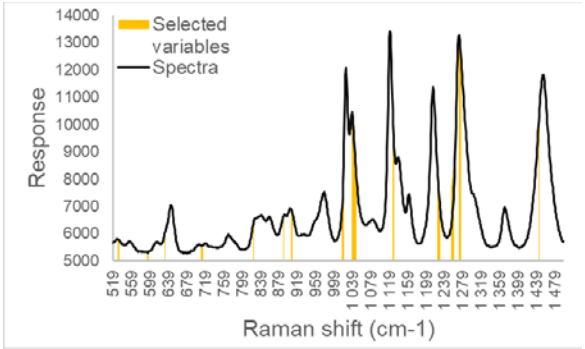




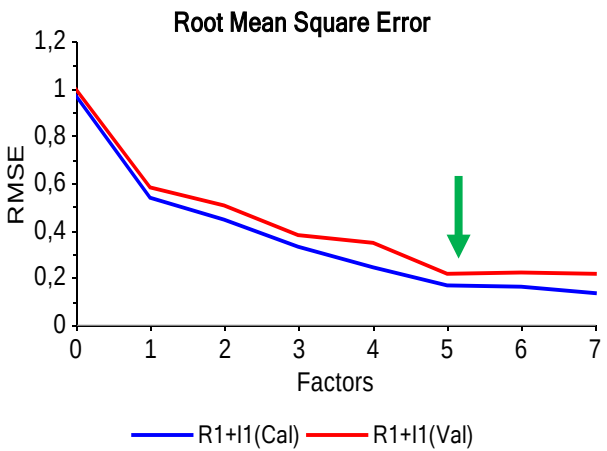
PLS ANALYSIS

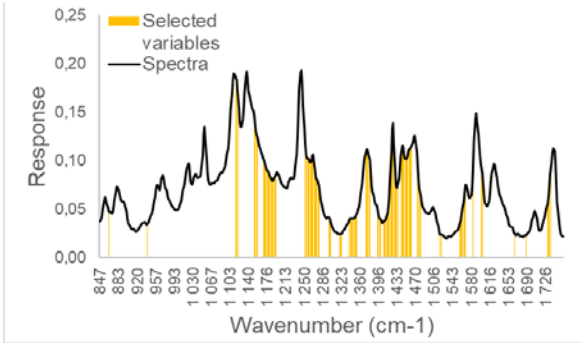
Raman



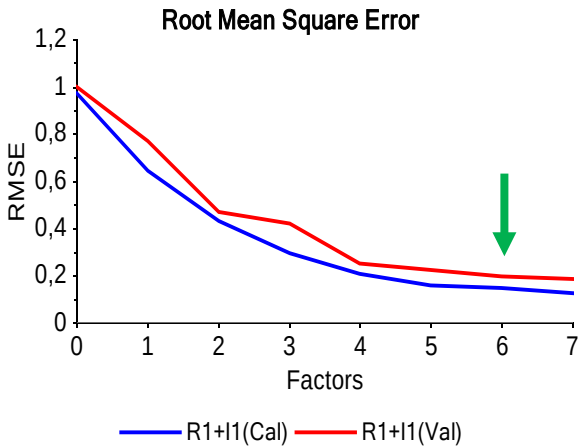


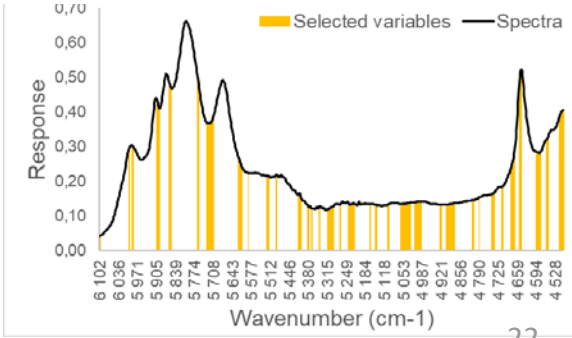
MIR





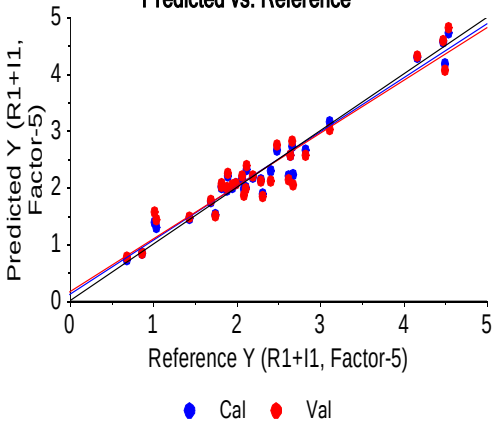
NIR



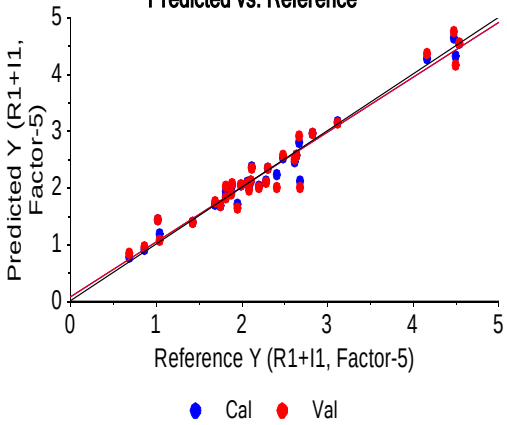


SPECTROSCOPIC QUANTIFICATION MODELS

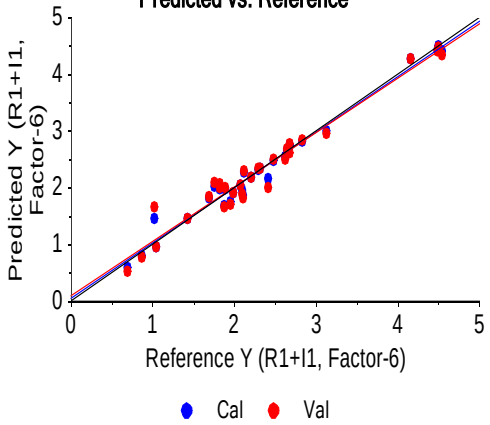
Raman



MIR

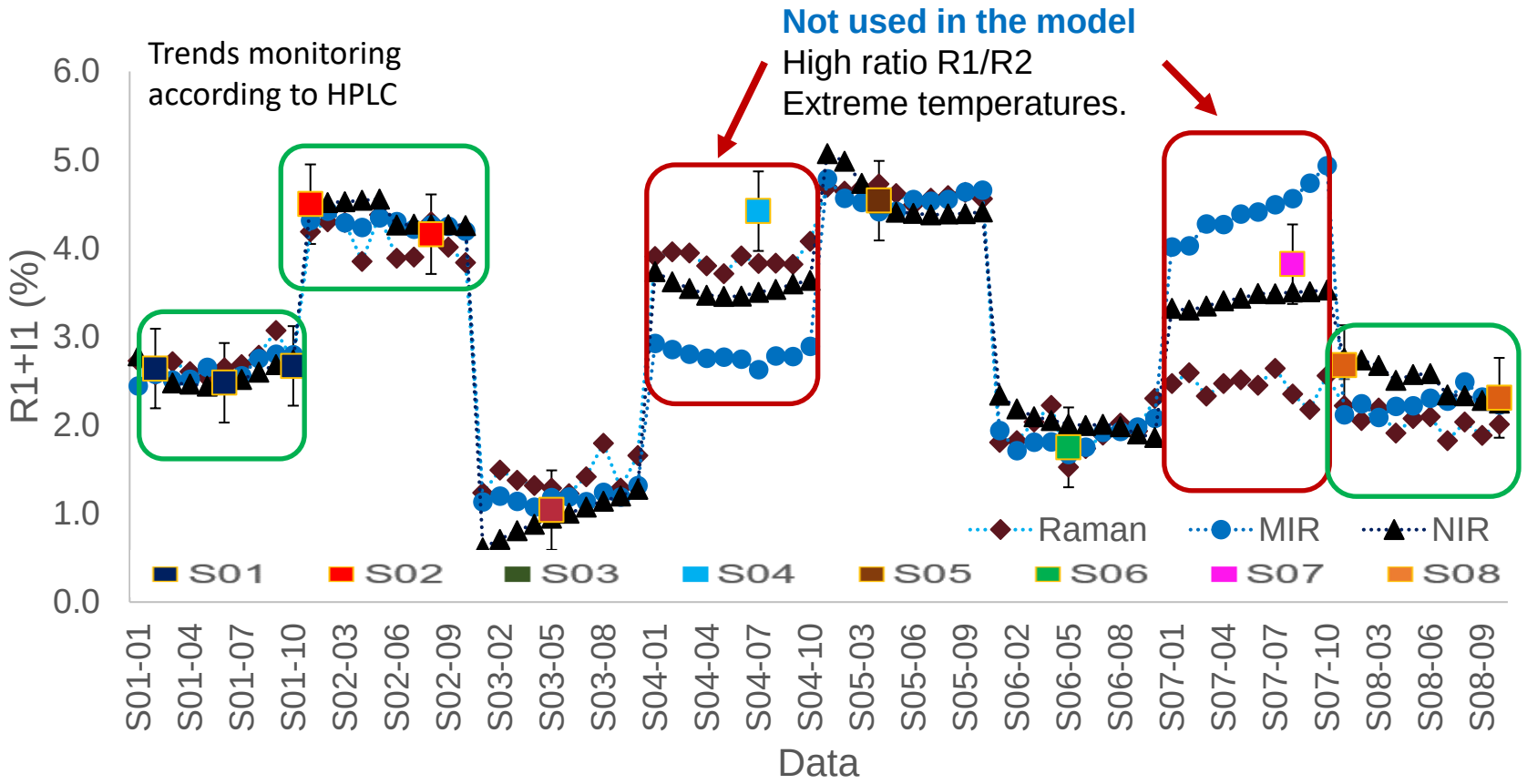


NIR



Parameter	Raman		MIR		NIR	
Set	Cal.	Val.	Cal.	Val.	Cal.	Val.
R^2	0.96	0.93	0.97	0.95	0.98	0.96
Slope	0.96	0.93	0.97	0.97	0.98	0.96
Offset (%)	0.10	0.16	0.07	0.07	0.05	0.08
RMSE (%)	0.20	0.27	0.17	0.22	0.14	0.20
Expanded Uncertainty (k=2) (%) (2xRMSEV)	0.54		0.44		0.40	

METHOD COMPARISON



CONCLUSIONS & PERSPECTIVES

Conclusions

- **Satisfactory models** for the 3 spectroscopic techniques **ranging from 0.7% to 4.5% of R1+I1**.
- **Raman, MIR, and NIR** models **equivalent to HPLC** in monitoring the final stage of the synthesis step with an **expanded uncertainty from 0.4 to 0.5%**.
- Raman results are more dispersed. **Raman implementation could be challenging** as **fluorescence and saturation were observed** in some spectra.
- **MIR and NIR were the most suitable** options for in-line monitoring under the evaluated conditions.

Perspectives

- Using the evaluated techniques for **in-line monitoring** at a higher level (pilot or production) would help **minimize risks and improve the representativity** of the results.
- **The quantification models could possibly be improved** by recalibrating using industrial data, reconsidering the variables to keep inside the model, and doing external validation.
- To select a definite technique, other parameters like **feasibility of implementation and costs should be considered**.

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