Applicazione della PAT per la valutazione degli Attributi Critici

(PAT application for CQAs assessment)

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Objectives of the presentation

1. Crystallization principles and CQAs
2. Analytical Techniques for PAT Application
3. Examples of PAT in Crystallization of API
4. Summary

CRYSTAL CHARACTERISTICS

***Crystals appear in many*:**

- **sizes,**
- **shapes and**
- **forms,**

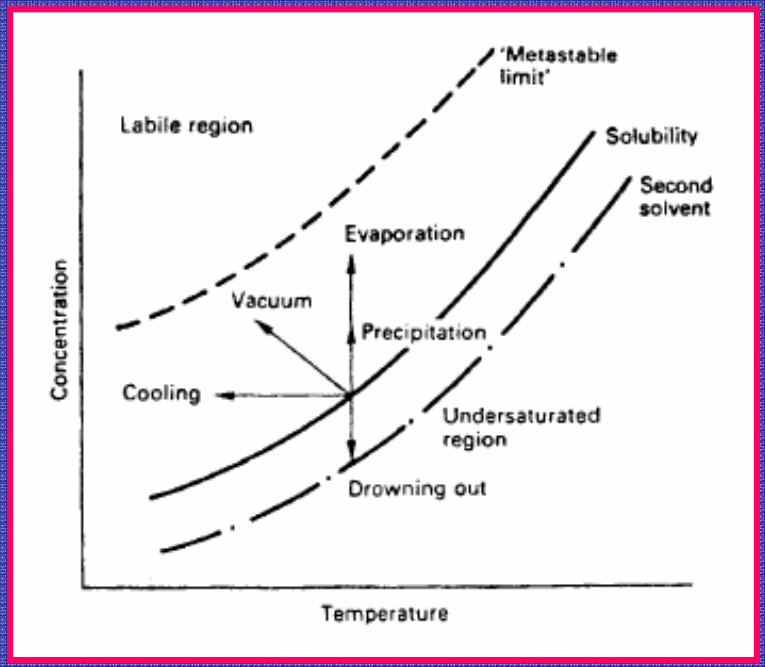
Which affect both:

- **performance during processing, and**
- **quality in application**

Phase Equilibria

- *Understanding phase equilibria is crucial to crystallizer operation*

- **Undersaturated** - crystals will dissolve
- **Metastable** - crystals will grow
- **Labile** - solution will nucleate spontaneously



Solubility-supersolubility diagram

Crystallization Kinetics

- Nucleation rate - *rate of formation of new crystals*

$$\frac{dN}{dt} = B = k_n \Delta c^b \qquad \textbf{nuclei/s m}^3$$

where b = 'order' of nucleation

B = nucleation rate –rate of increase of crystal number

- Crystal growth – *rate of increase of crystal dimension*

$$\frac{dL}{dt} = G = k_g \Delta c^g \qquad \textbf{m/s}$$

where g = 'order' of growth

G = growth rate rate – rate of increase in crystal size

particle formation processes depend upon supersaturation

Process Analytical Technology (PAT)

in the control of the

Critical Variables (CQAs)

in Crystallization Processes

The application of PAT to the crystallization means

understand

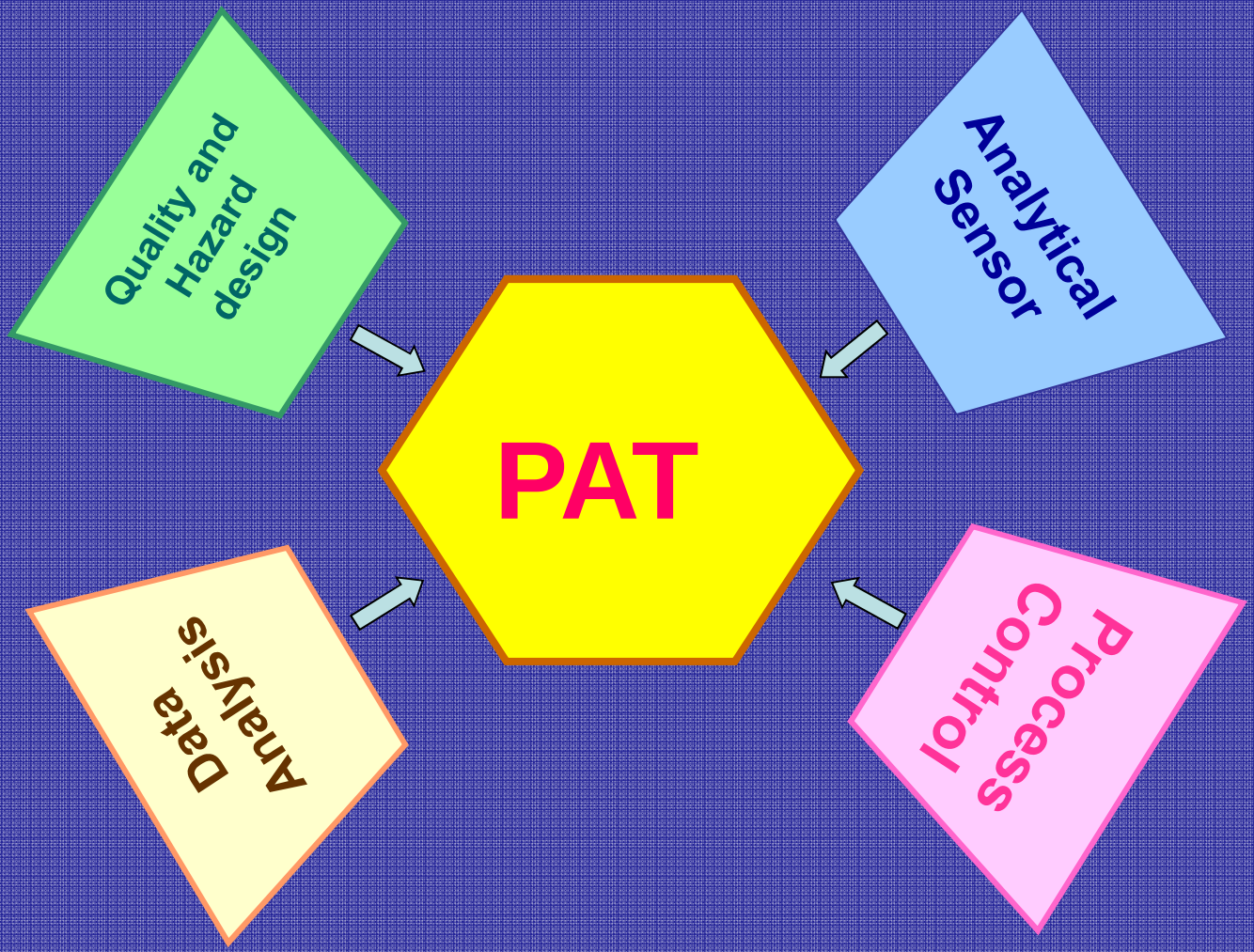
IDENTIFICATION

MEASUREMENT

PREDICTION

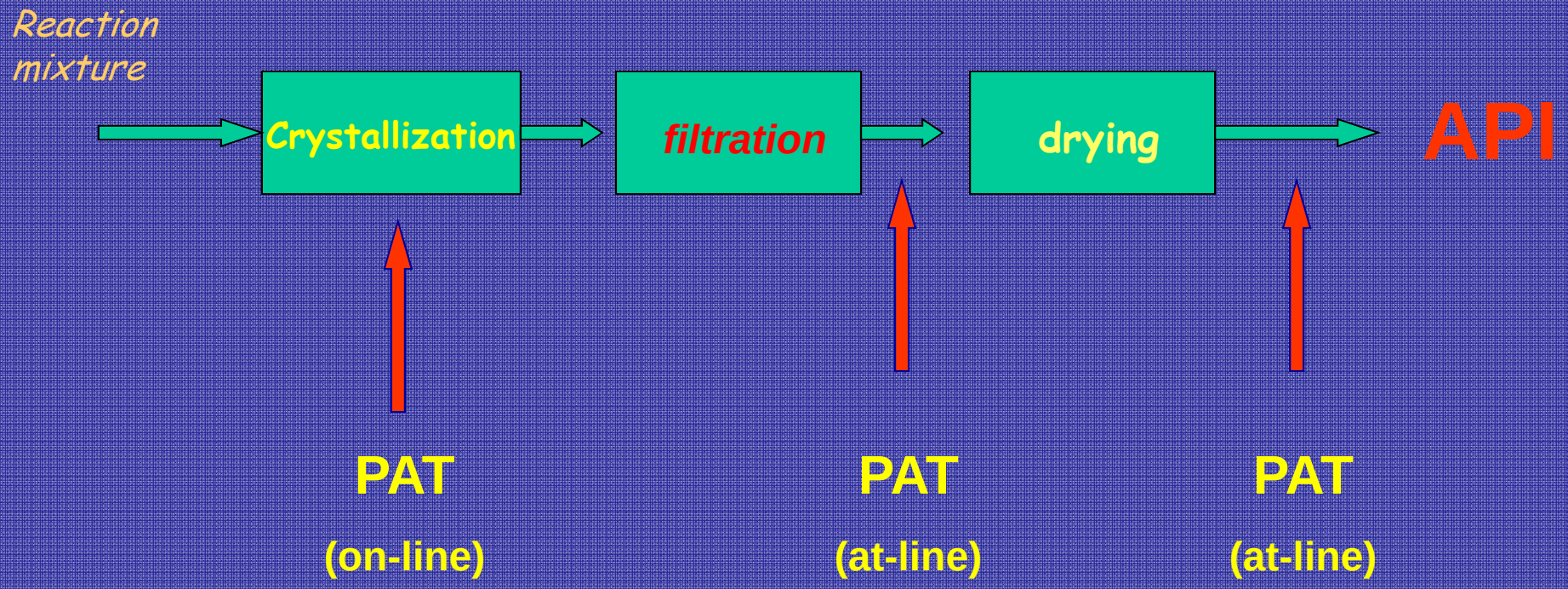
} ***PAT***

Scientific Contributions for the application of the PAT



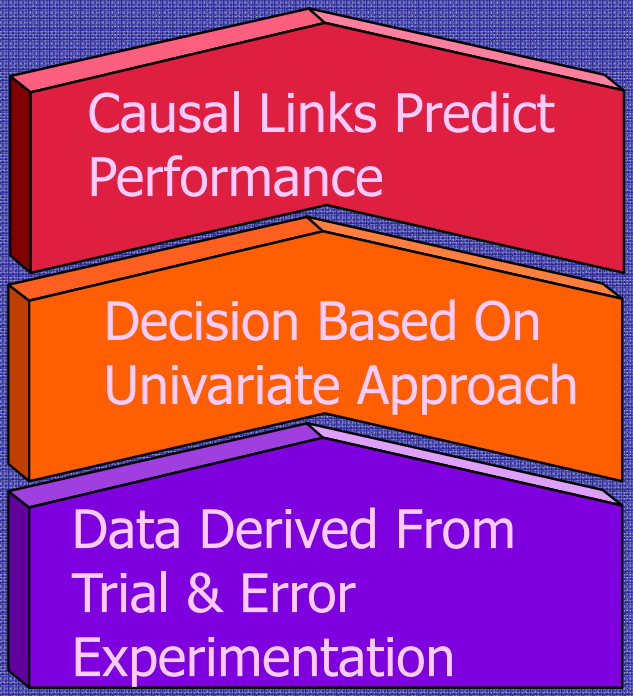
application strategy

PAT in production process of an active product

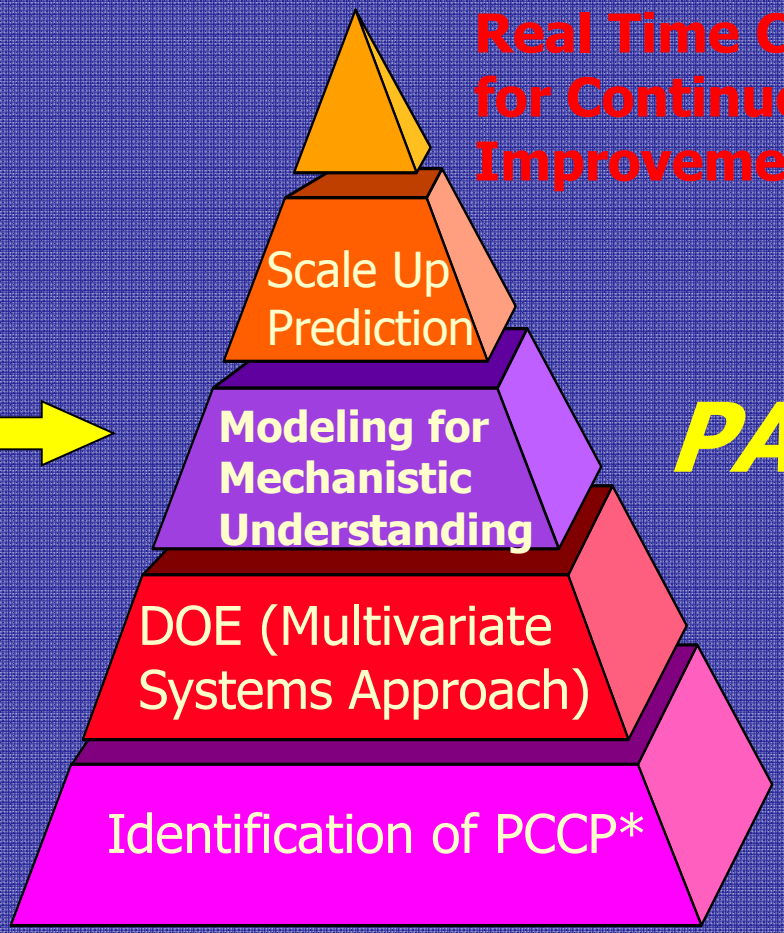


Fundamental Approach in Development

Traditional Approach



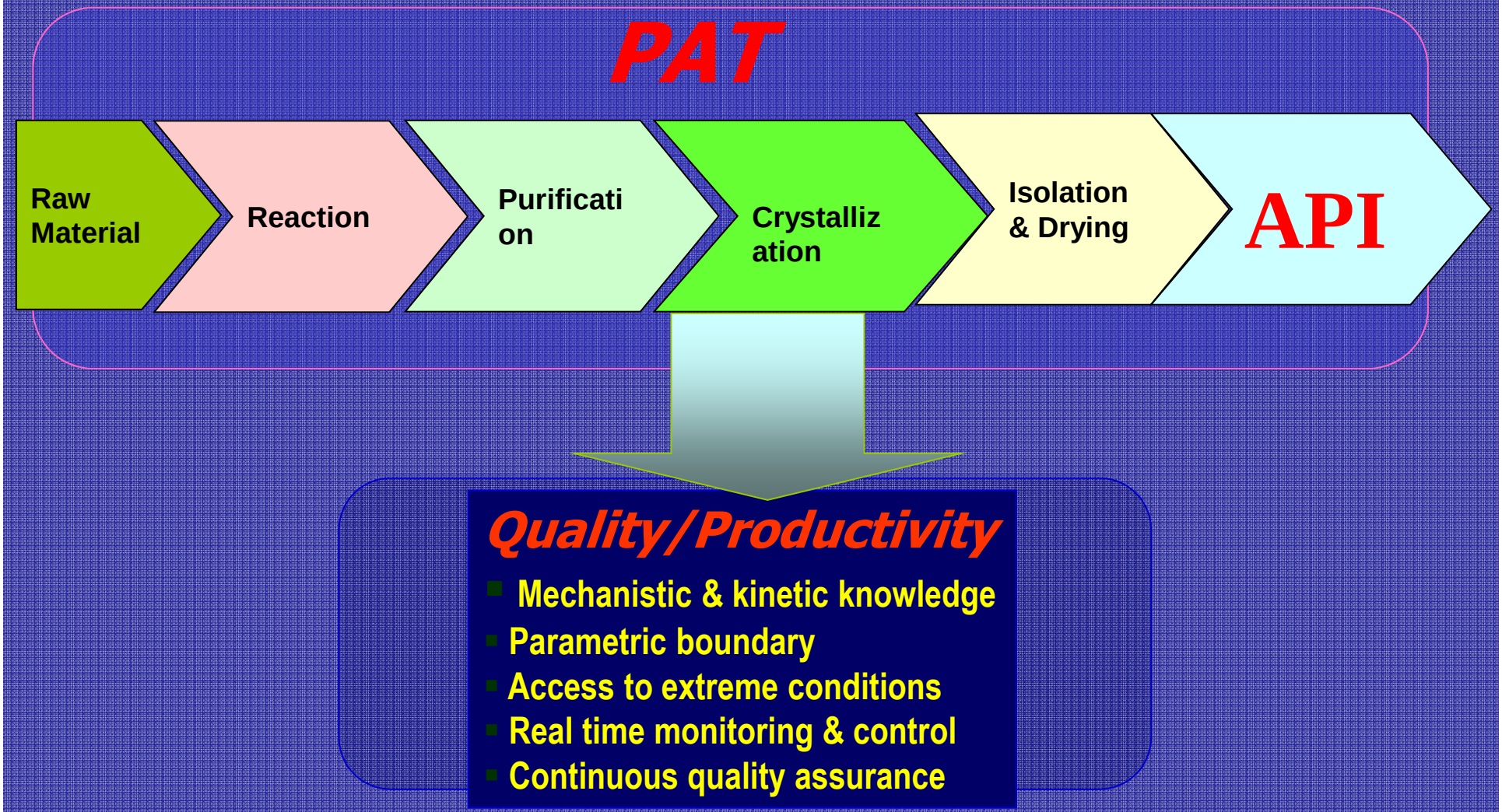
Quality by Design



PAT

PCCP* – Process Critical Control Parameter

Impact of On-line Process Analyzers
- Crystallization -



Application for On-line Process Monitoring
- Crystallization -

SOLID STATE

Physical properties

intrinsic

- Reaction Calorimetry
- FT-IR/ATR spectroscopy
- Raman Spectroscopy

external

- FBRM -Focuse BeamReflectance Measurements

Instrument characteristic requirements for on-line process monitoring

1. *Able to acquire and memorise in real time large quantity of analytical data*
2. *Easily located in a process without changing the environment*
3. *Record the data with accuracy of a final step of a desired process.*
4. *Operability and affidability of data recorded in relation to process variation.*

Analytical Techniques available on the market

Spectroscopic Techniques

- NIR
- FT-IR/ATR
- Raman
- Light Scattering (laser)
- Mass-Spectrometry
- X-ray (Diffraction & Fluorescence)

Turbidimetric and Rifractometric Techniques

- Turbidimetry
- Densitometry – rifractometry

Particles physical and morphologic properties

- Particle Size (FBRM)
- Photoacustic
- Etc.

REVIEW

Applications of Process Analytical Technology to Crystallization Processes[1]

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Use of PAT for

- Monitoring PSD and Polymorphism during crystallization
- Monitoring PSD during
  - downstream
  - processing
  - i.e. filtration, drying
- Scale up assessment

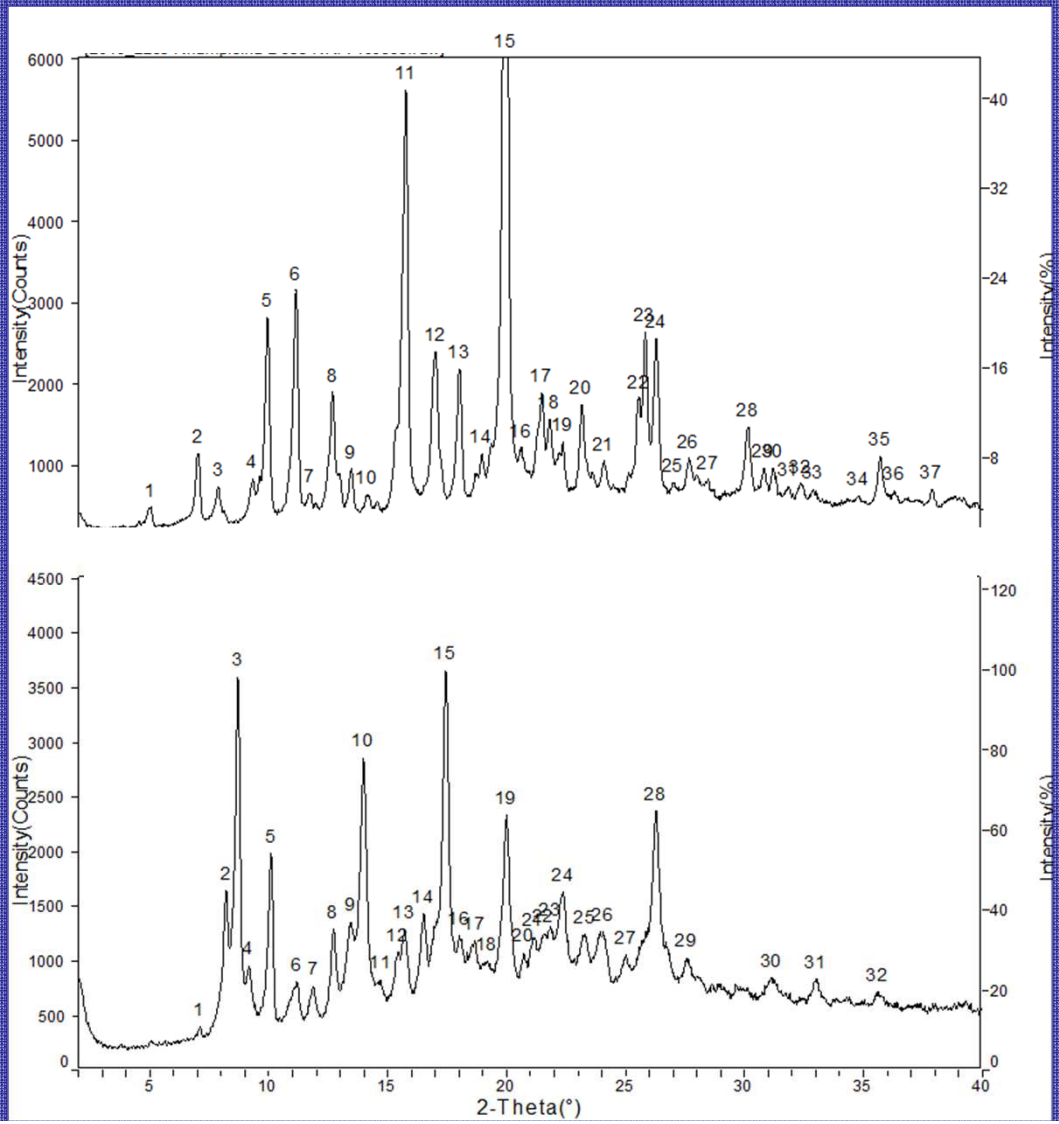
Control of polymorphism and Particle Size in crystallization

Example:

A Drug Substance can exist into two polymotphic forms: Form I (stable form) and Form II (less stable with low dissolution profile.

In relation to the crystallization process parameters (temperature, concentration, stirrer speed, etc.) different Forms, morphology, dissolution, stability and different Particle Size can be obtain

Physical property
Form I and Form II



XRPD

Form I

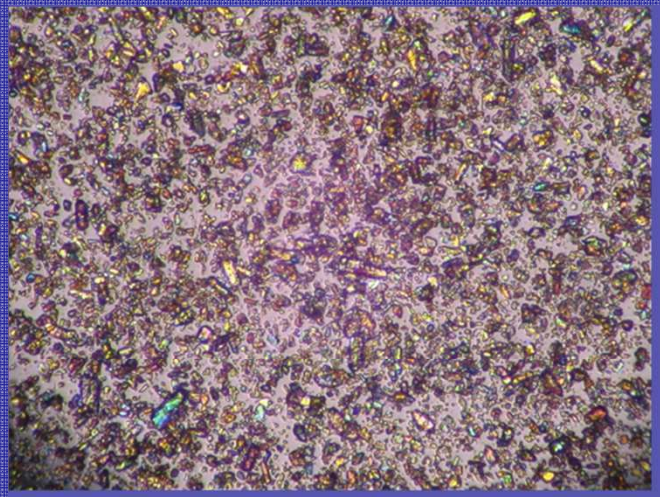
Form II

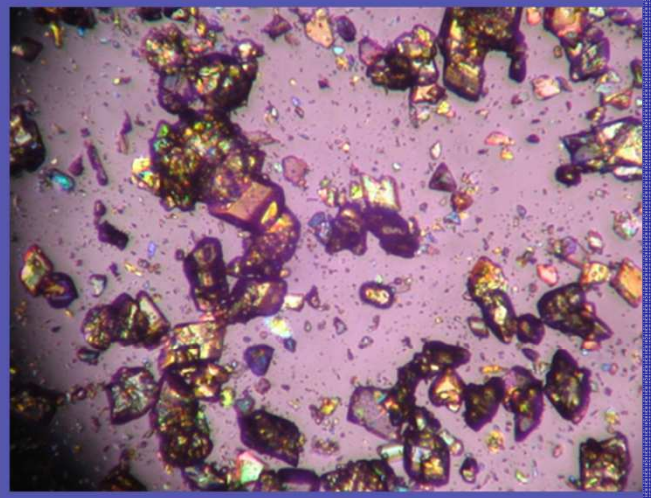
Particles Morphology

Form II

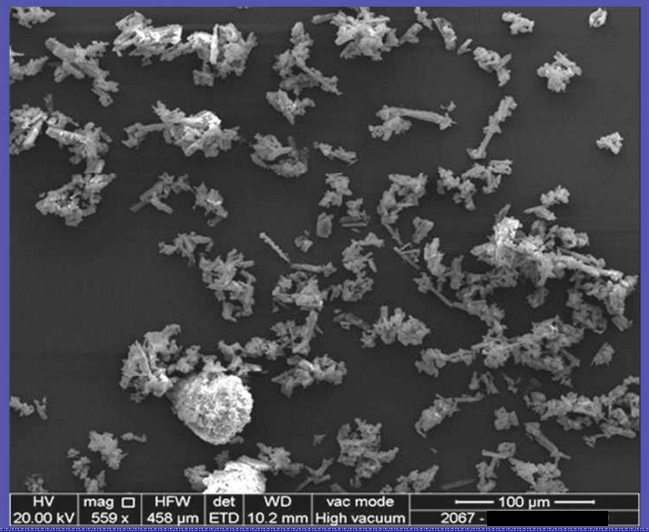
Form I

HSM



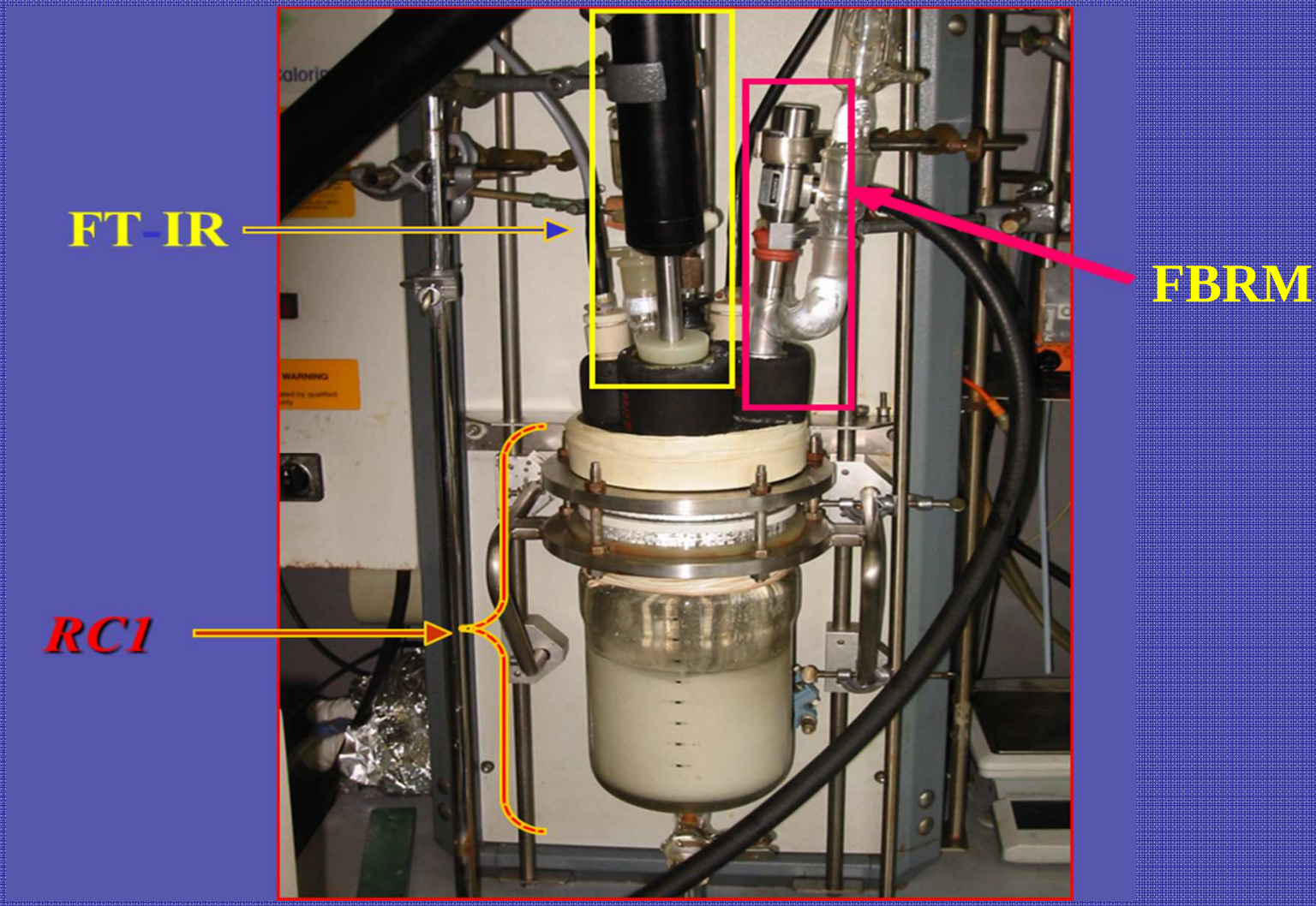


SEM



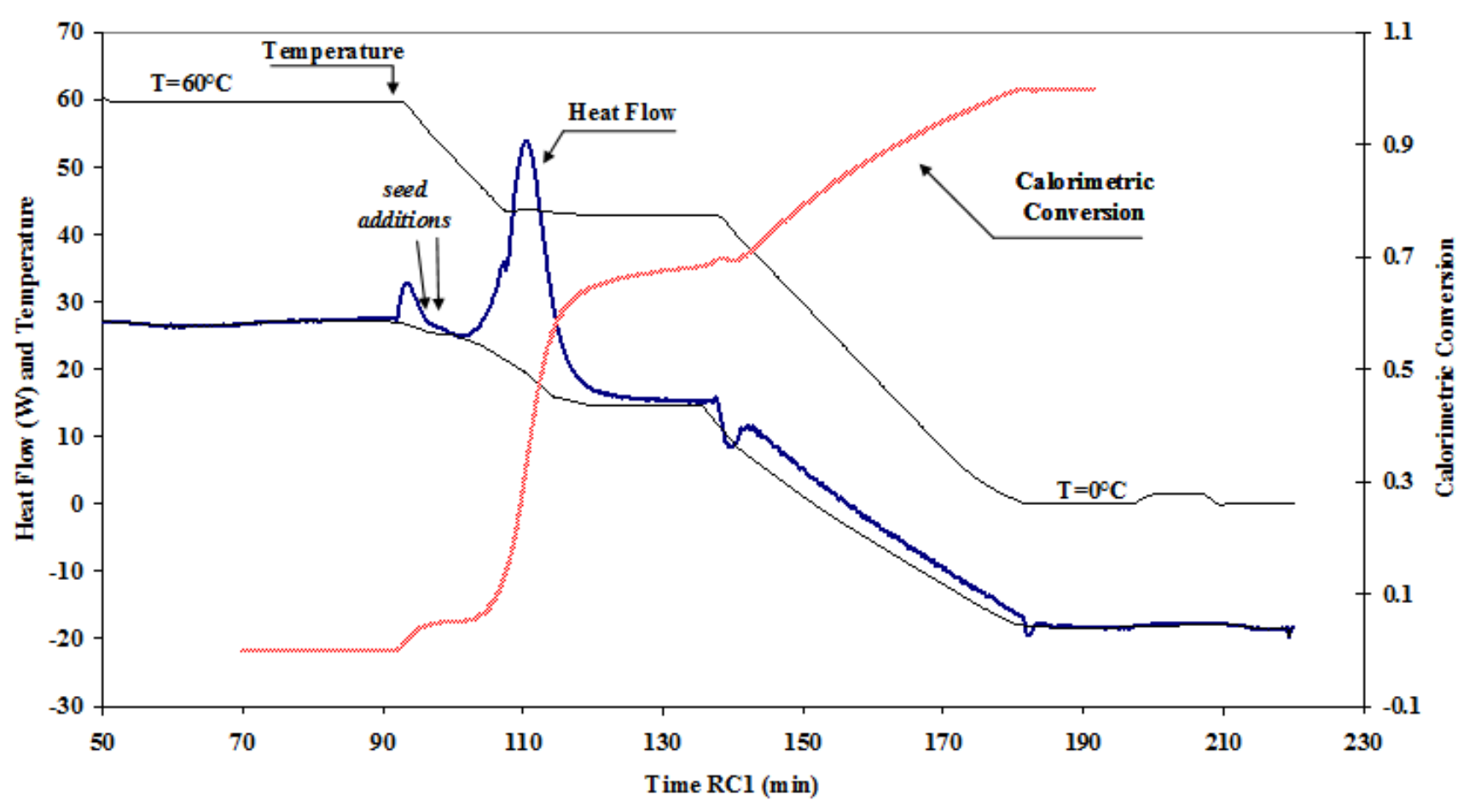
Simultaneous Analyses for CQAs

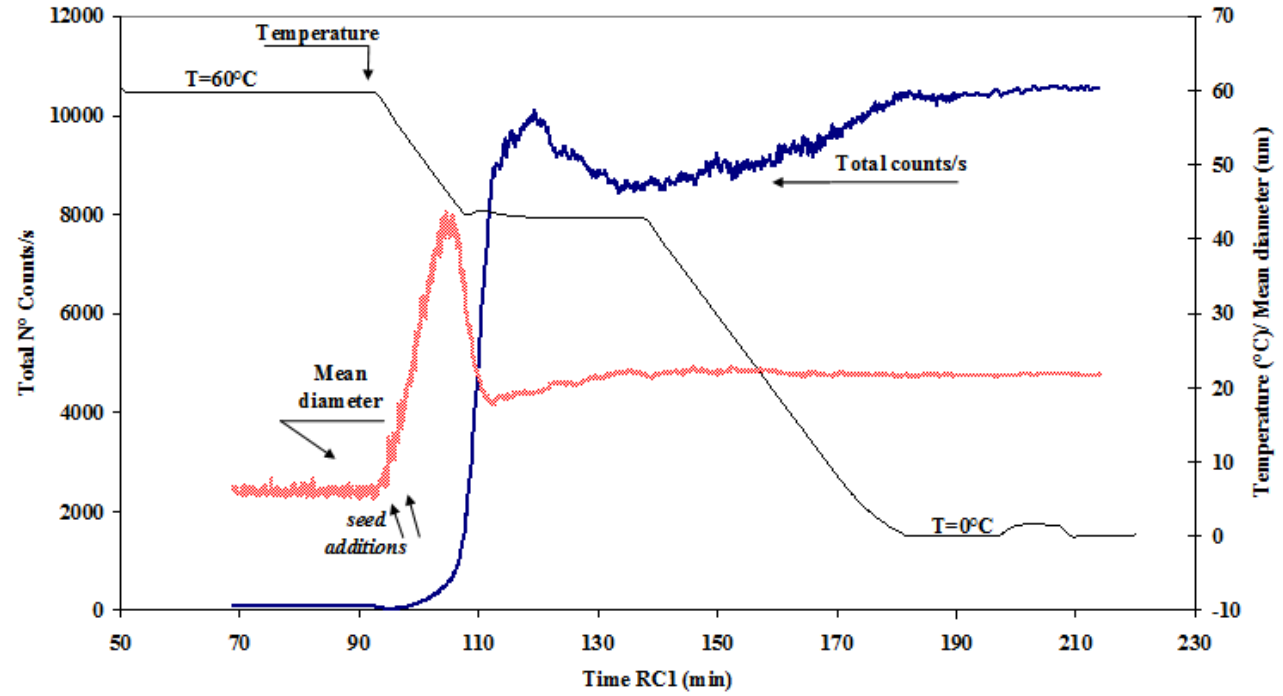
(RC1 & FT-IR/ATR & FBRM)



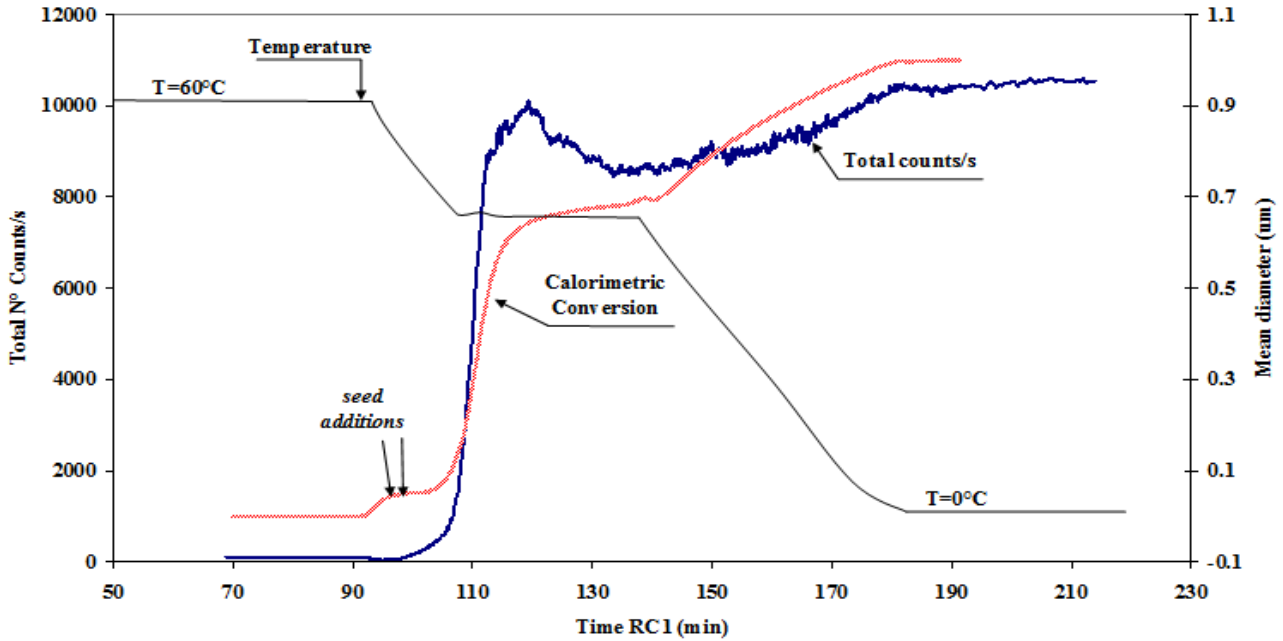
Crystallization under standard conditions

Calorimetry





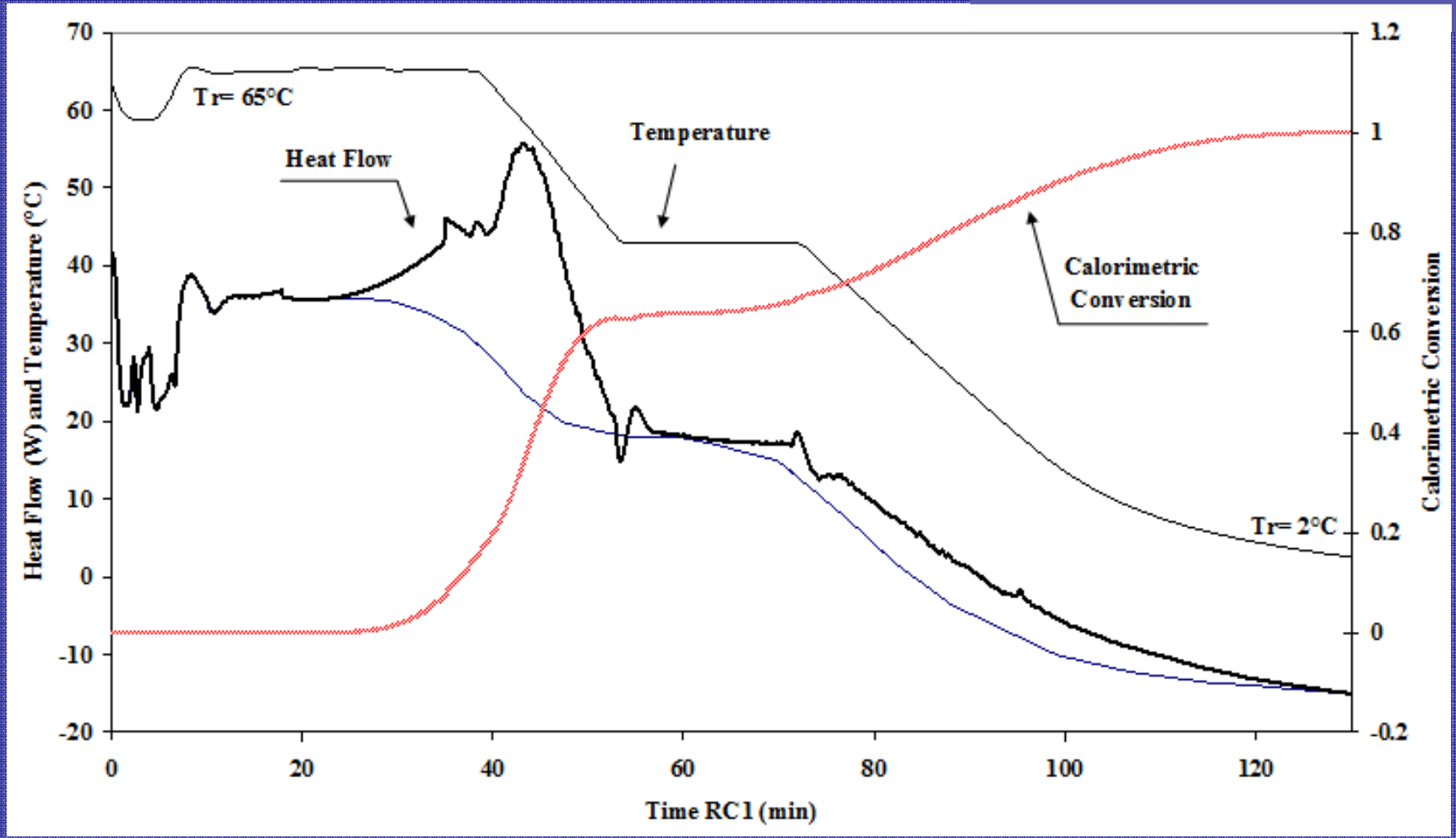
FBRM
Particle Size Counting VMD & number particles

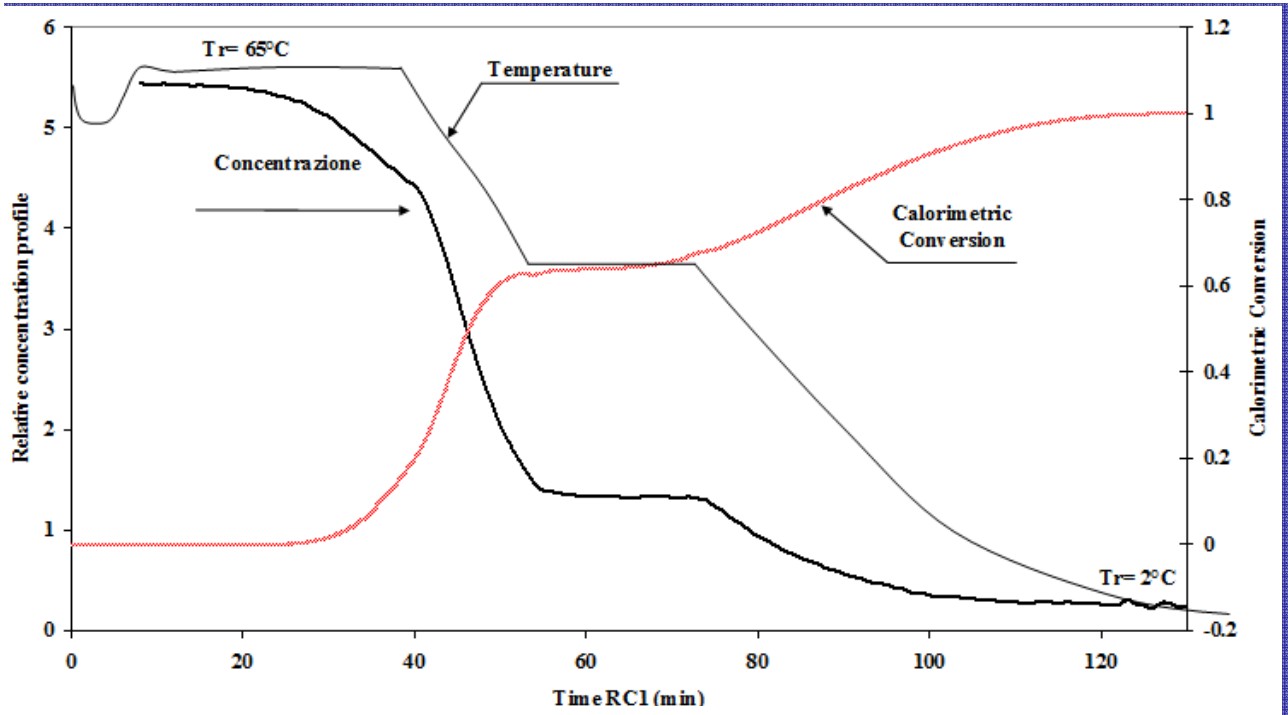


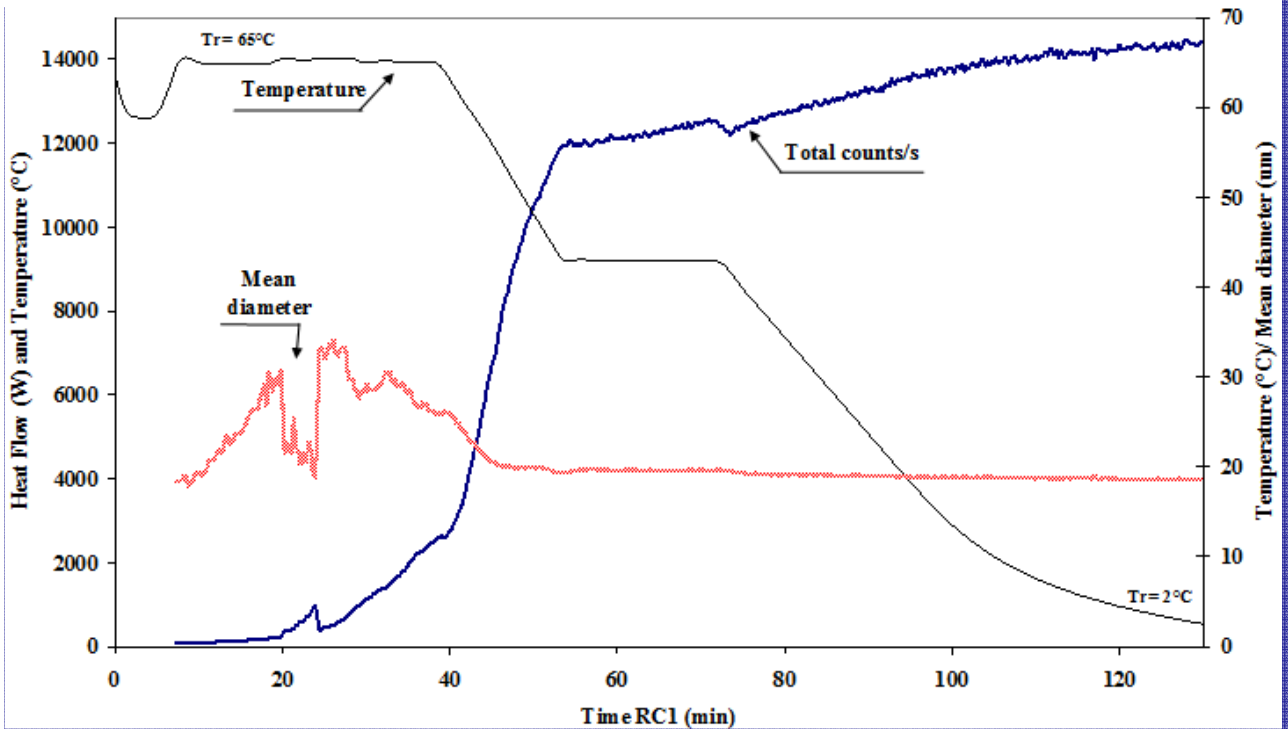
FBRM – RC1
Calorimetric Conv & number particles

Change of Process Crystallization Parameters

Calorimetry







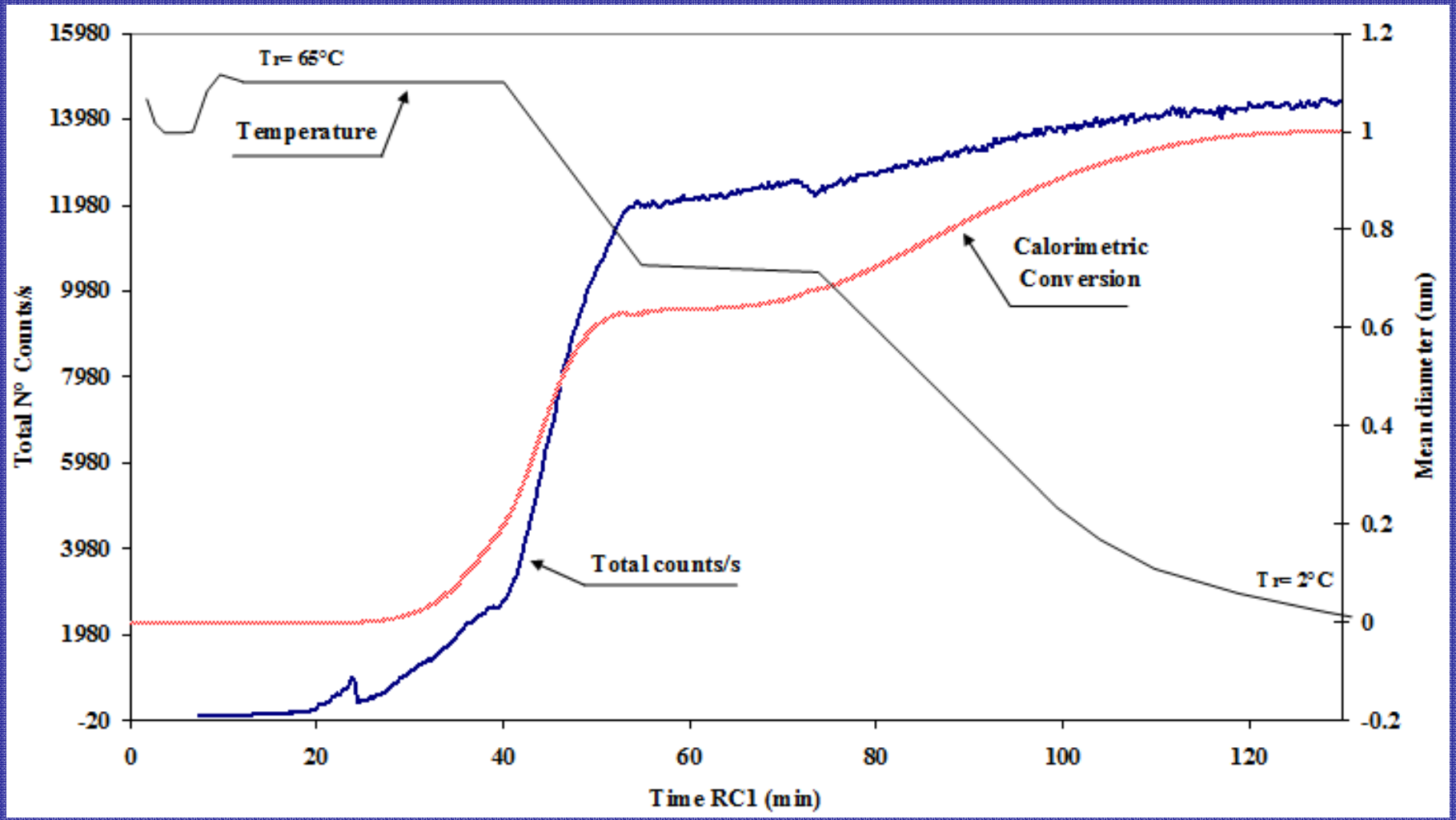
FT-IR/ATR & RC1

Concentration vs Calorimetric Conv.

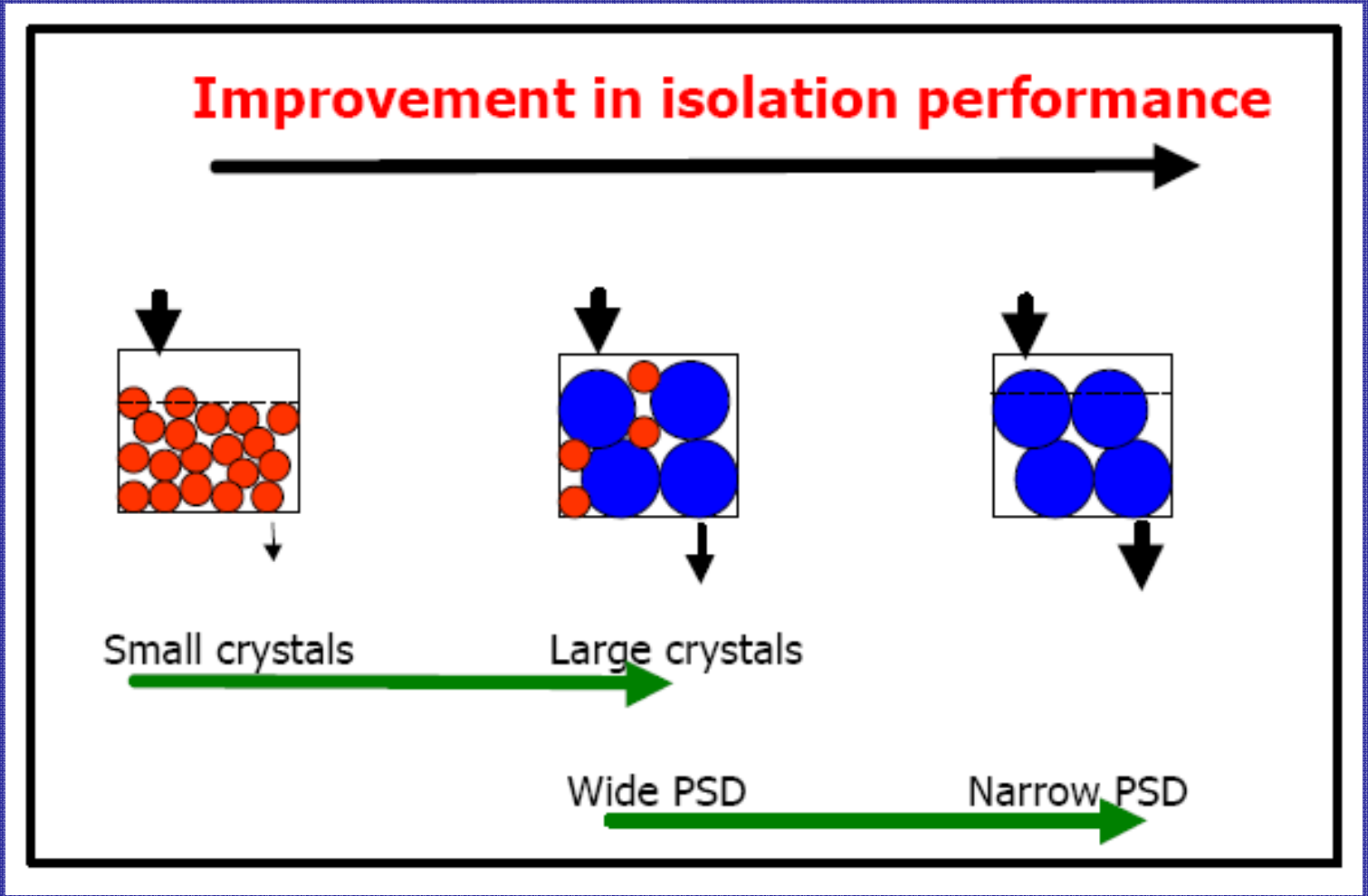
Temperature & FBRM

Temp. vs PSD

Correlation between Calorimetry and Particle Size



Impact of Crystal Properties on Isolation/Washing



Motivation

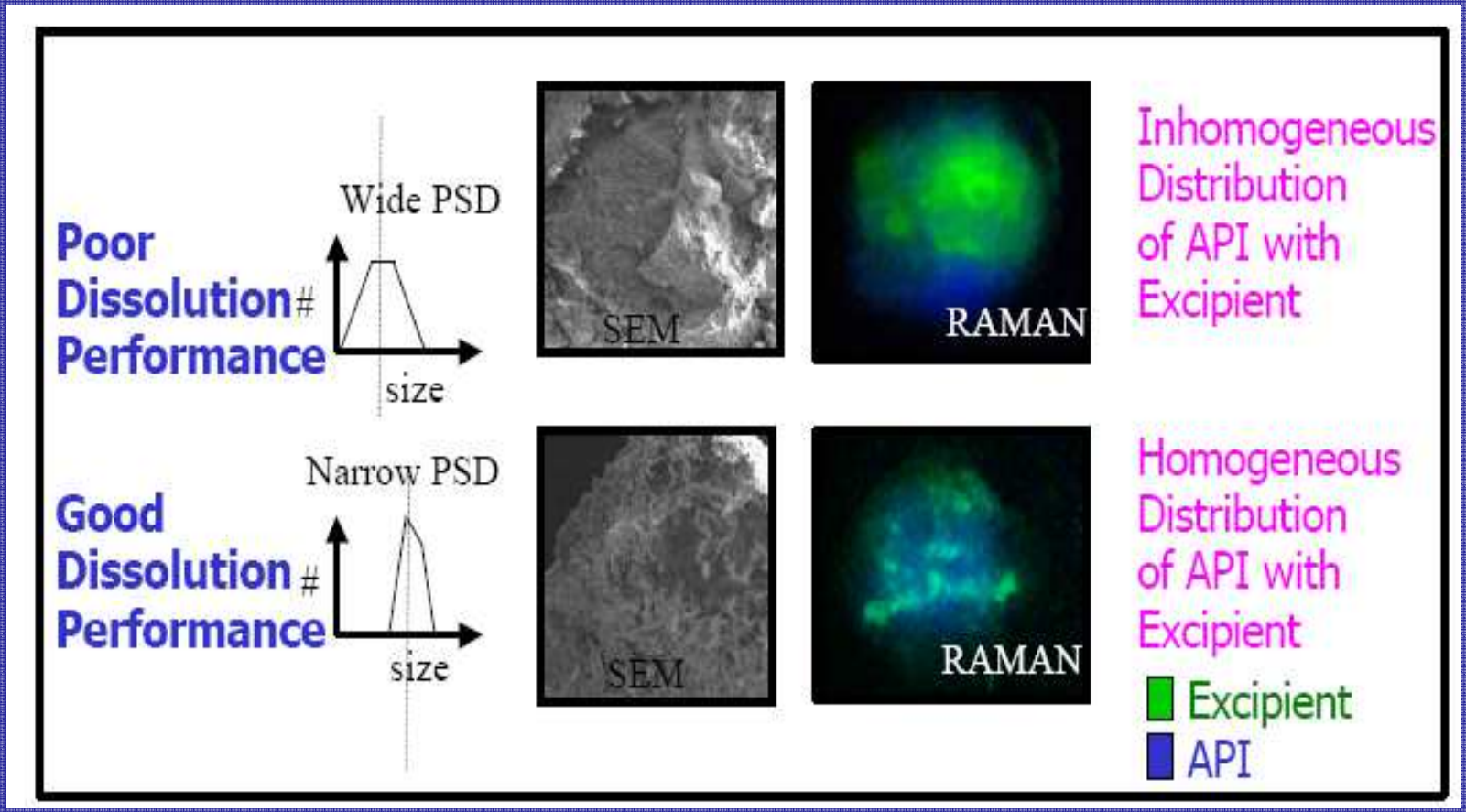
During Formulation

- Dusting
- Equipment dependence
- Variability of binder amount

Post API Synthesis

- Dryer-dependent performance of API
- No analytical method to judge performance except final dissolution testing

Impact of Crystal Properties on Formulation



Narrower particle size distributions (PSD) minimize segregation problems during mixing, rendering a more homogeneous distribution of components in the final product

On-line Particle Size Control of an API from the crystallization to the drying steps

Example of PAT application:

1. 'In-Process' acceptance criteria to replace existing release PS test

2. Validation of PAT process for Regulatory Strategy (confidence factors))

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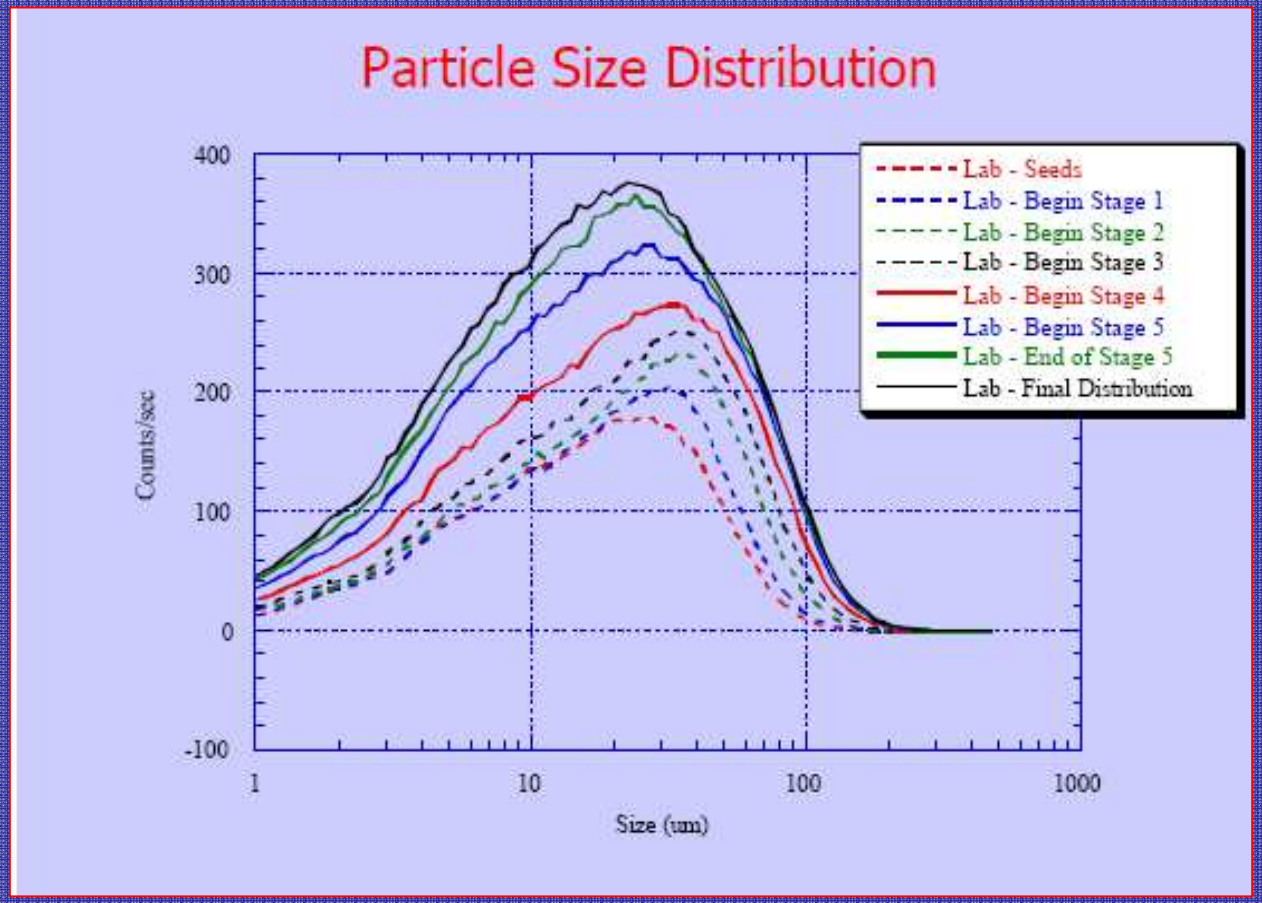
ENGINEERING
TECHNOLOGY

Lab Scale Crystallization



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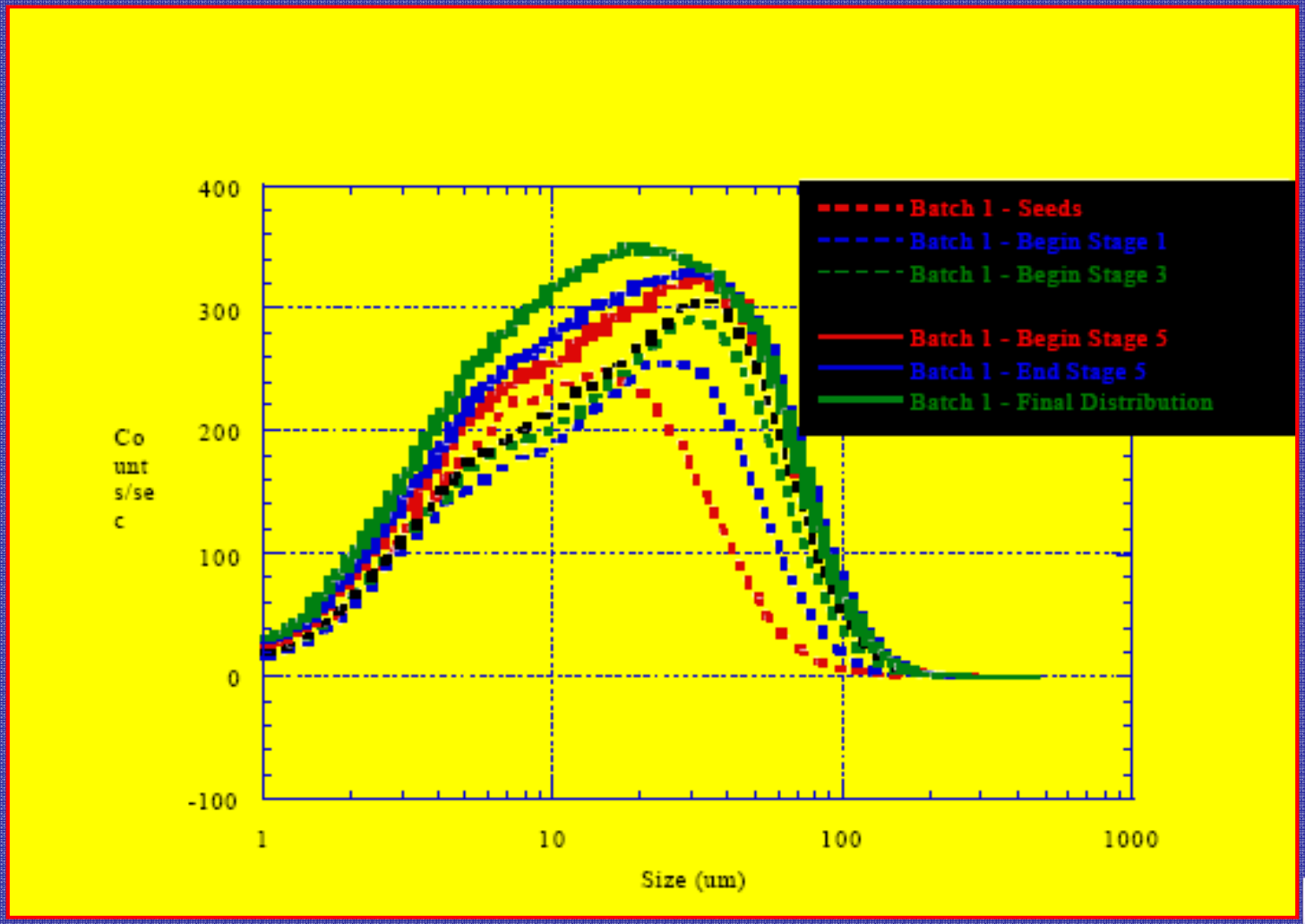
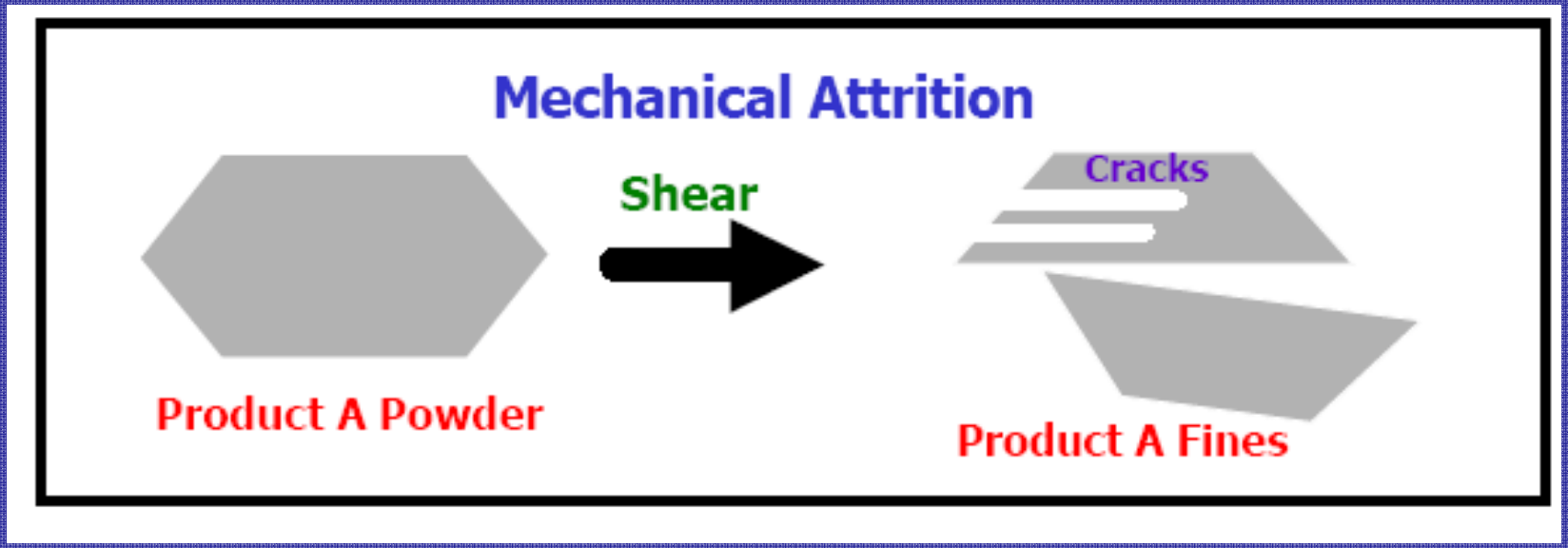
ENGINEERING
TECHNOLOGY

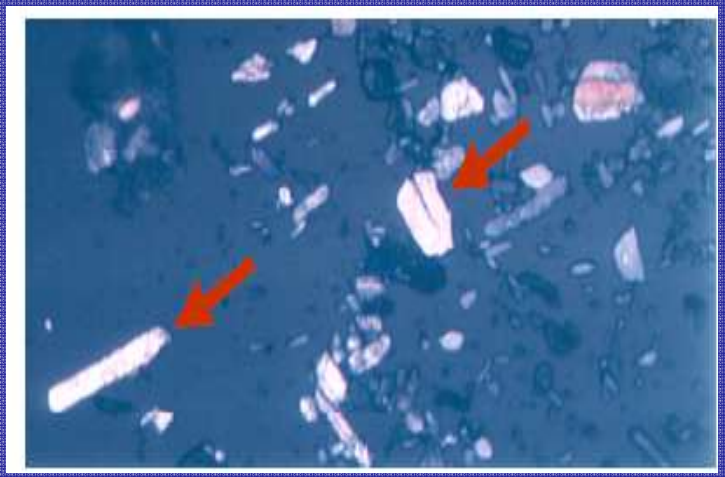
One BMS

Production Scale (4 mg)

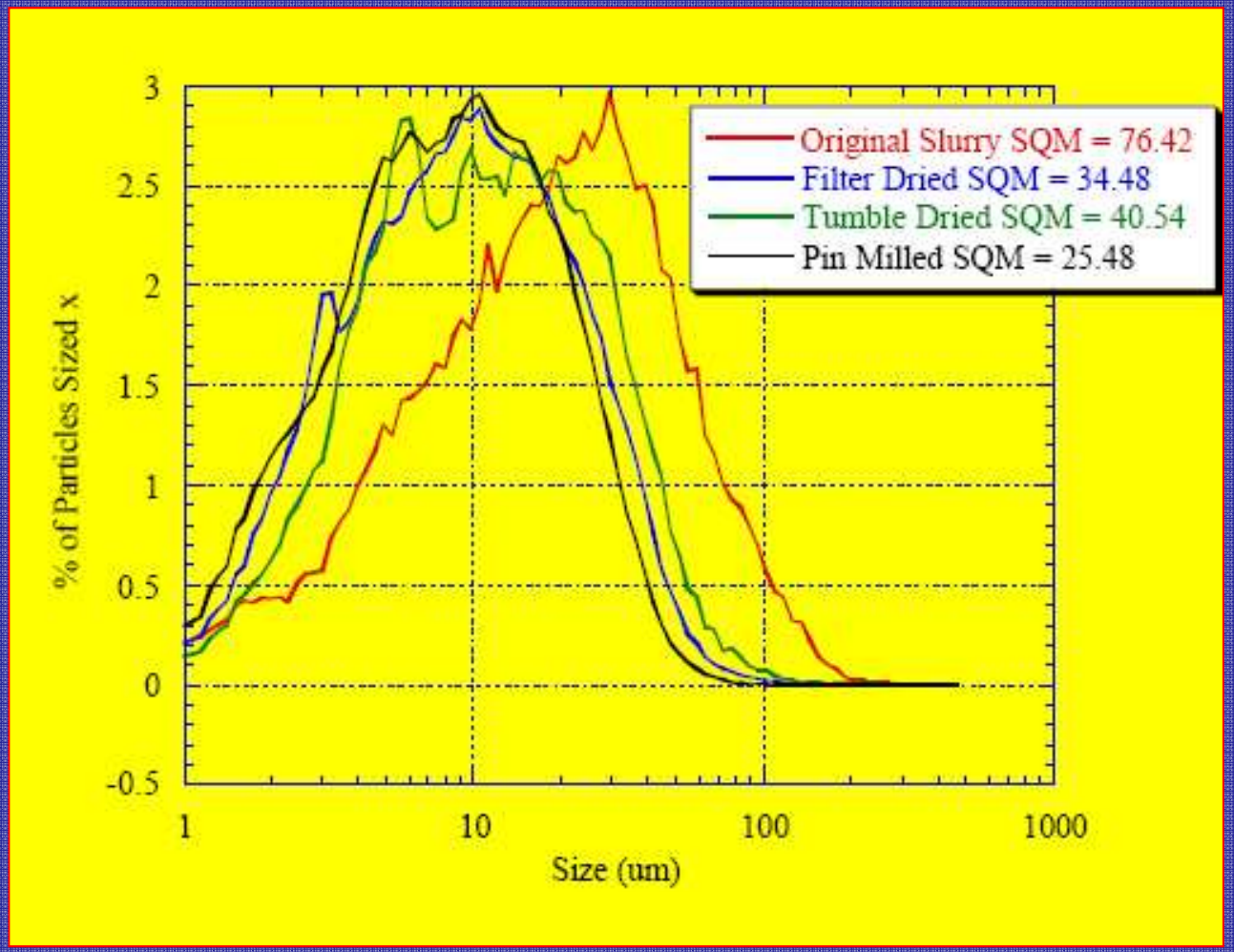


Impact of Agitation on Particle Size Distribution

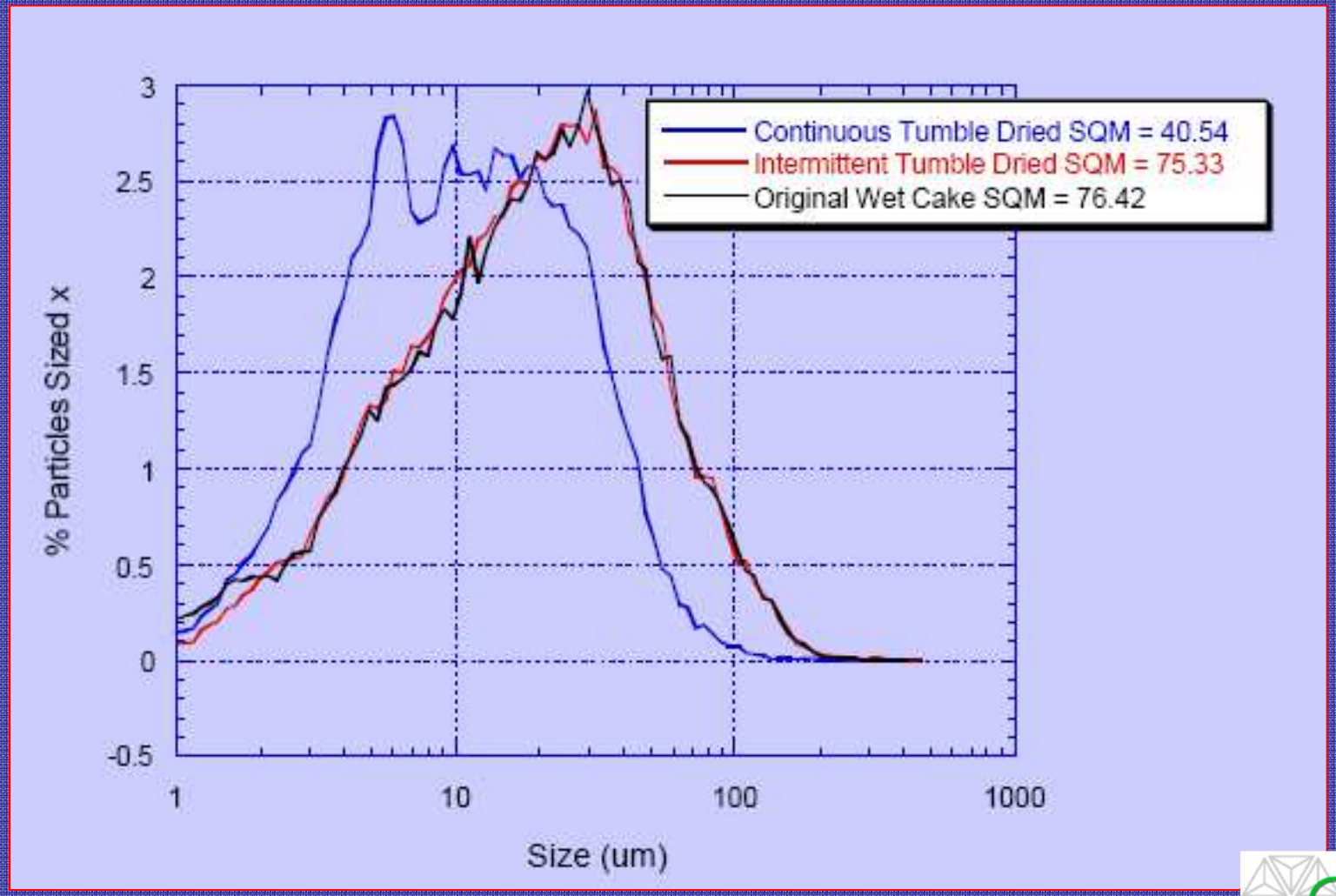




Effect of Agitated Drying

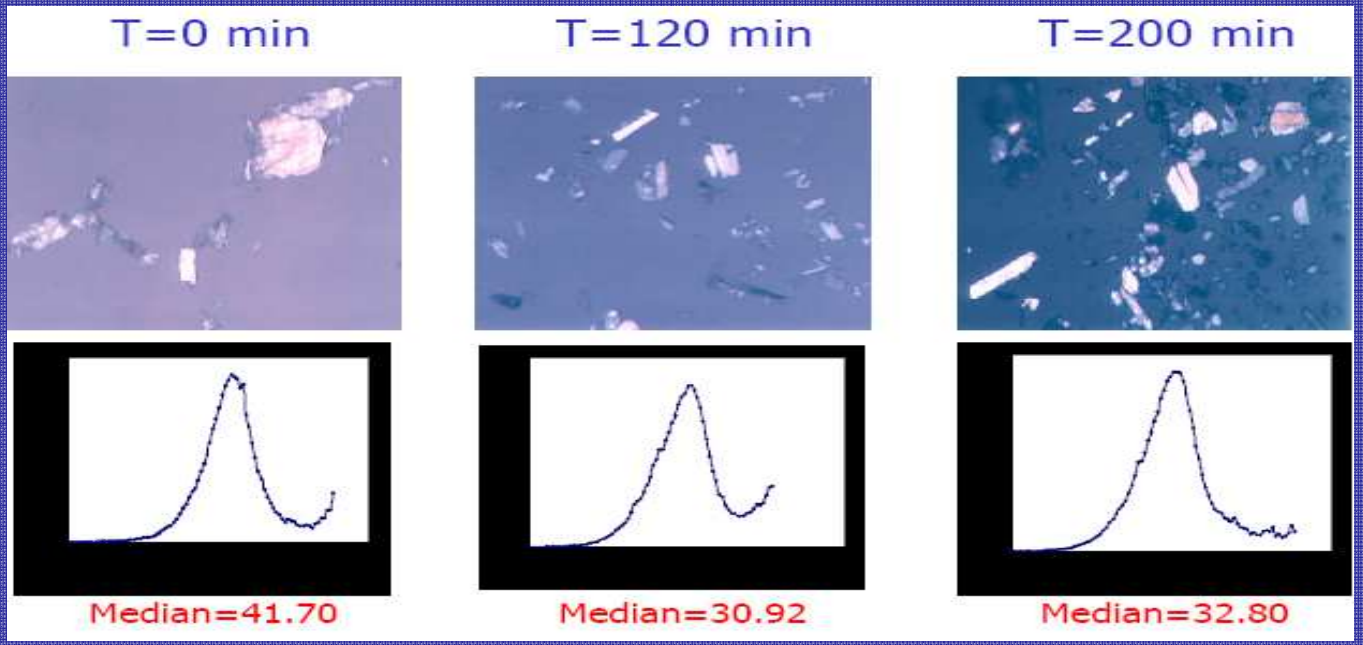


Monitoring in Tumble Dryer

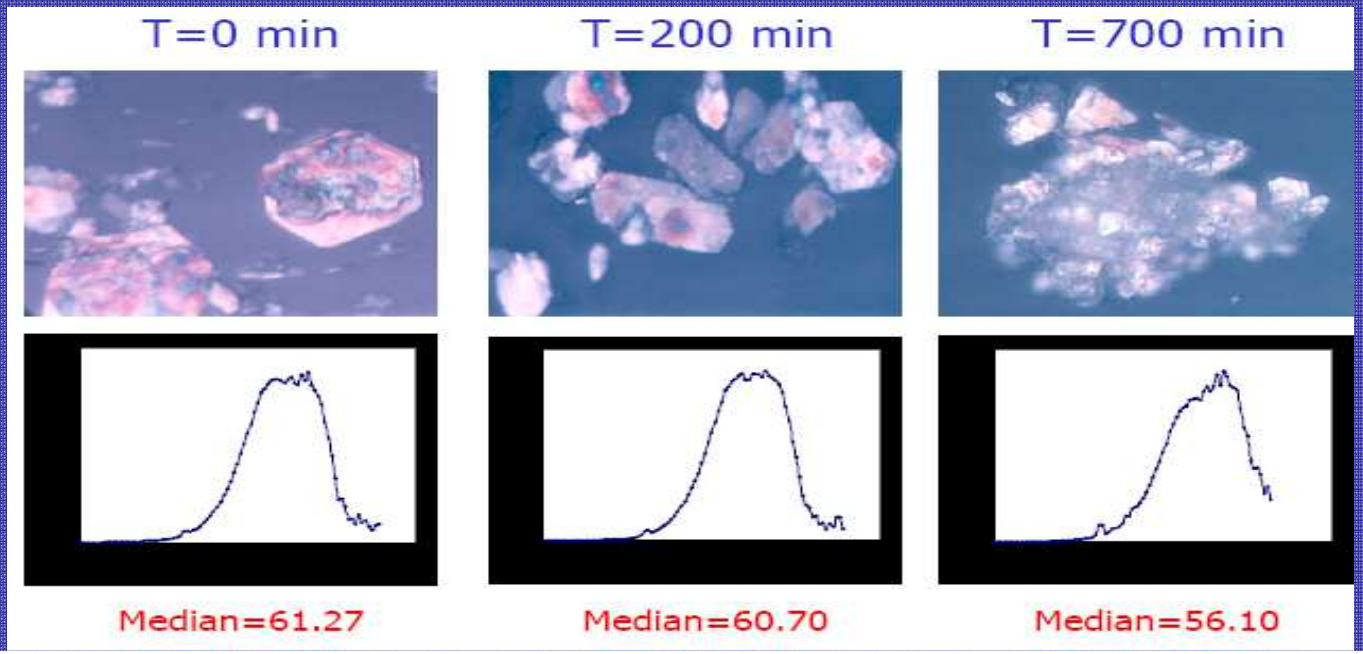


Cracking during the drying

High shear



Low shear



PAT demonstrated that :

- used in crystallization process development in CQAs monitoring
- improves confidence during scale up
- applied in monitoring of downstream operations
- for better PSD control during the crystallization
- crystallization & downstream process optimization
- for better control of API attributes leading to consistent performance of formulation process and drug product performance

Advantage of PAT application

There are primary components of risk assessment:

i) Understanding of the uncertainties of the process;

ii) Identification and quantification of the failure mechanisms on the process

iii) Estimation of the risks associated with each step of the process.

iv) Documentation of physical characteristics for the Regulatory Requirements

Thanks for your attention

M. Nebuloni