

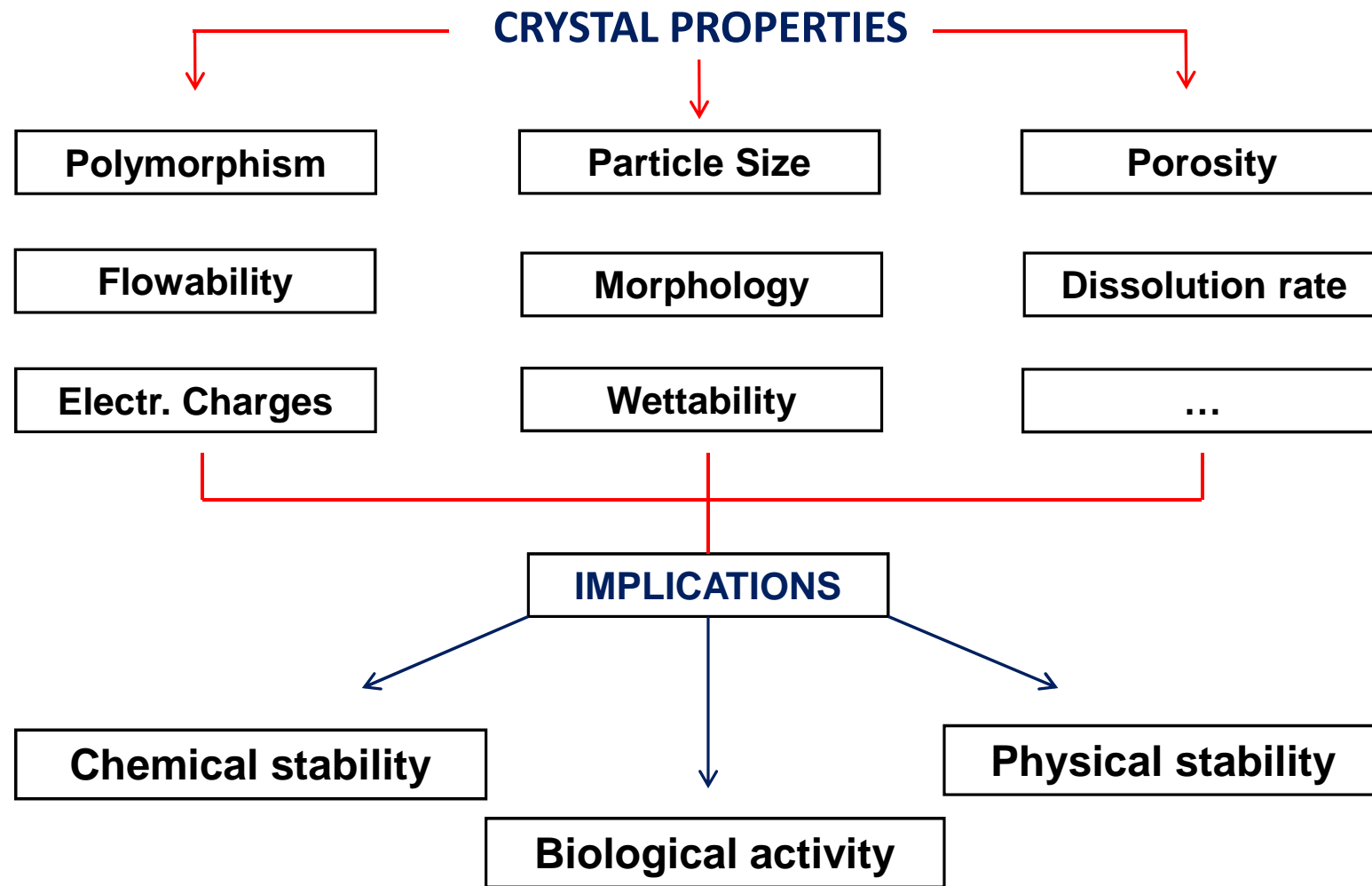


Crystallization Development Strategy in support to GMP compliance

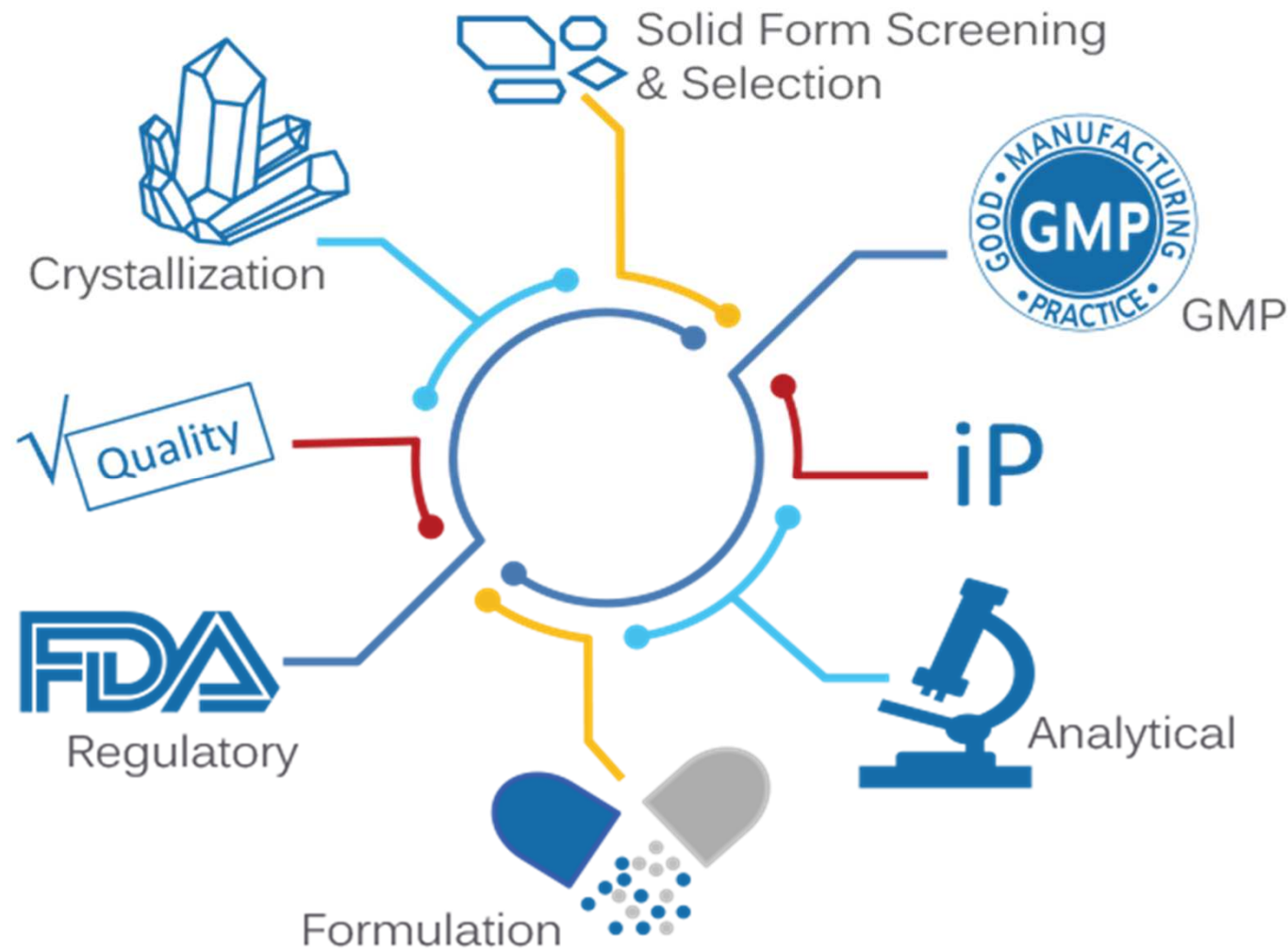
Marino Nebuloni

INTRODUCTION:

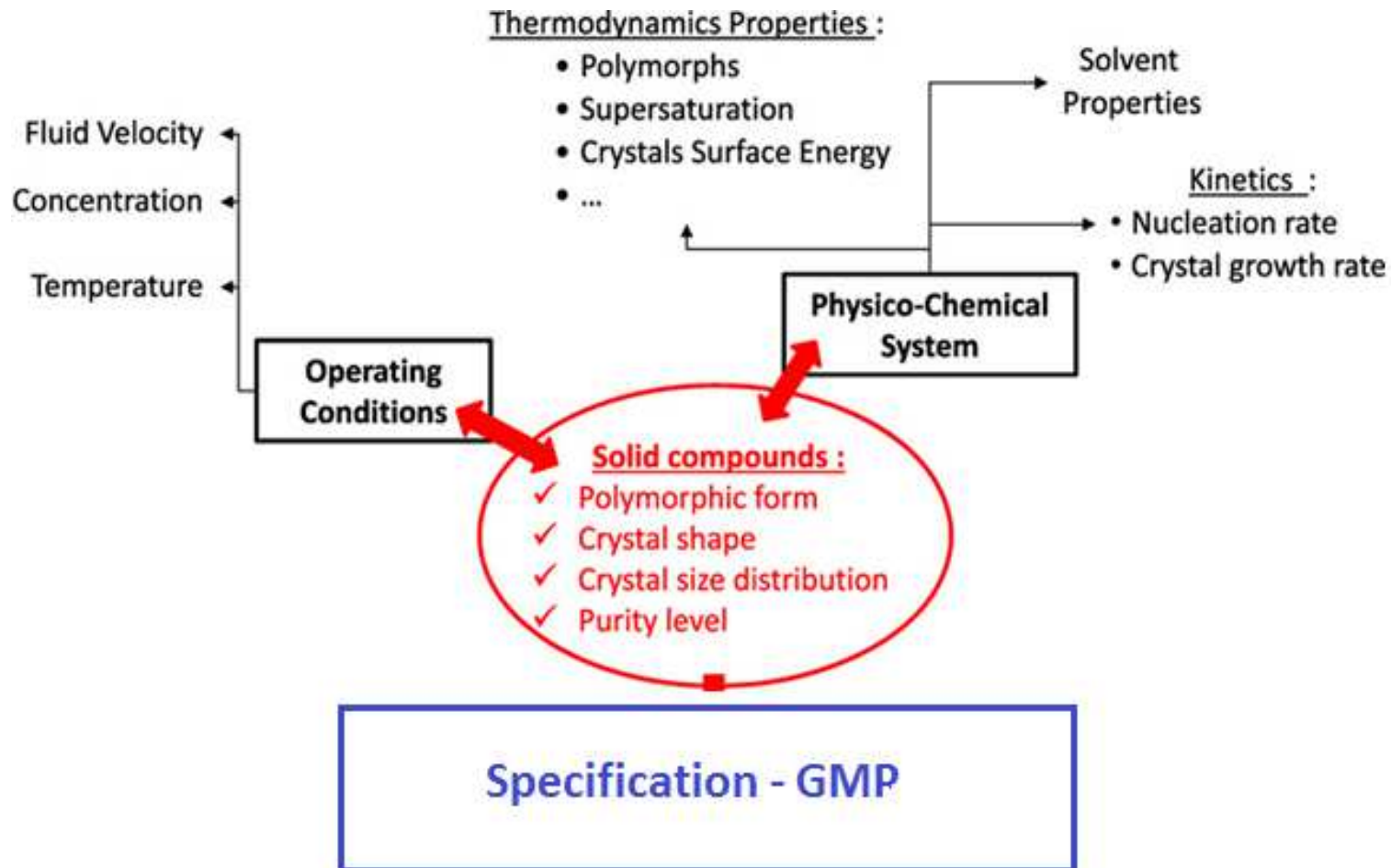
Solid state



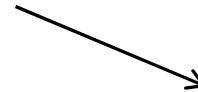
Crystallization- GMP - Regulatory



Physical parameters of solid in relation to the crystallization process



CRYSTAL PROPERTIES



Internal

Polimorphysm
Dissolution rate
Melting point
Adducts

...

External

Particle Size
Morphology
Porosity
Filtrability

...

INFLUENCE PARAMETERS ON CRYSTALLIZATION



Process Temperatures

Reagent Loading

Stirring

Equipment Material

Impurities

...

ANALYTICAL

ANALYTICAL CONTROL

ON-LINE

Particle Size (FBRM)

Calorimetry (RC1)

FT-IR/ATR

Raman

Turbidimetry

OFF-LINE

Particle Size (Laser Diffraction)

XRPD

SEM

Optical Microscopy



LIMITS

Long acquisition time

Process interaction during sampling

...

CRUCIAL POINTS TO BE DETERMINED FOR A ROBUST CRYSTALLIZATION:

Definition of:

- ❖ MSZW: Solubility/Concentration vs Temperature
- ❖ **Kinetics Parameters**
- ❖ **Process Parameters: Temperature profiles, Time, Cycling experimental profiles**
- ❖ **Validation method for quantitative assessment as per specifications**

MSZW: META-STABLE ZONE WIDTH

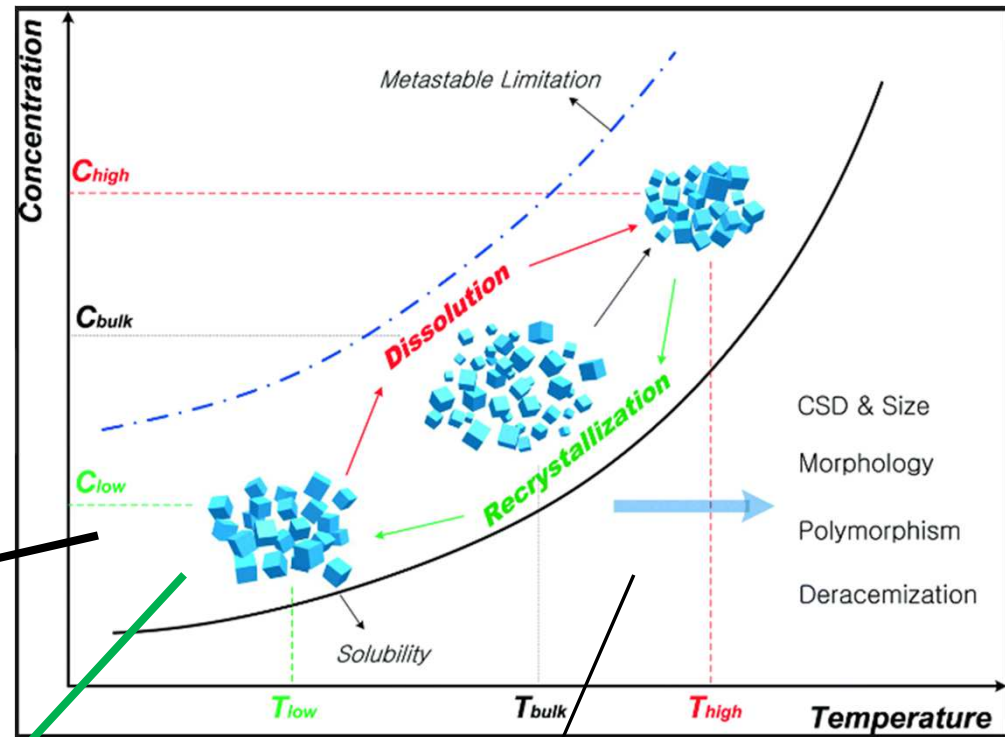
Understanding phase equilibria is crucial in crystallization operation

LABILE:

Spontaneous Crystallization

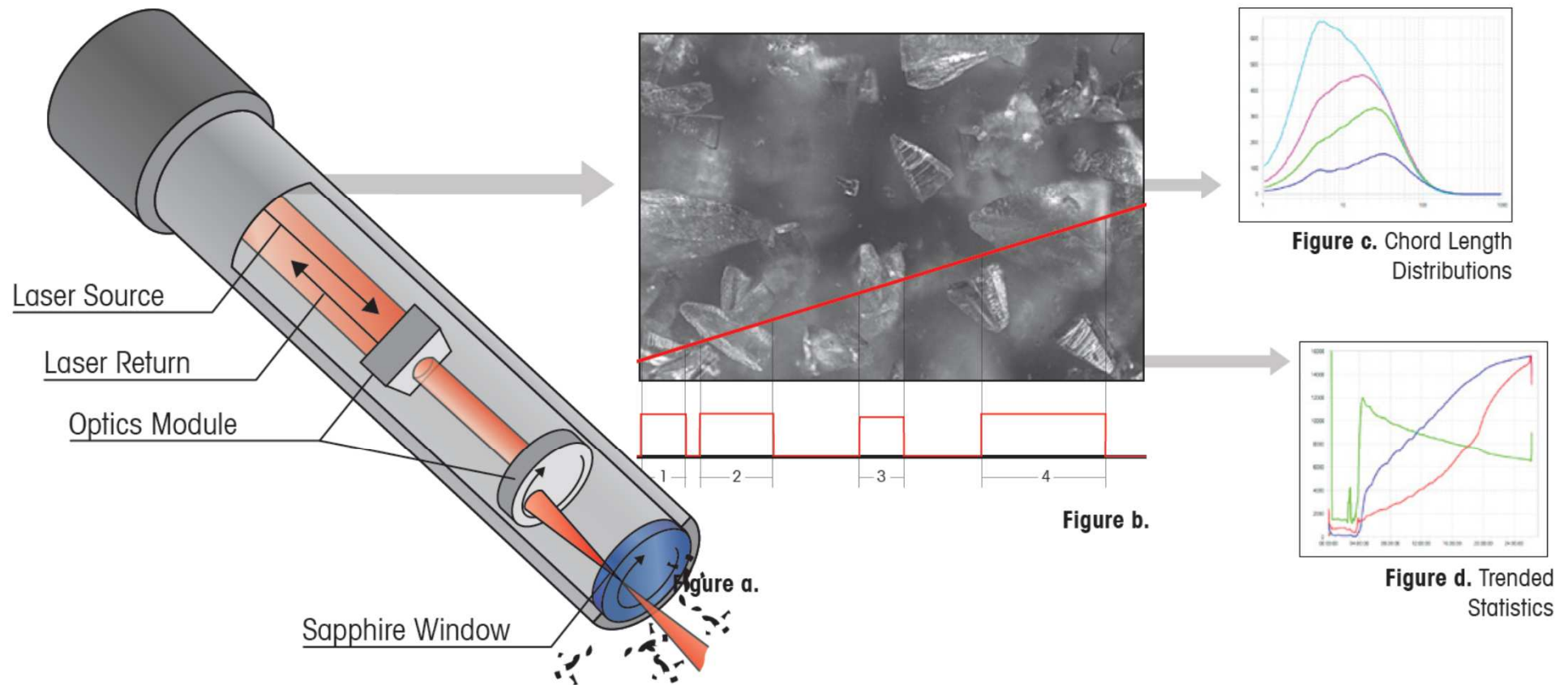
SUPERSATURATED (METASTABLE):
Crystal Growth

UNDERSATURATED: Crystal Dissolution

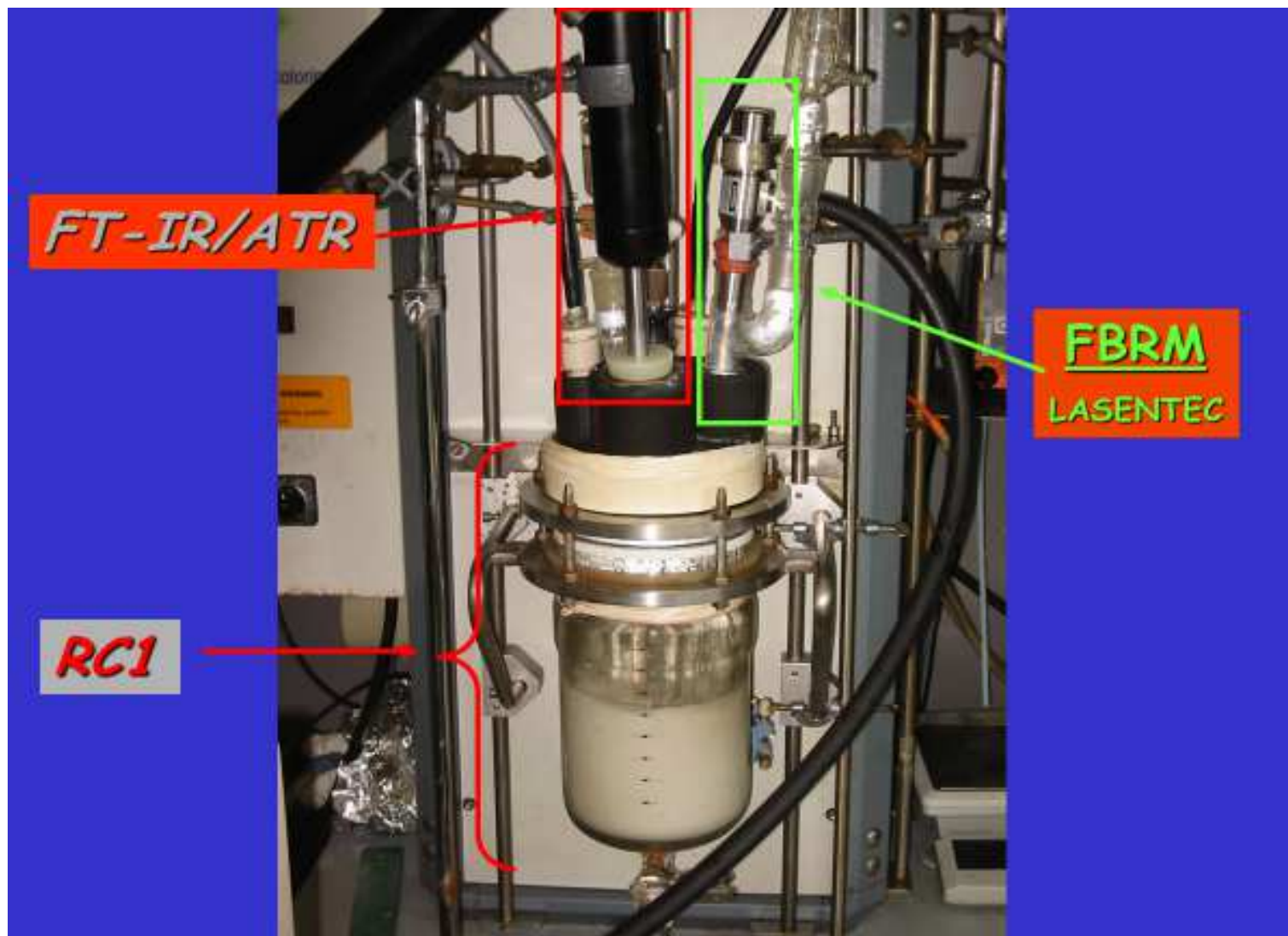


MSZW determination

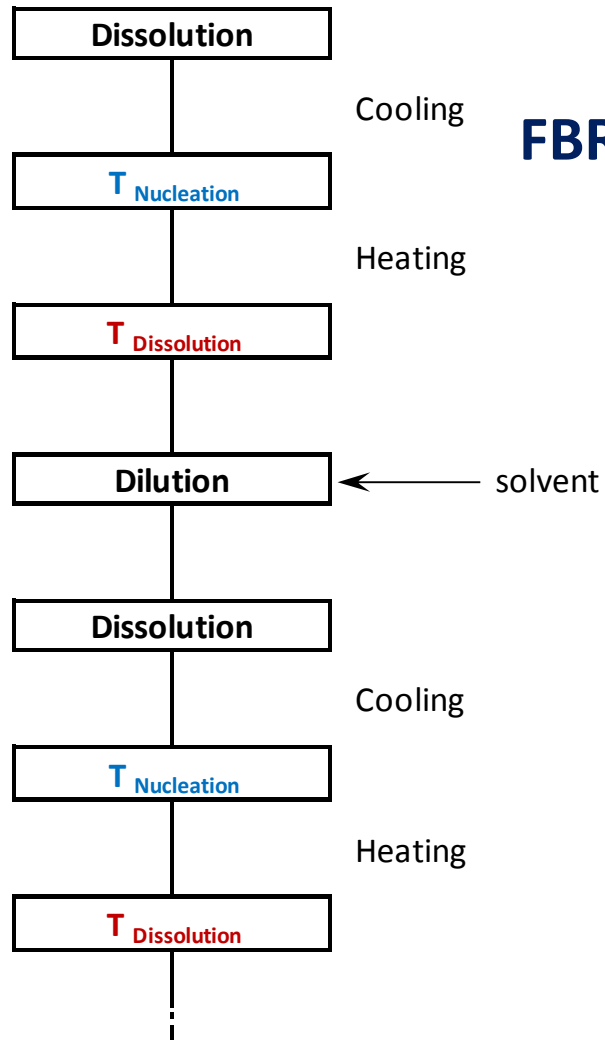
FBRM: FOCUSED BEAM REFLECTANCE MEASUREMENT



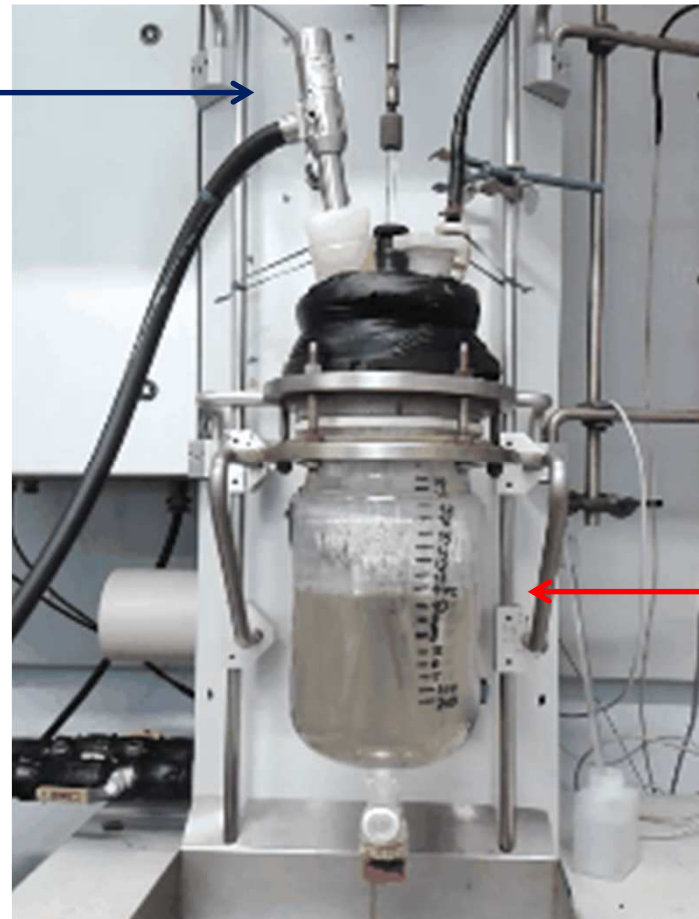
Temperature and Kinetic Control by Calorimetry



Test procedure by RC1 and FBRM techniques



FBRM



RC 1

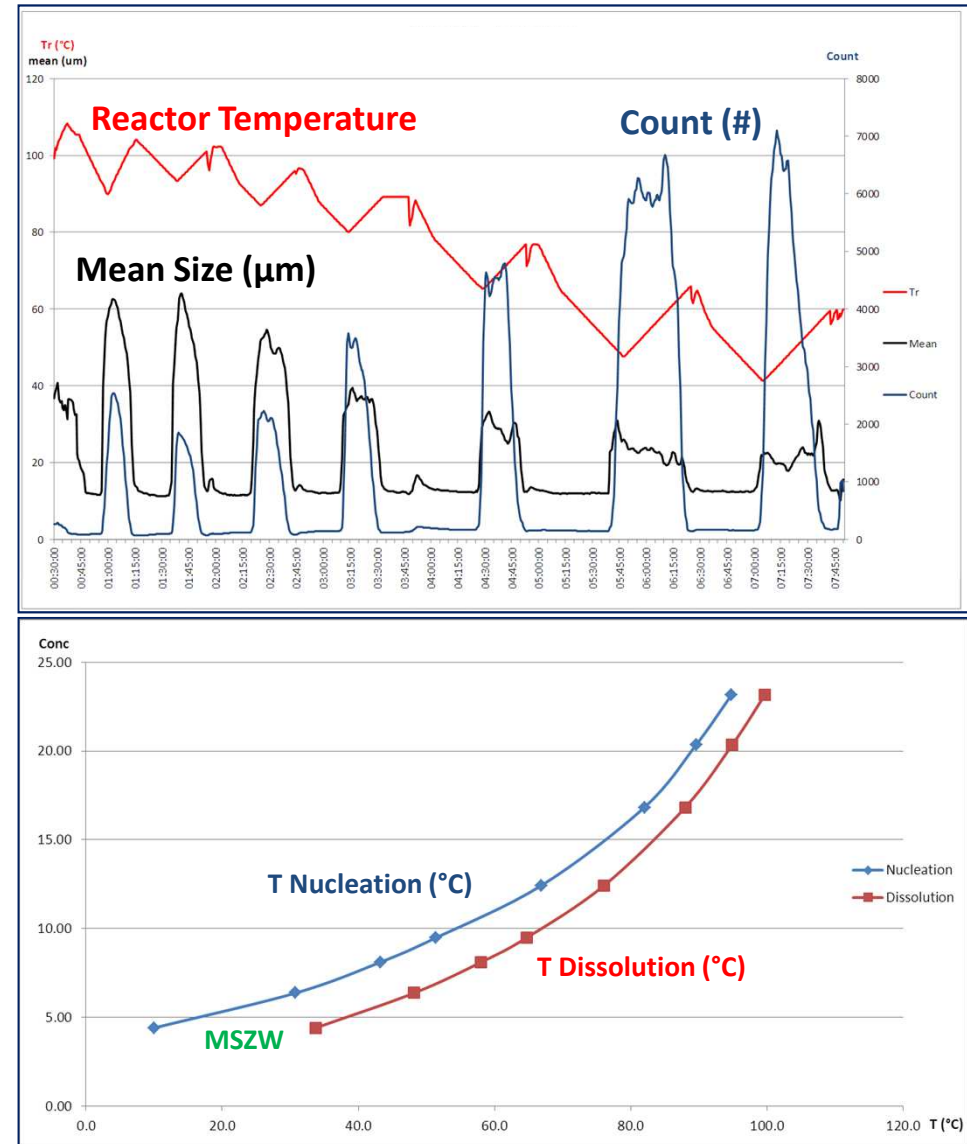
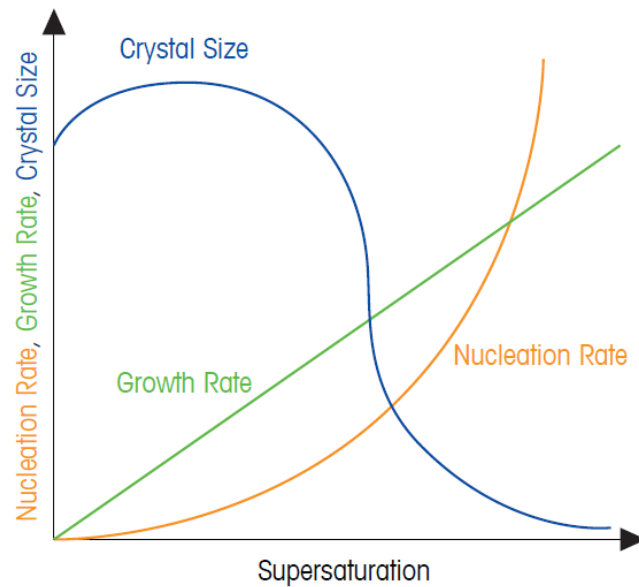
Definition of Kinetic parameters

NUCLEATION RATE:

$$B = k_b \Delta C^b$$

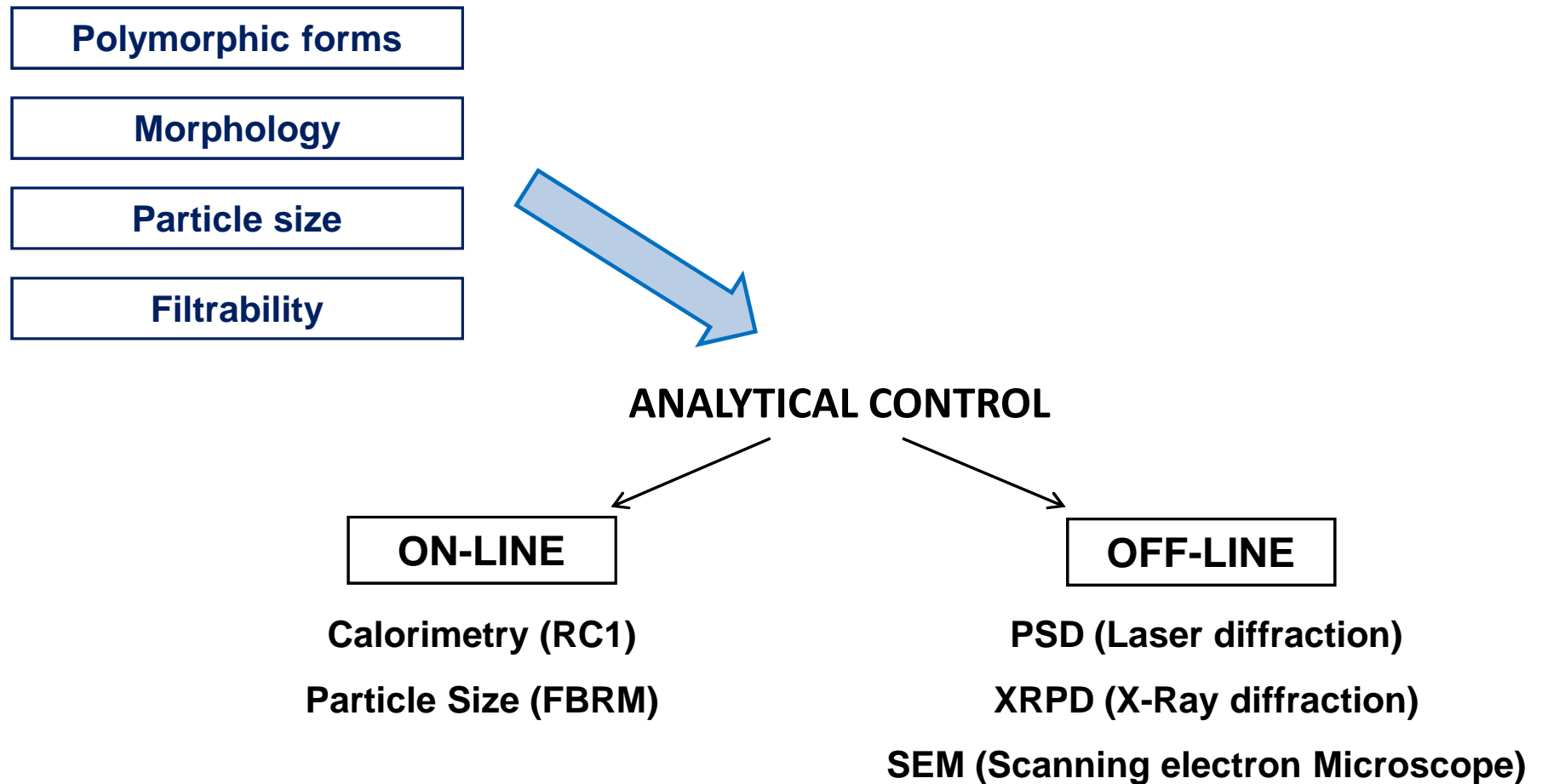
GROWTH RATE:

$$G = k_g \Delta C^g$$



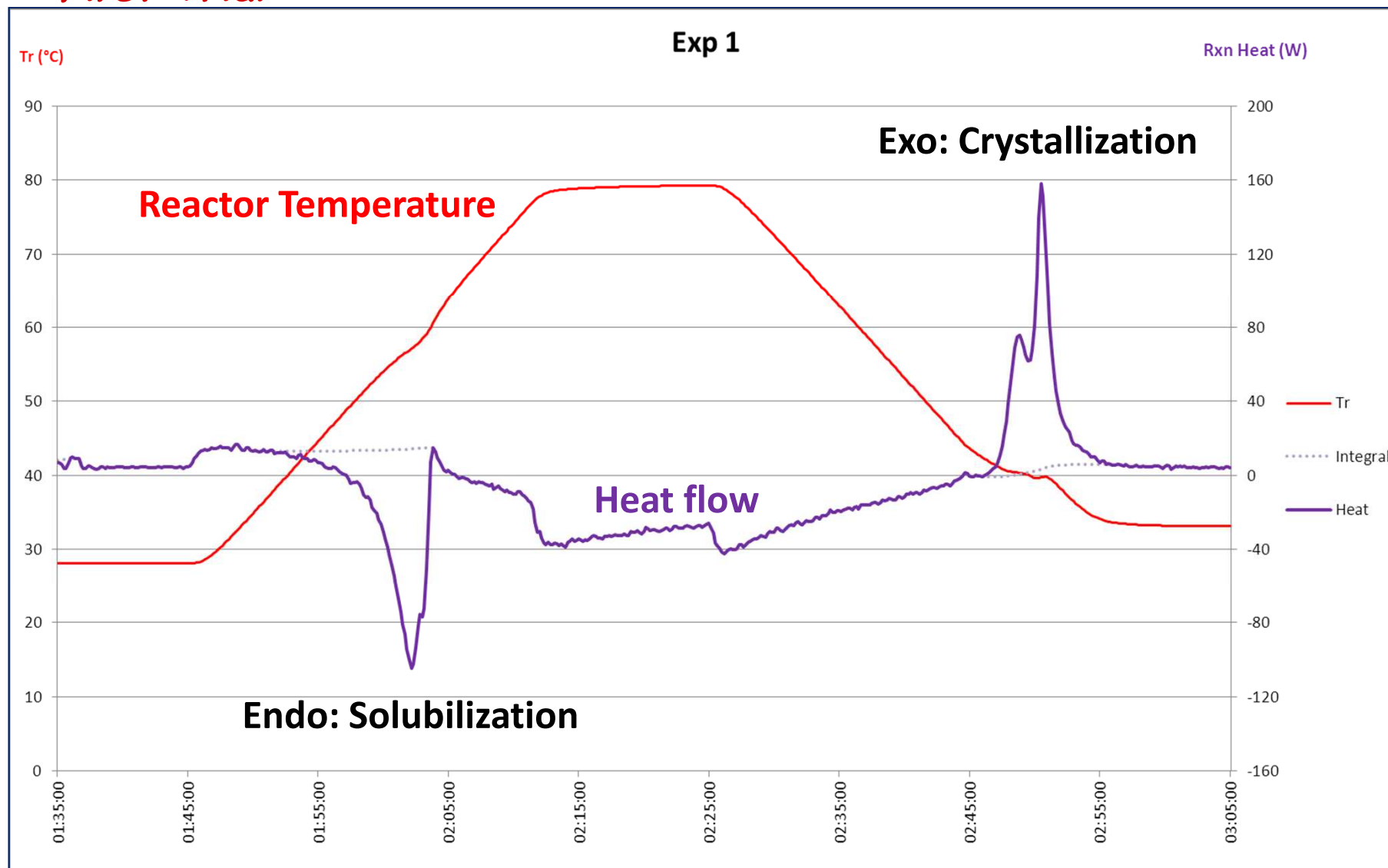
*Example of an **API** Crystallization investigation for GMP assessment*

Problems encountered during an industrial crystallization process:

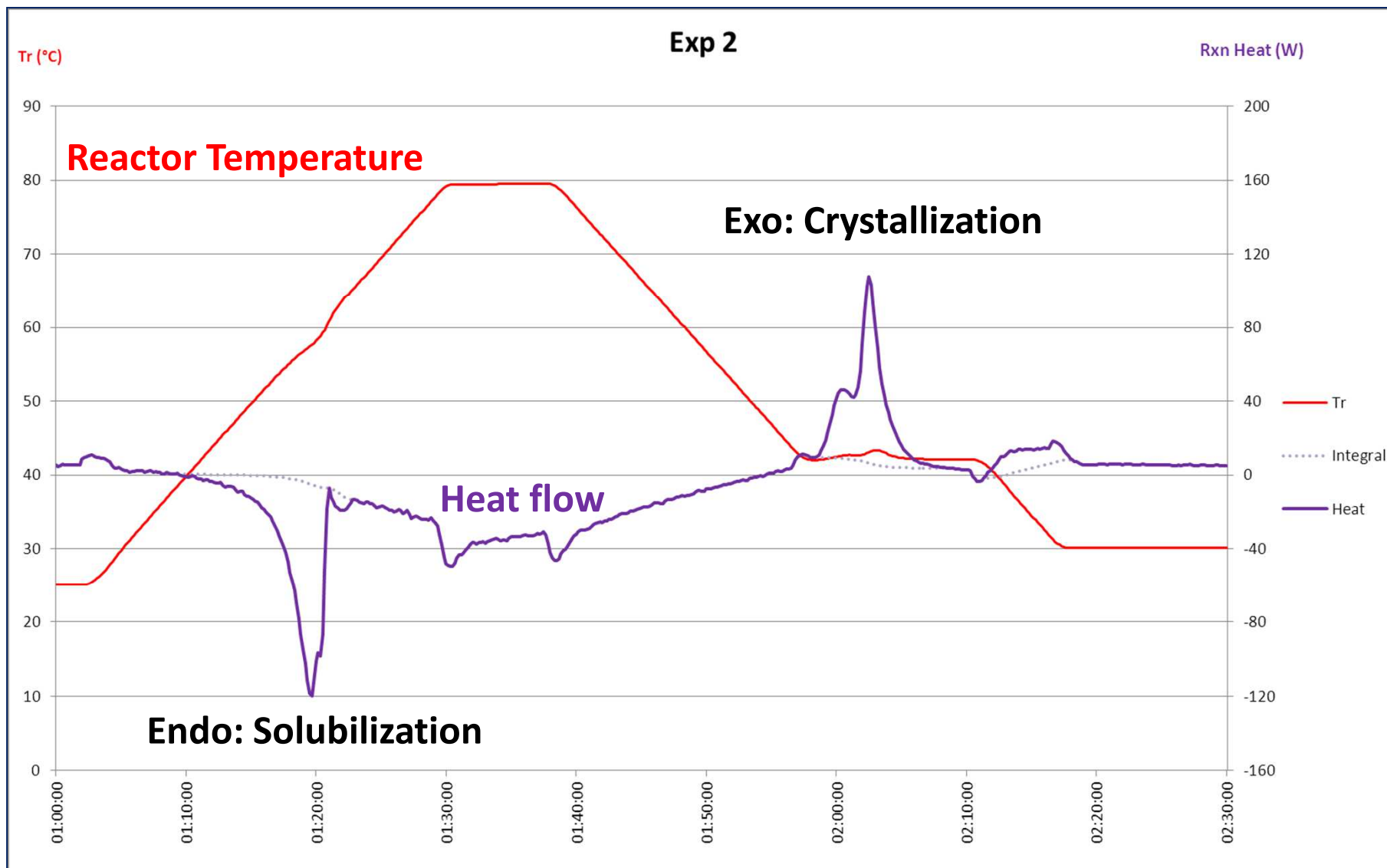


On-Line control by calorimetry (RC1)

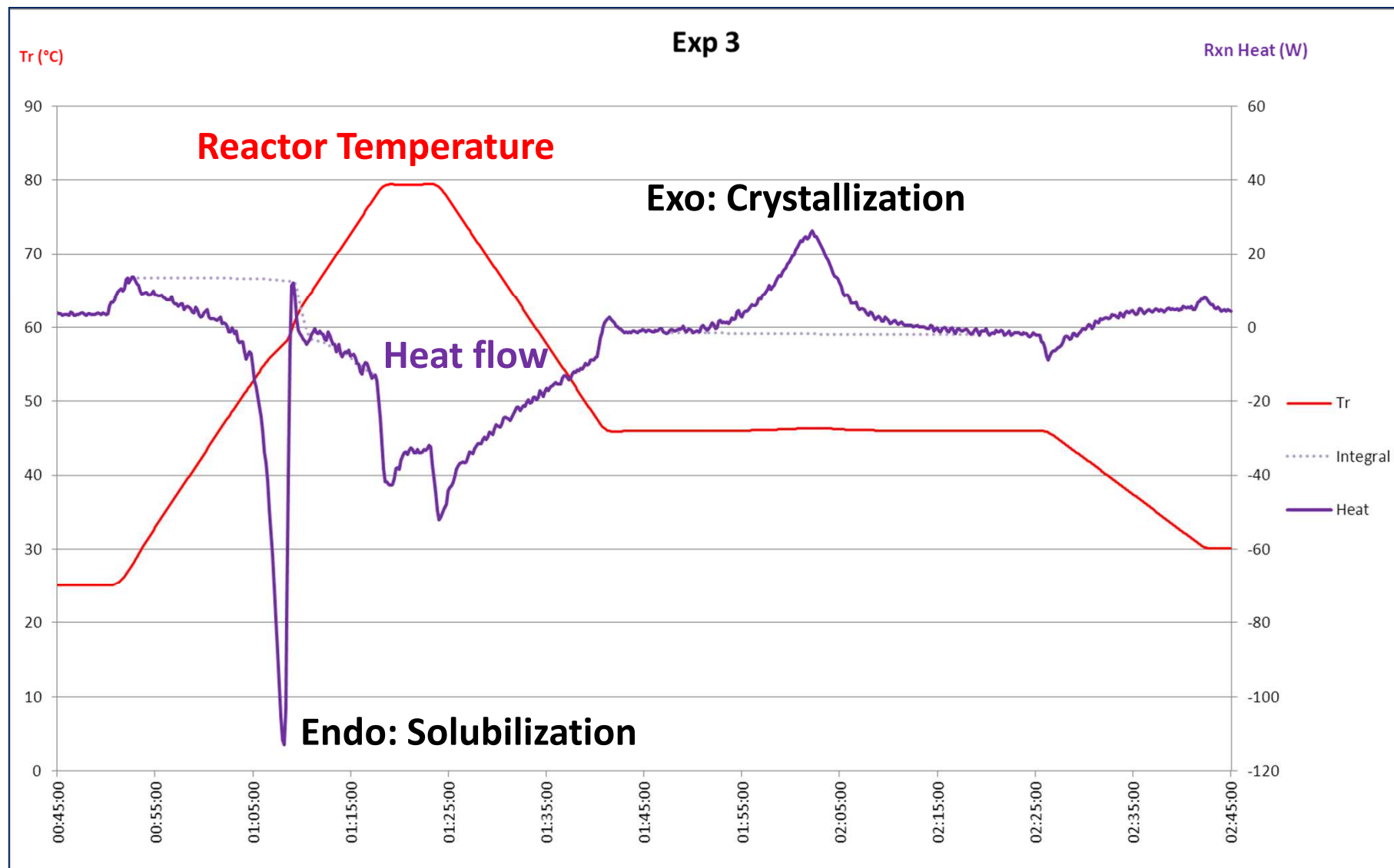
First Trial



Second Trial

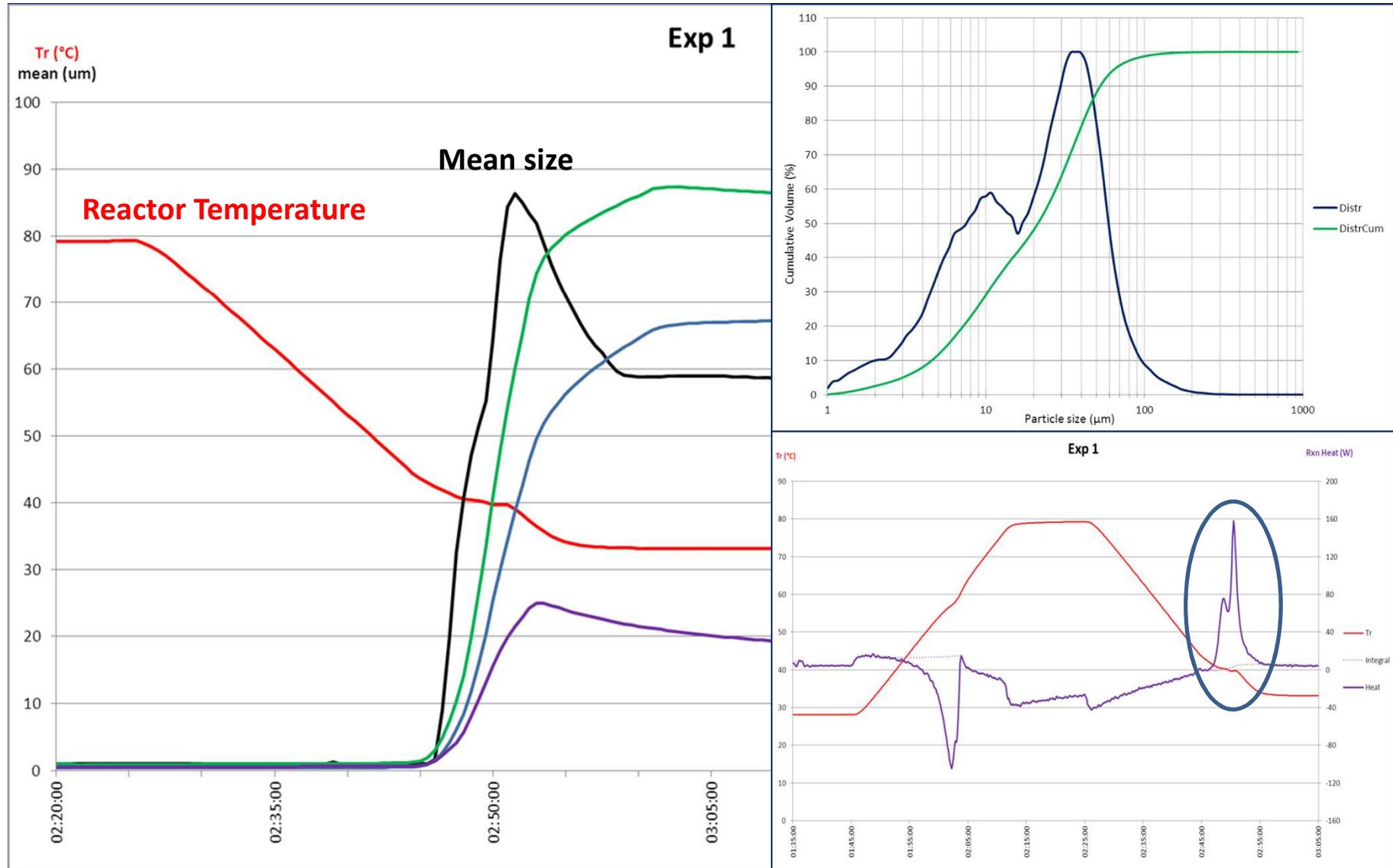


Third Trial



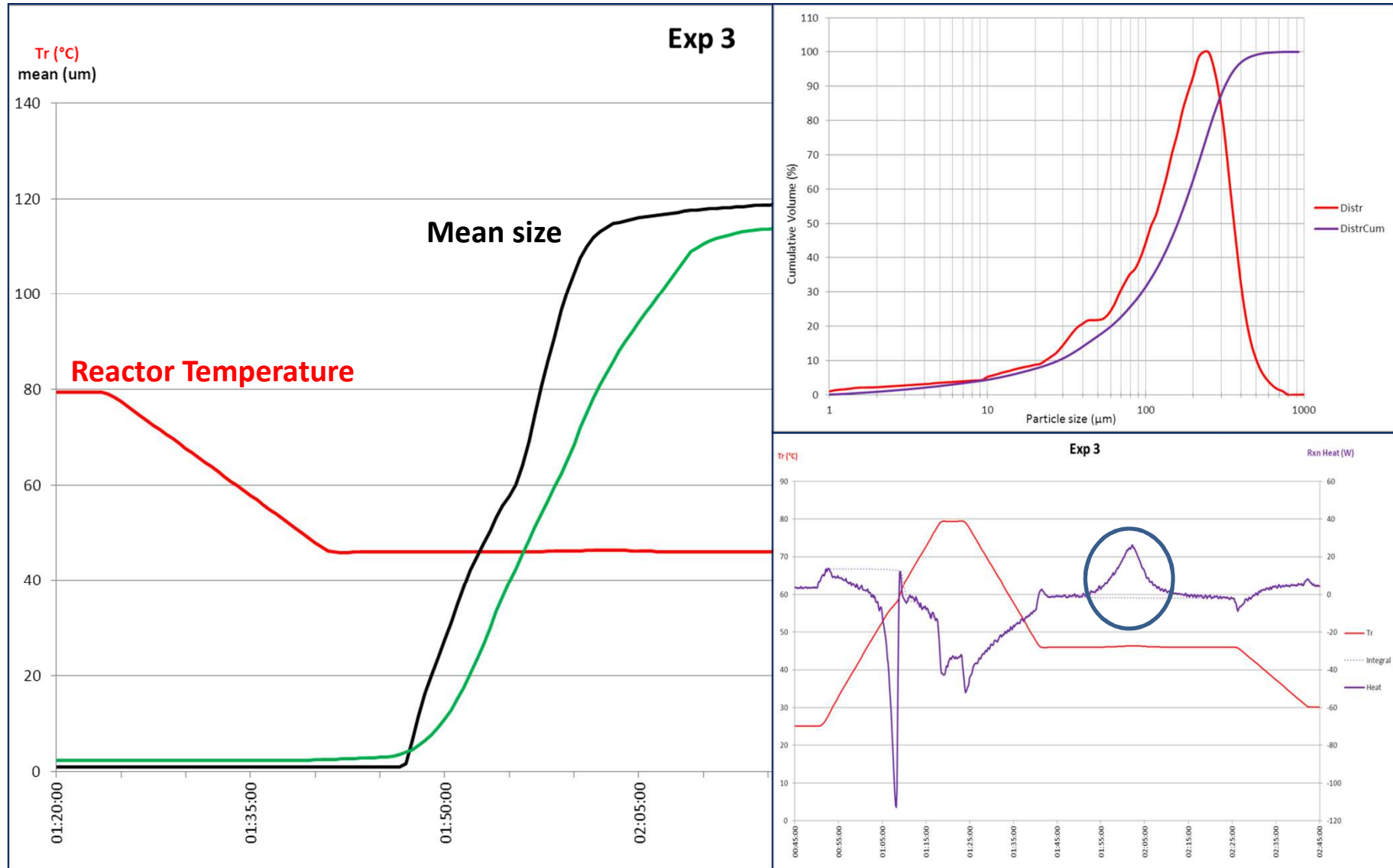
On-Line analysis of PSD by FBRM

Example 1



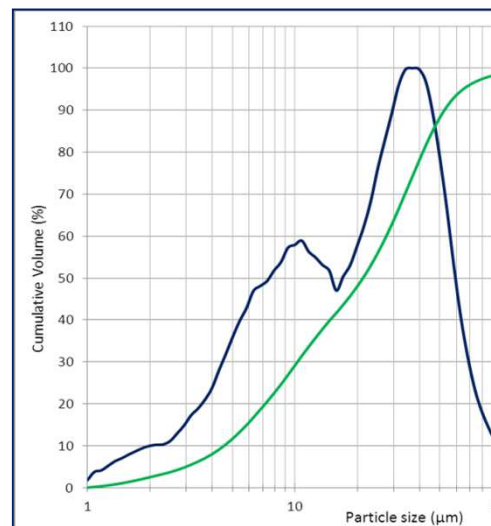
On-Line analysis of PSD by FBRM

Example 3

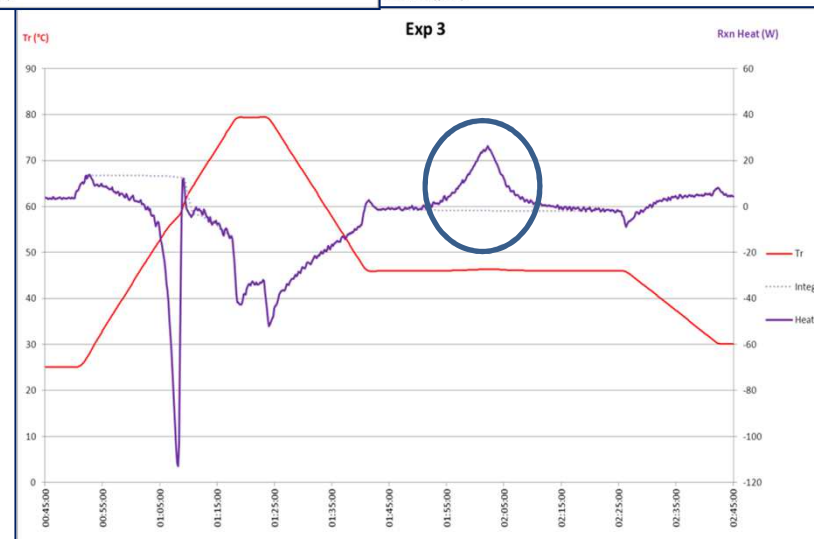
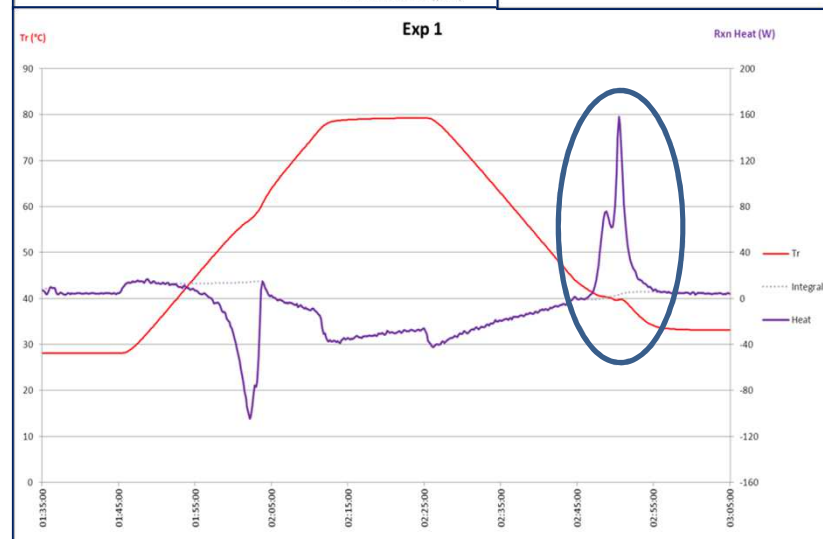
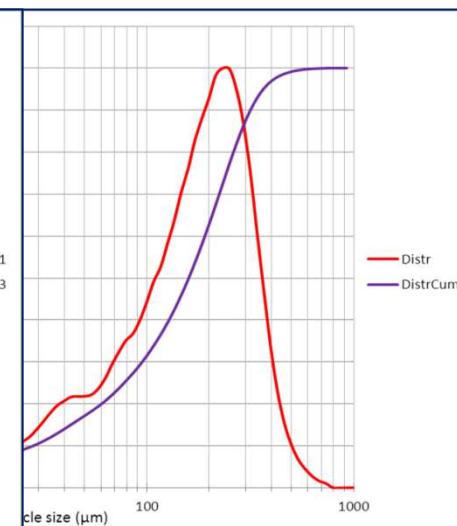
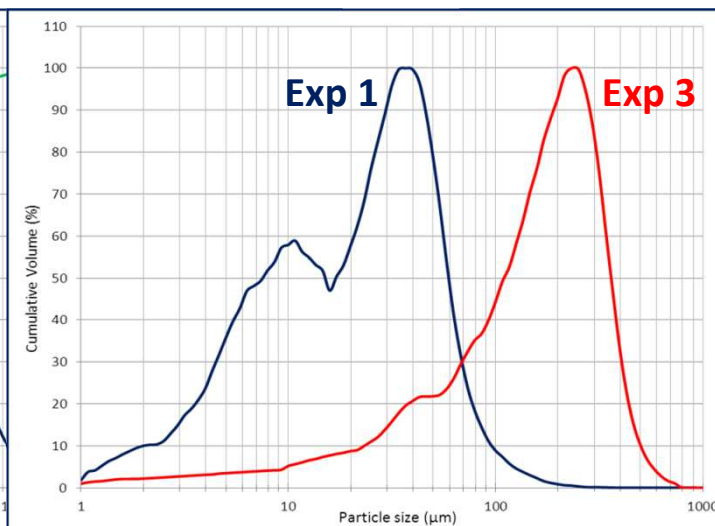


Comparison of Calorimetry and PSD data of the trials

Exp 1

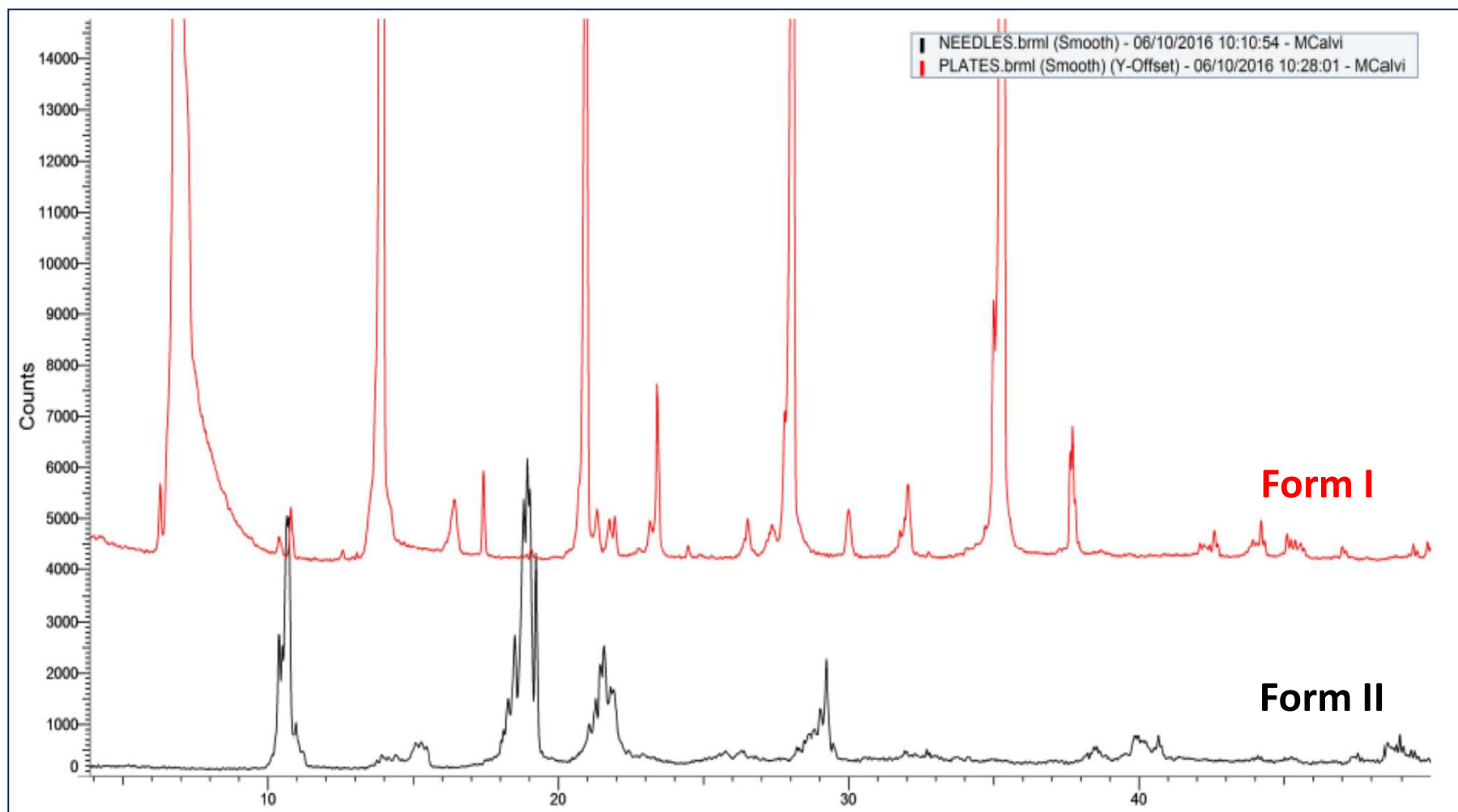


Exp 3



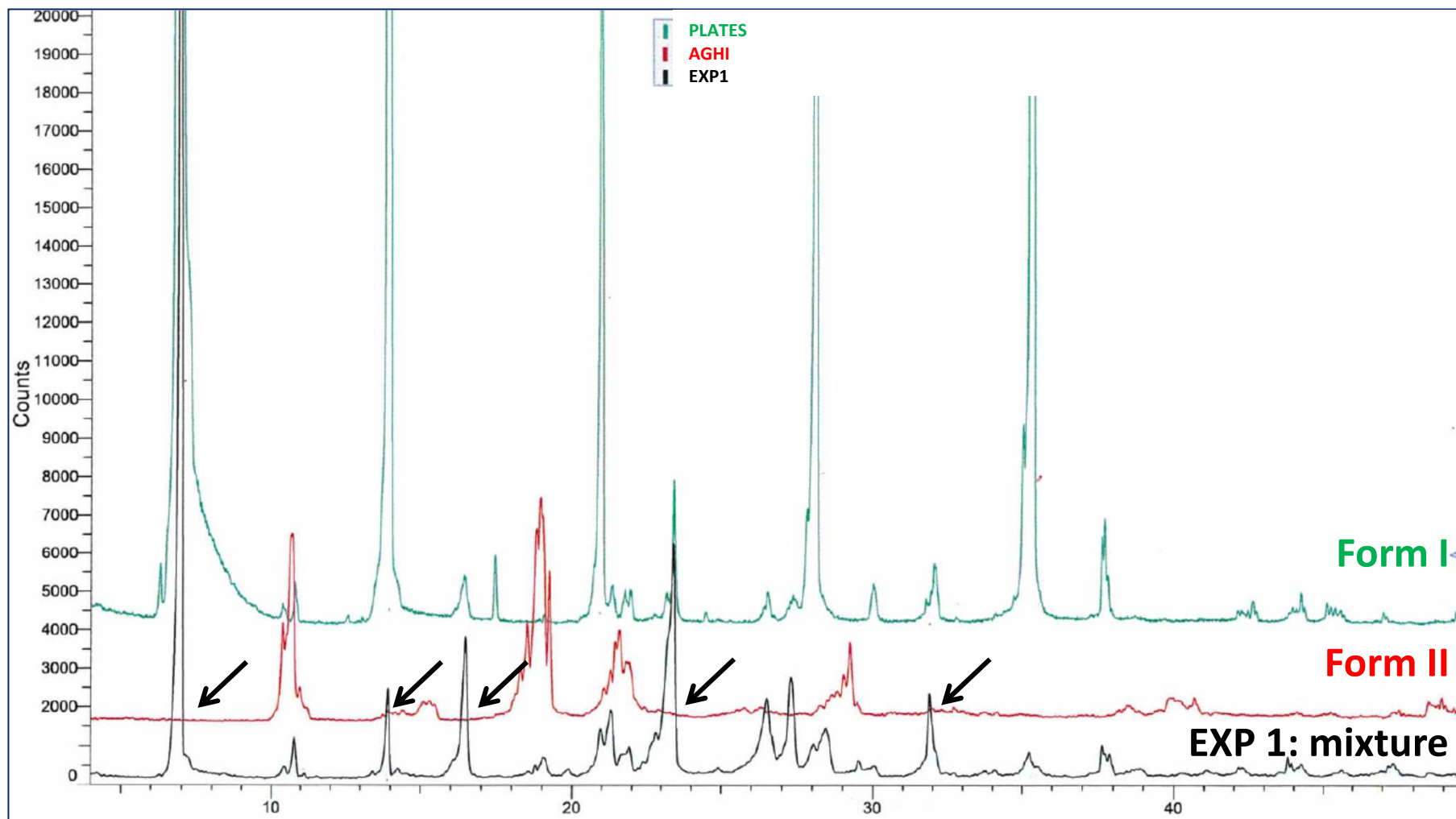
Off-Line Analyses - Polymorphism

XRPD – X-RAY POWDER DIFFRACTION



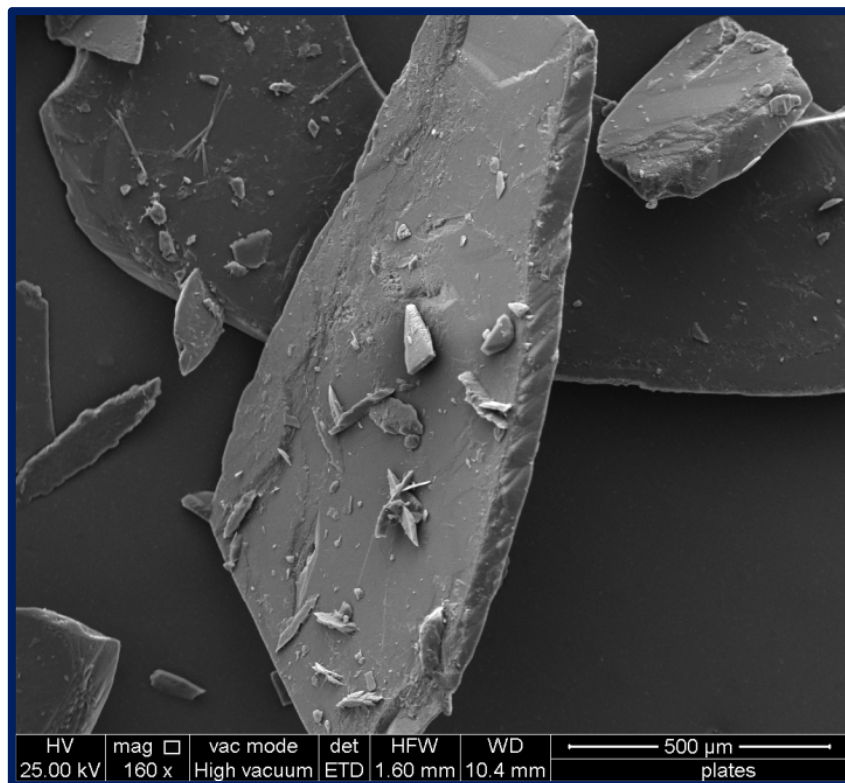
Polymorphic Mixture of solid froms Test 1

XRPD – X-RAY POWDER DIFFRACTION

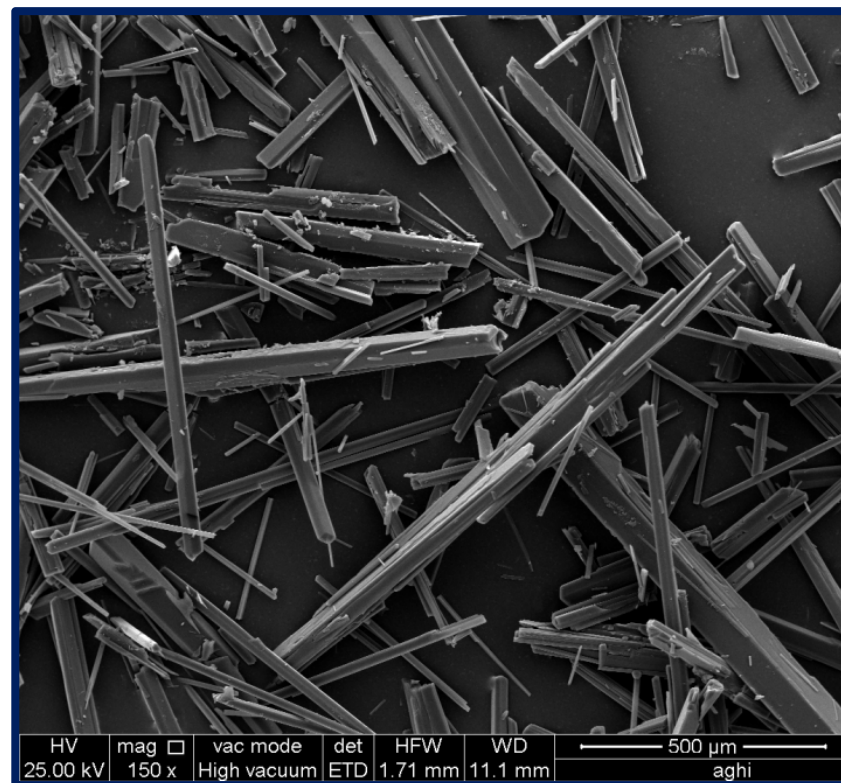


Crystal Morphology of different polymorphs

SEM – SCANNING ELECTRON MICROSCOPE



FORM 1 - PLATES

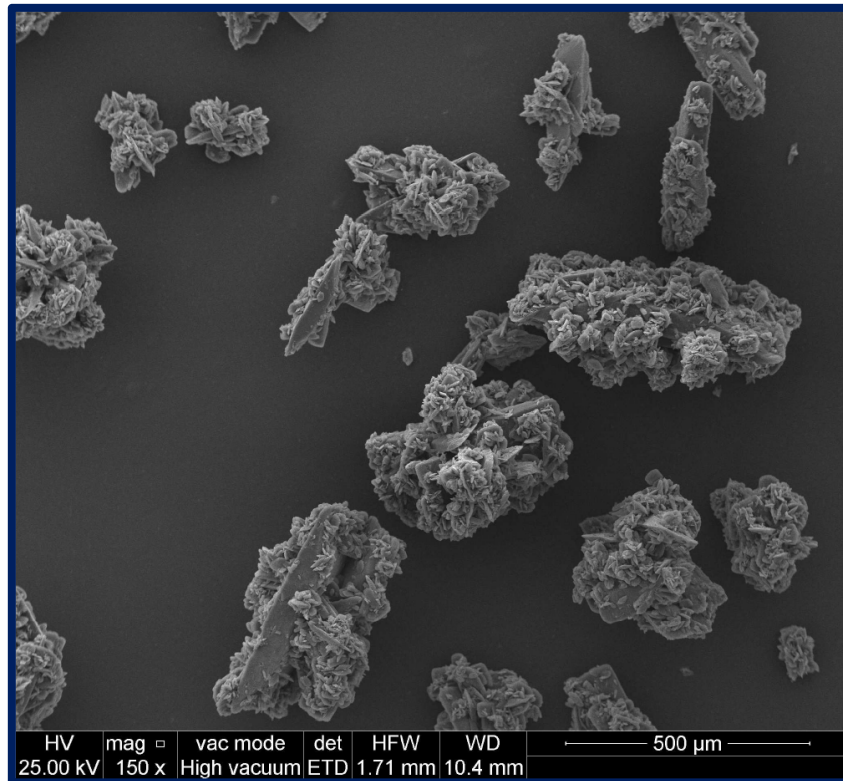


FORM 2 - NEEDLES

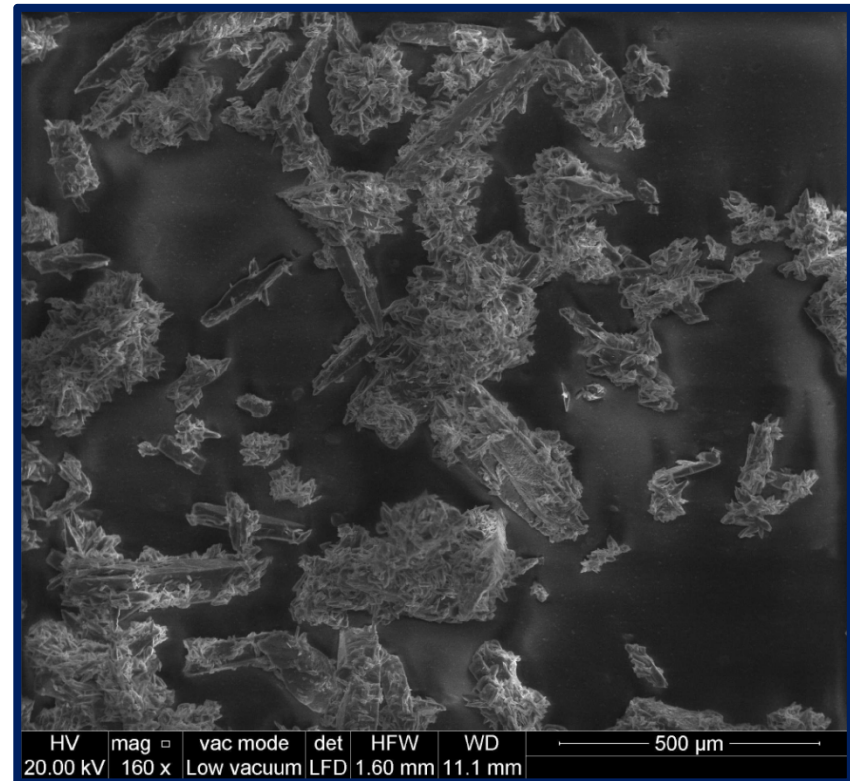
STANDARD FORMS

Crystal morphology of the polymorphic mixtures

SEM – SCANNING ELECTRON MICROSCOPE



EXP 1

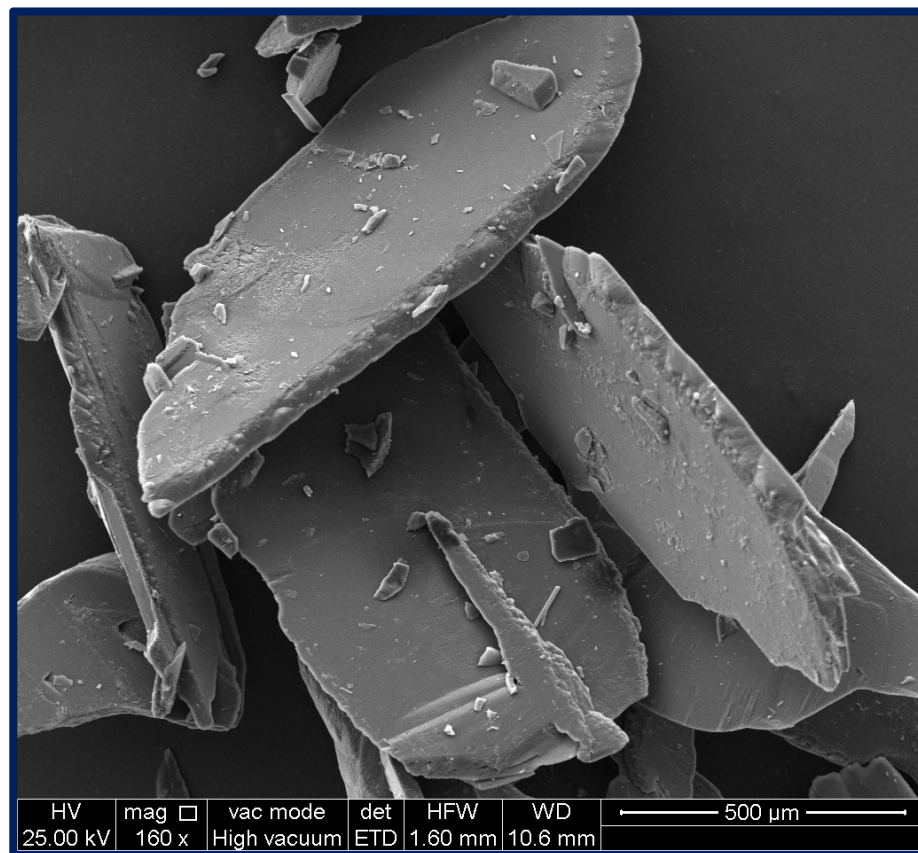


EXP 2

MIXTURE OF POLYMORPHIC FORMS

Crystal Morphology of Trial 3

SEM – SCANNING ELECTRON MICROSCOPE

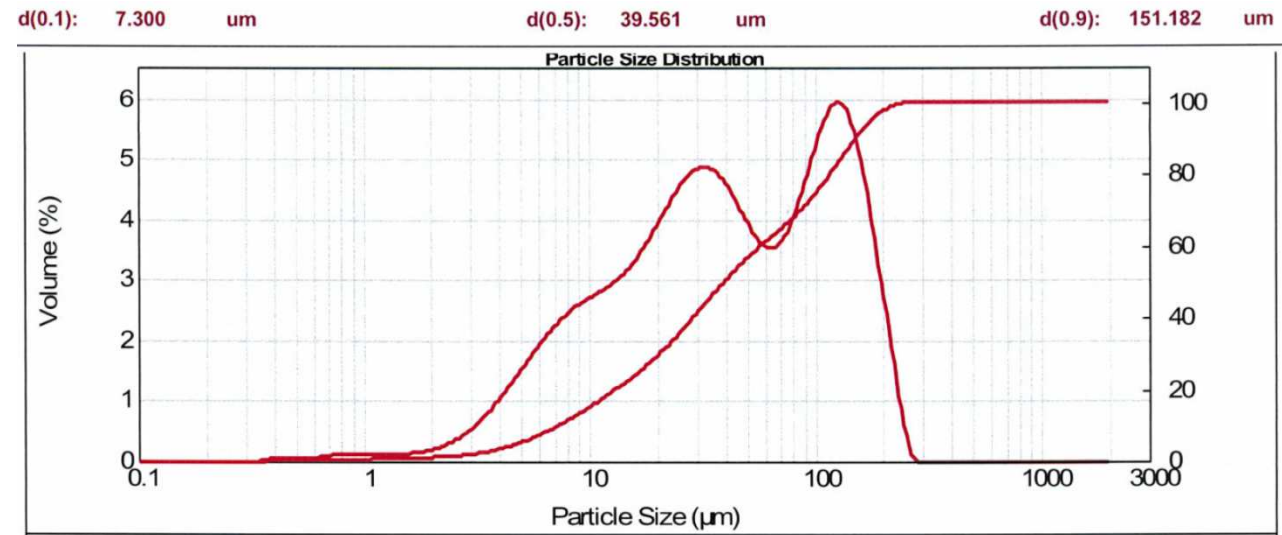


EXP 3

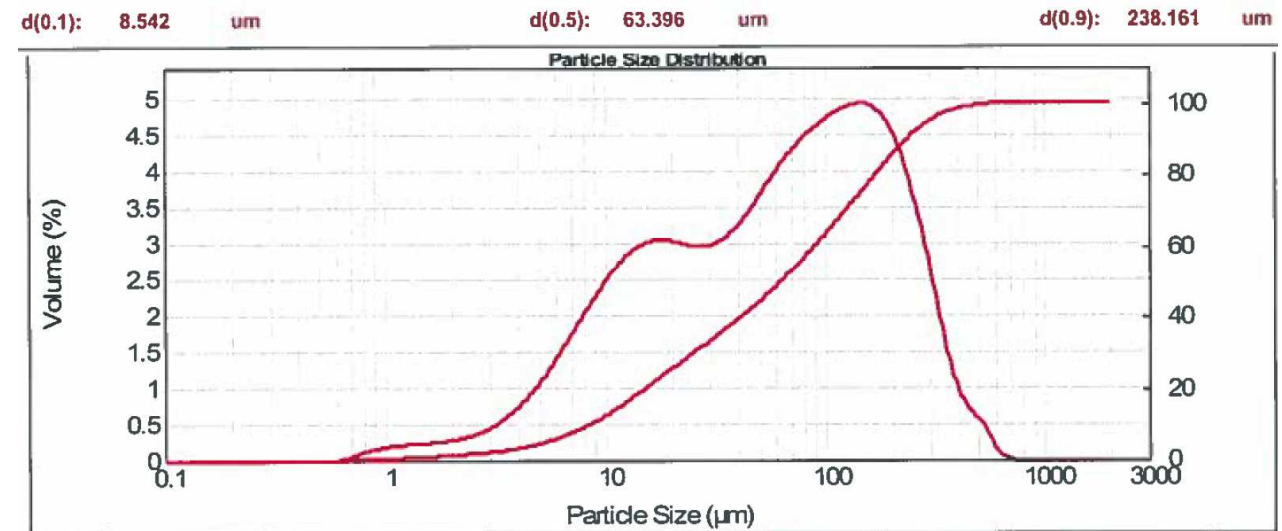
TARGET: FORM I

PSD by Laser Diffraction method - Malvern -

EXP 1



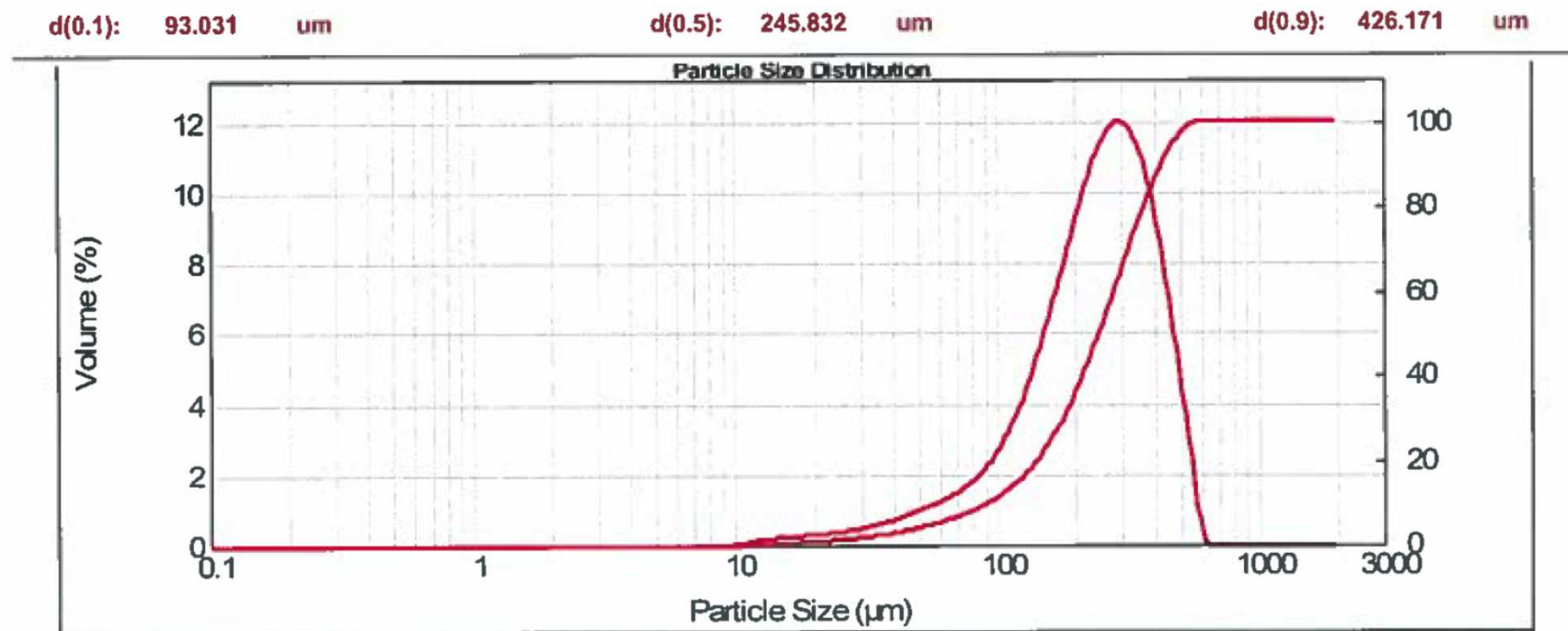
EXP 2



PSD Trial 3

- Malvern -

EXP 3



Critical Quality Attribute (CQAc) determined by limited number of experiments

	Process temperature °C	Event of Crystallization #	Polymorphic form Plates/Needles	Morphology	PSD (with FBRM) d(0.5), [μm]	PSD (Malvern) d(0.5), [μm]
EXP 1	42-32 (cooling)	2	Mixed	Aggregates	22	39
EXP 2	43 + 43-30 (cooling)	3	Mixed	Aggregates	38	64
EXP 3	46	1	Plates	Not aggregated	158	245



FBRM/Granulometer: PSD, filtrability

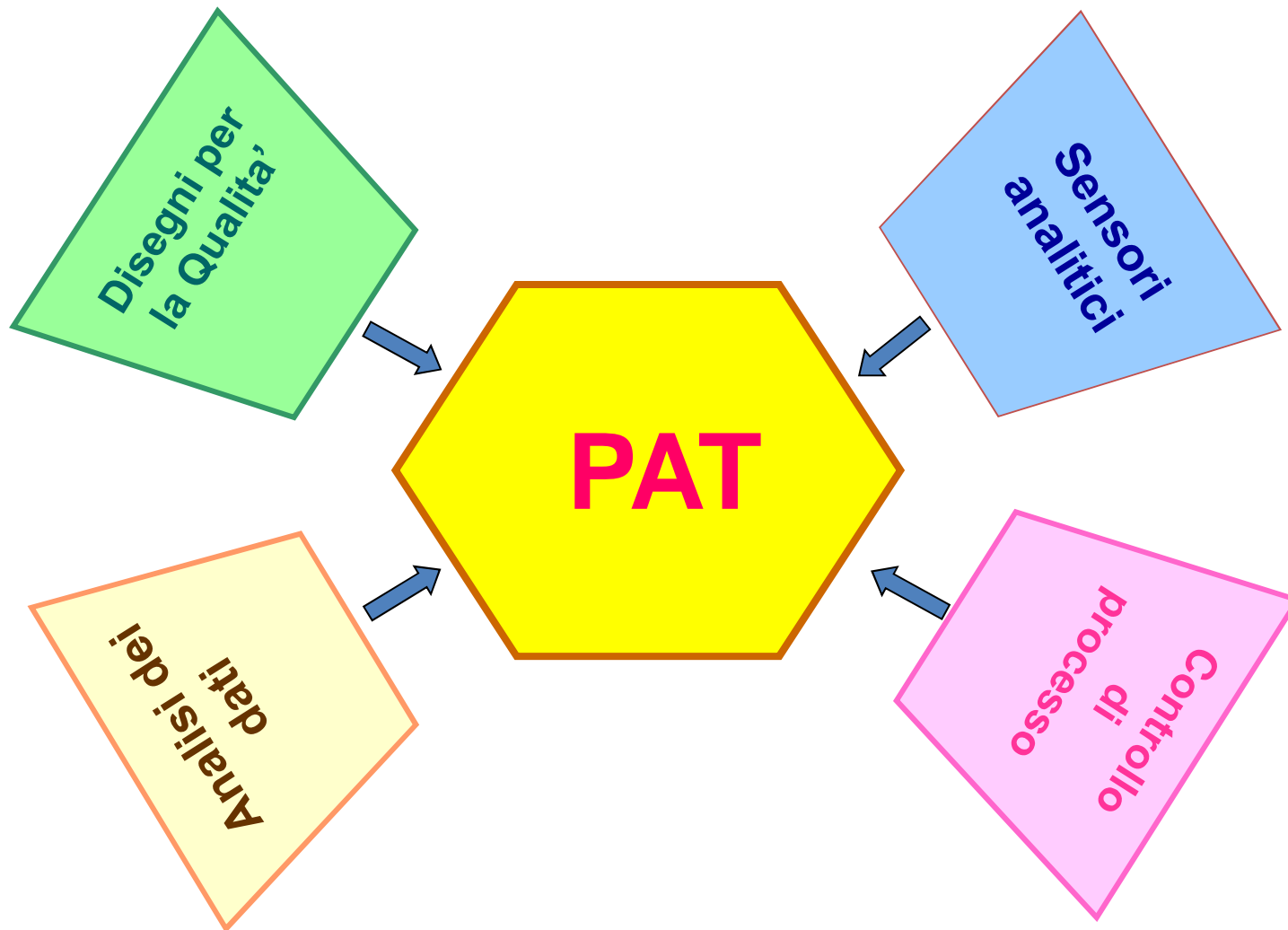
SEM: Morphology

XRPD: Polymorphic form definition

RC1: Process Parameters definition



*From Development to On-Line Process Control
for PAT application in support to the GMP
requirements*



Conclusion

- ❑ *Definition of Crystallization Temperature profiles in relation to the desired Polymorphism*
- ❑ *Rapid assessment of MSZW*
- ❑ *Evaluation of PSD plots along the process in relation to Temperature and Time*
- ❑ *Prediction at Lab-scale of Critical Quality Attributes (CQA) on the crystallization profiles*
- ❑ *Definition of Critical Process Parameters (CPP) to be controlled in large scale process*
- ❑ *Quality Consistency of final product in term of Polymorphism and Particles External Properties (PSD, Morphology) in support to **Regulatory Registration***
- ❑ *Reduction of manufacturing costs (saving solvent, product, time...)*

Thanks for your attention



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THANKS FOR YOUR KIND ATTENTION