Solid State:

why the increasing interest for solid state of API ?

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EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

Guideline on Active Substance Master File Procedure

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4.3. Characterisation

Physico-chemical Characteristics

Information set out under the relevant headings below should cover aspects of physicochemical characteristics which have been investigated, whether or not they are included in the specification for the active substance.

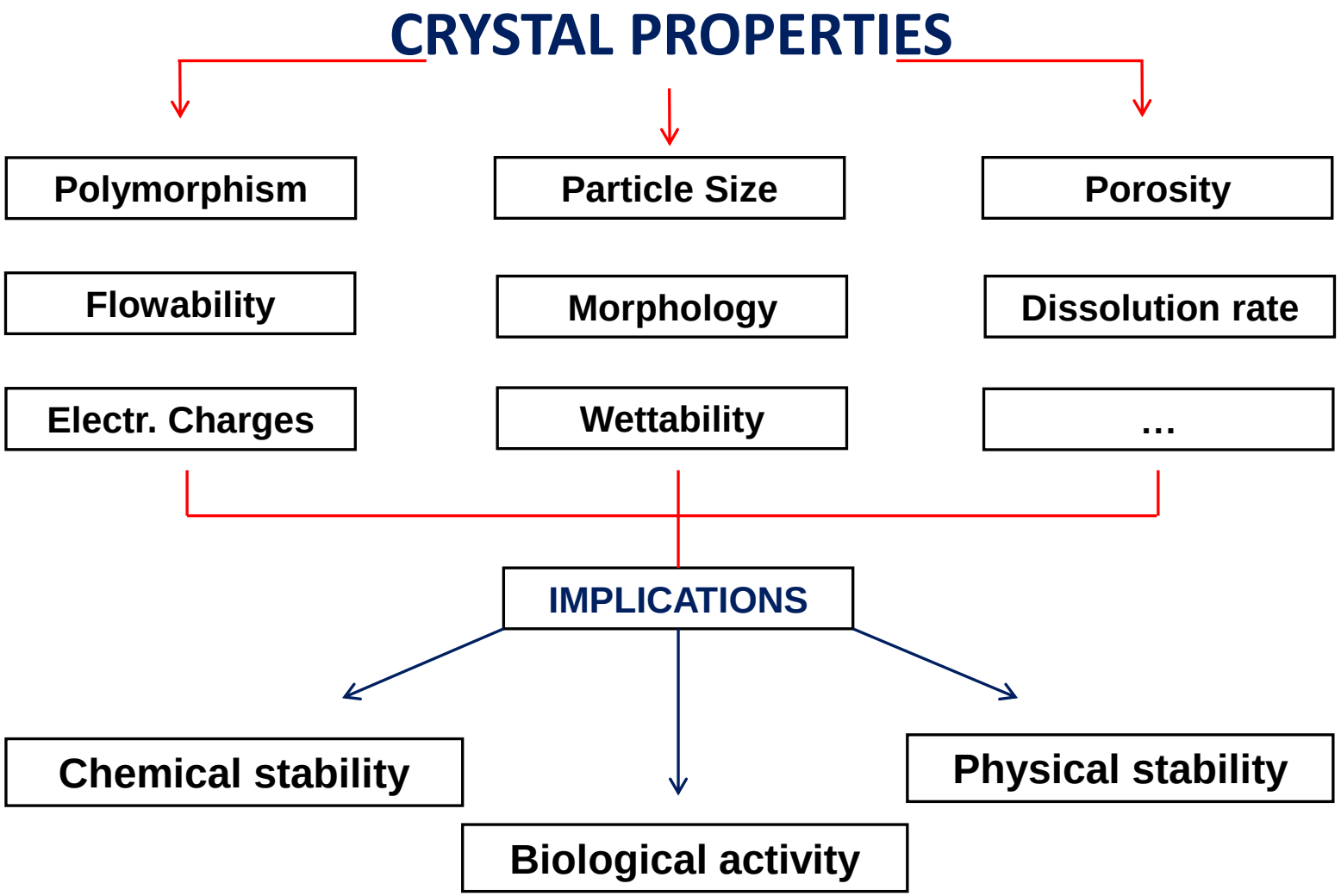
Polymorphism

Polymorphism is the property of a solid state chemical substance to exist in the solid state in different crystalline forms. Some active substances exist in different polymorphs possessing different physico-chemical properties. These forms may affect processability, stability, dissolution and bioavailability of the drug product.

Physical characteristics

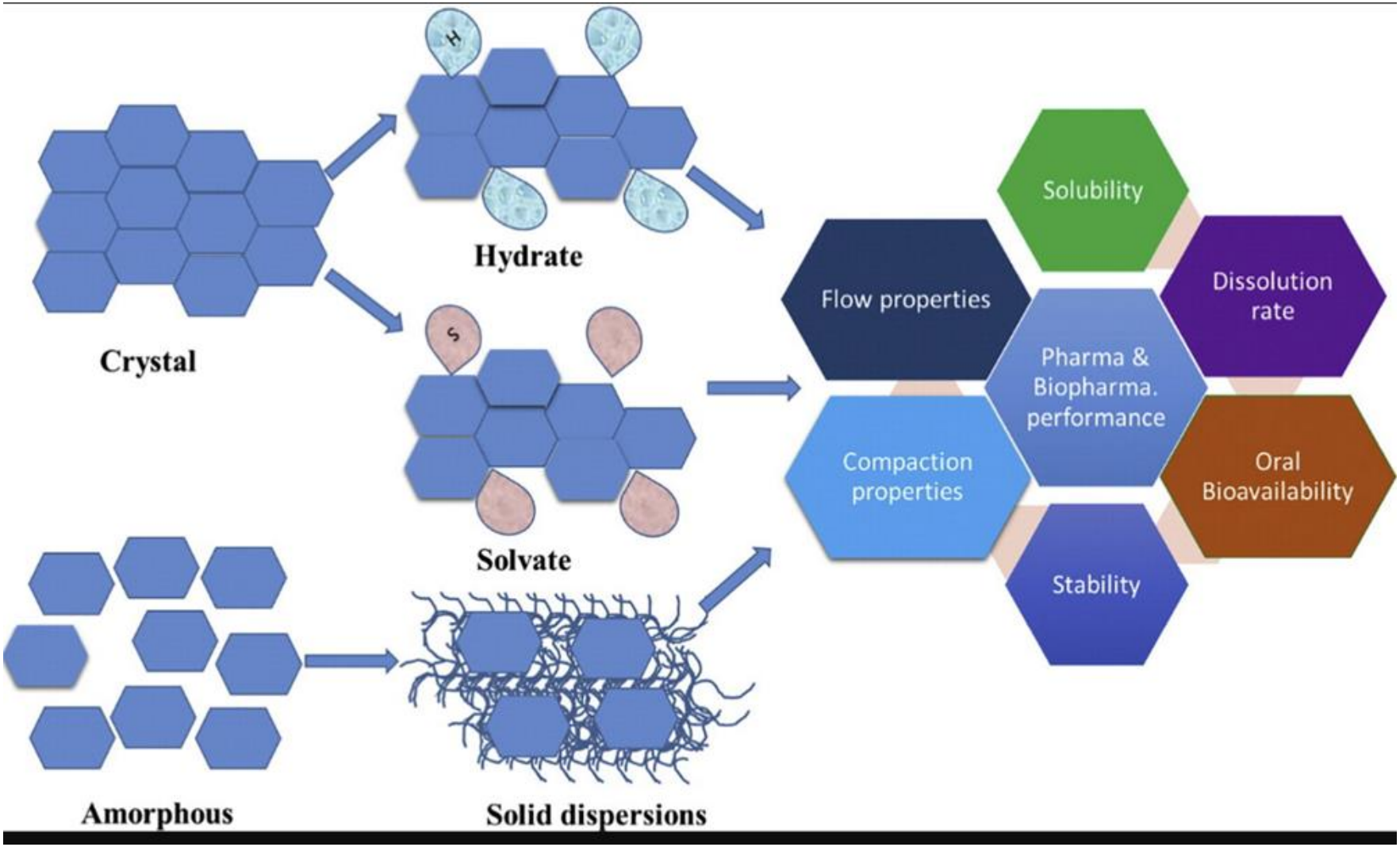
Physical properties should be stated here and, if significant, information on particle size (distribution), solvation, melting point, hygroscopicity and boiling point should be added.

INTRODUCTION:
Solid state

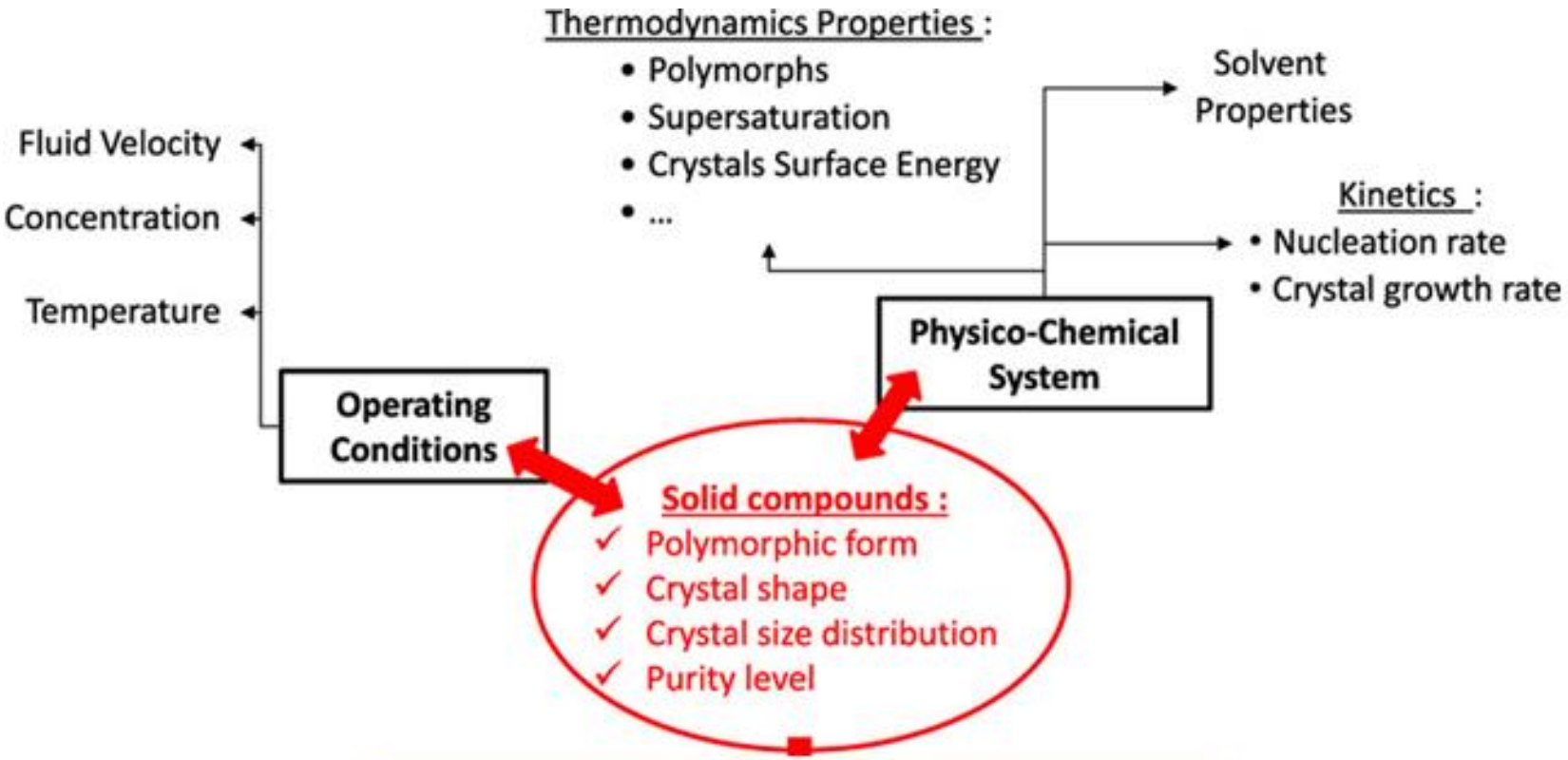


The starting point for the knowledge of the solid state

CRYSTALLIZATION



Physical parameters of solid in relation to the crystallization process



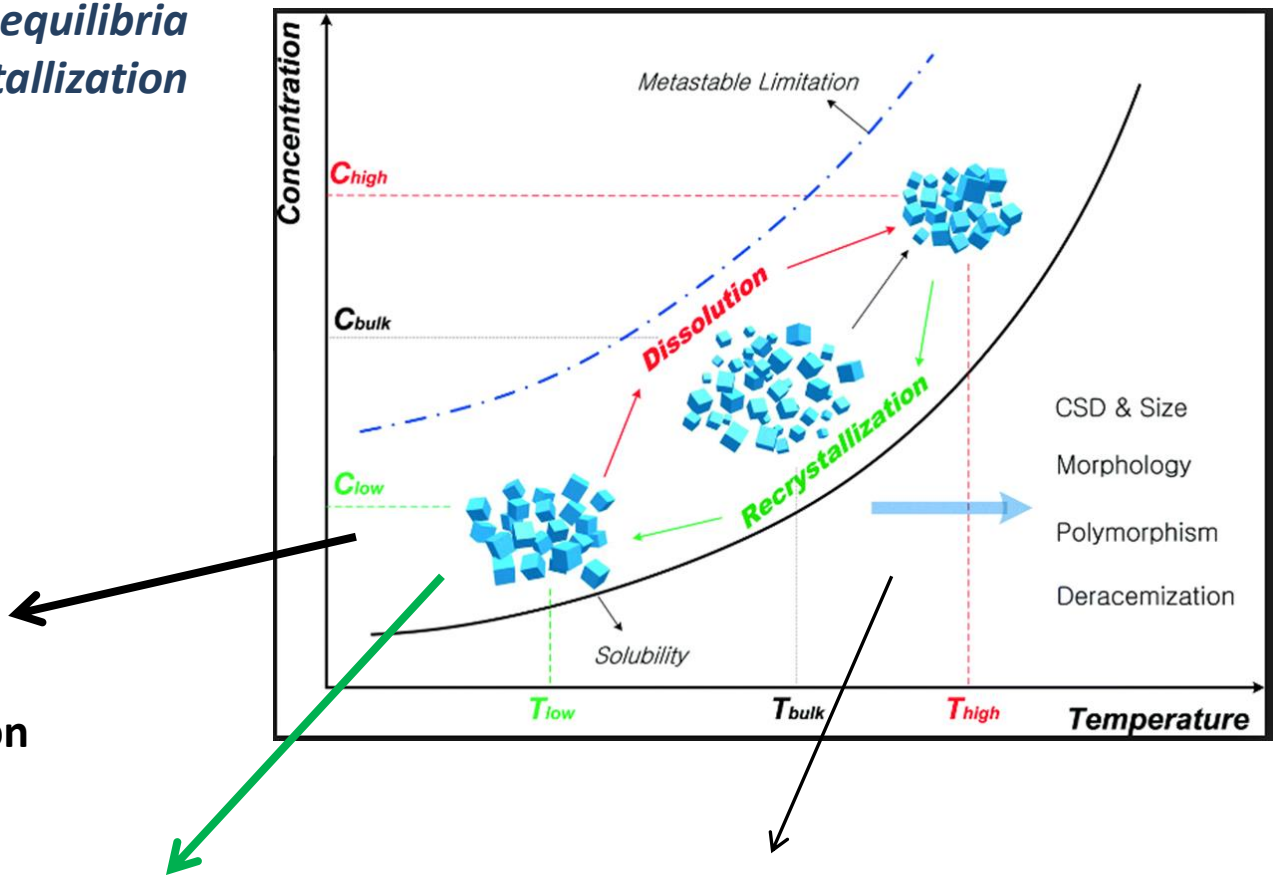
CRUCIAL POINTS TO BE DETERMINED FOR A ROBUST CRYSTALLIZATION:

Definition of:

- **MSZW: Solubility/Concentration vs Temperature**
- **Kinetics Parameters**
- **Process Parameters: Temperature profiles, Time, Cycling experimental profiles**

MSZW: META-STABLE ZONE WIDTH

Understanding phase equilibria is crucial in crystallization operation

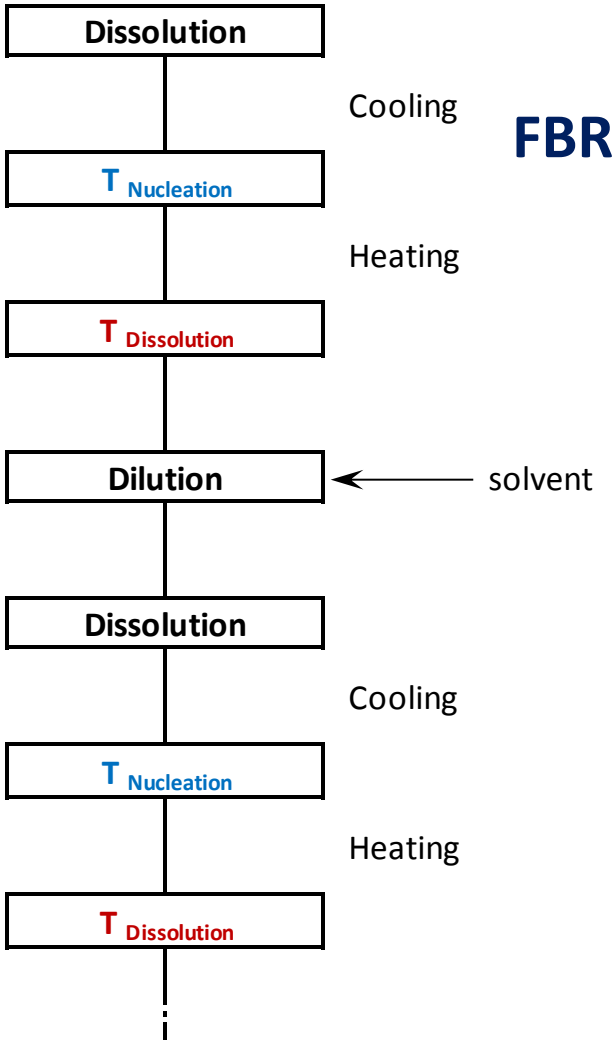


LABILE:
Spontaneous Crystallization

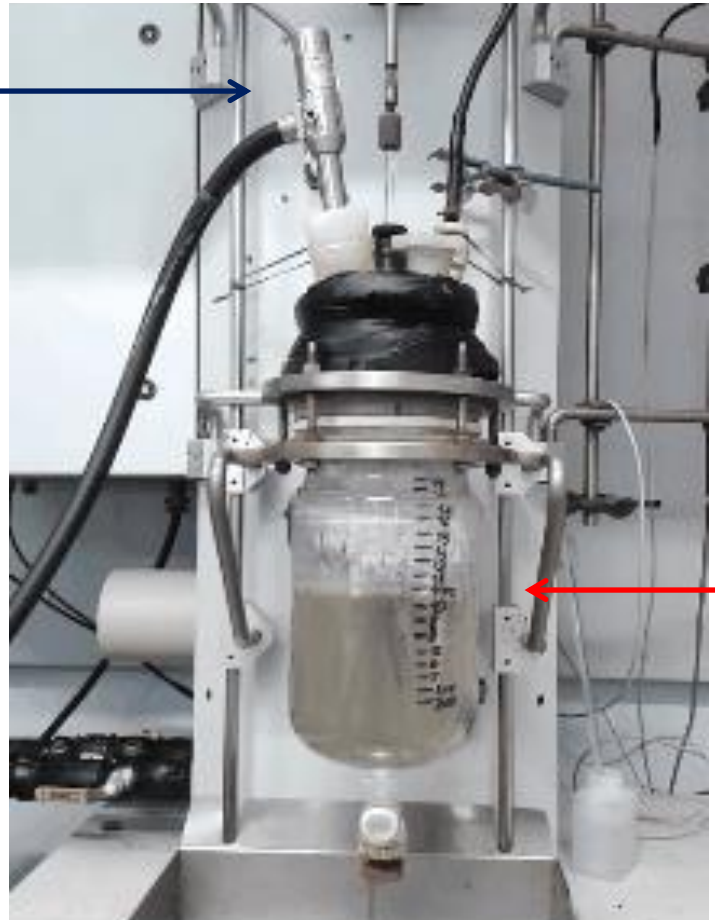
SUPERSATURATED (METASTABLE):
Crystal Growth

UNDERSATURATED: Crystal Dissolution

Test procedure by RC1 and FBRM technique

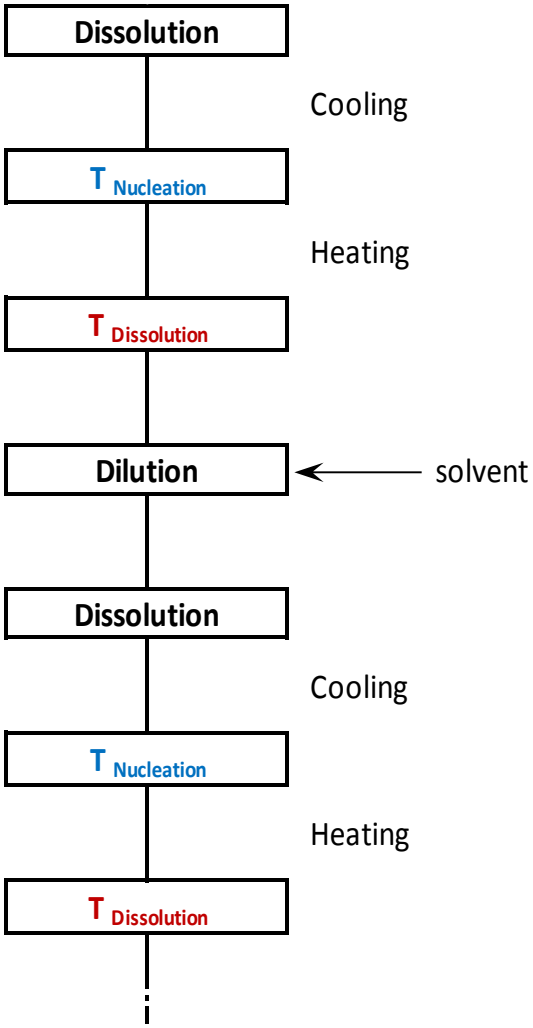


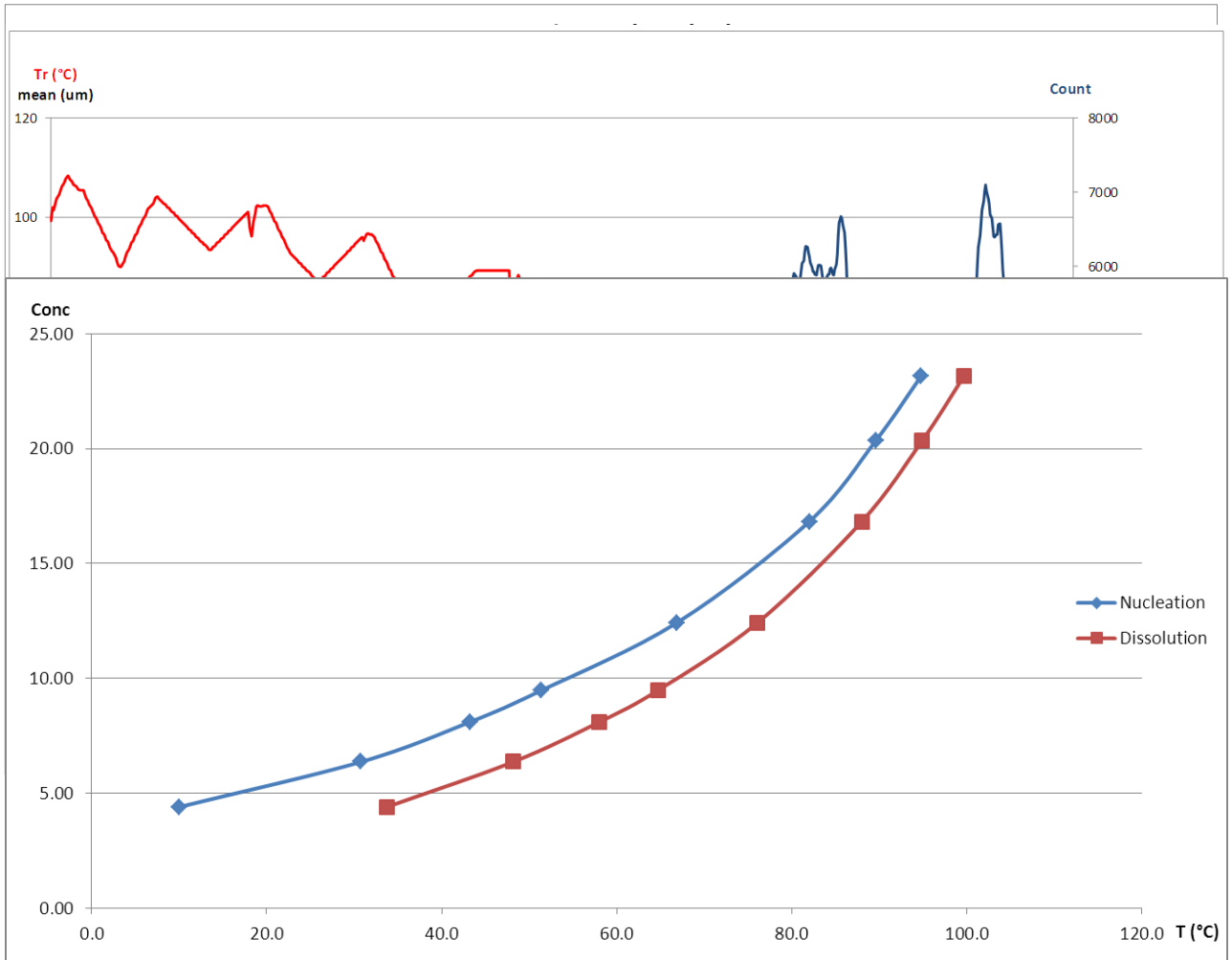
FBRM



RC 1

MSZW determination procedure

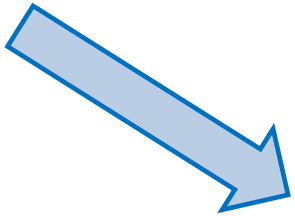




Example of an API Crystallization investigation for ASMF

Problems encountered during an industrial crystallization process:

- Polymorphic forms
- Morphology
- Particle size
- Filtrability

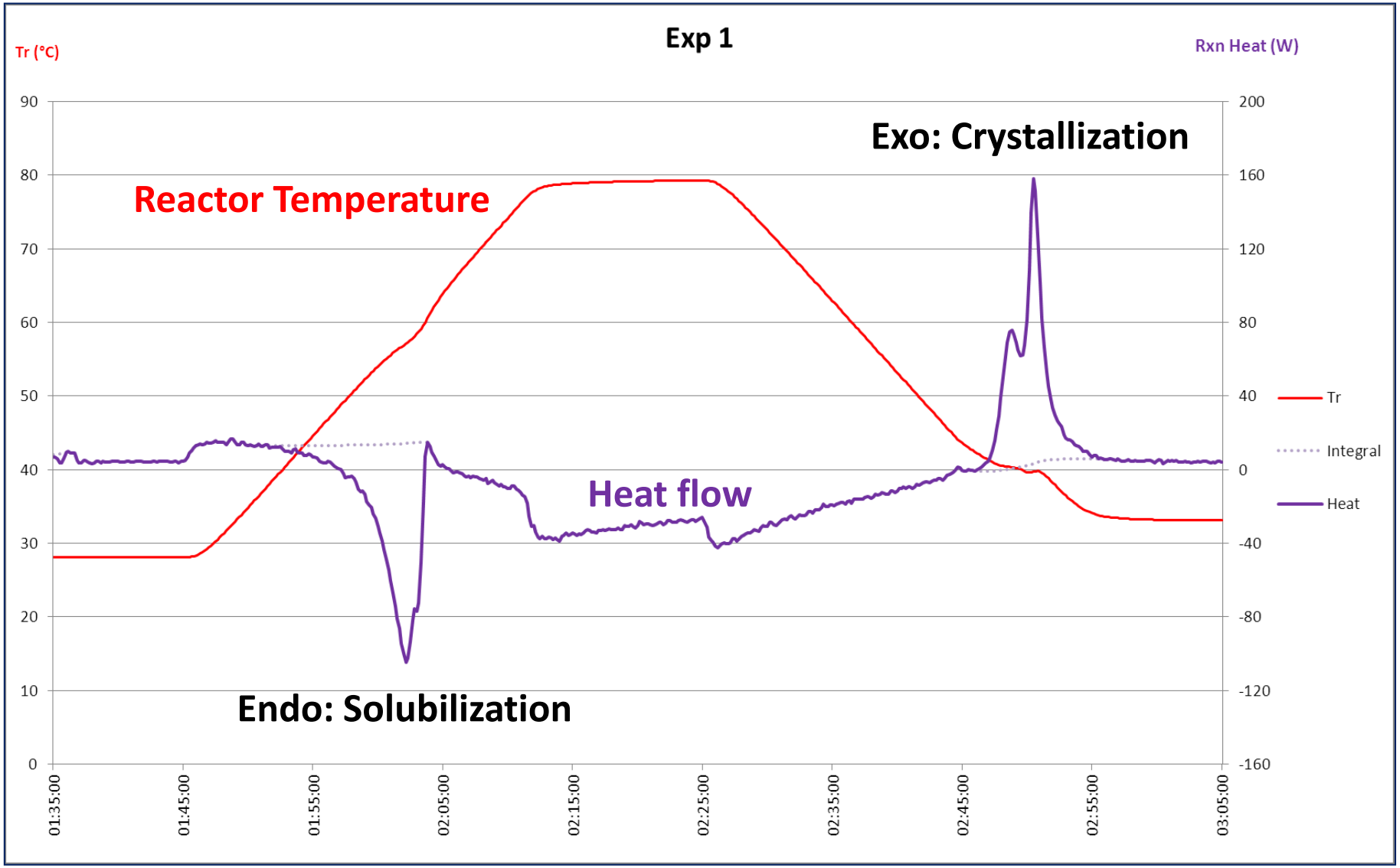


ANALYTICAL CONTROL

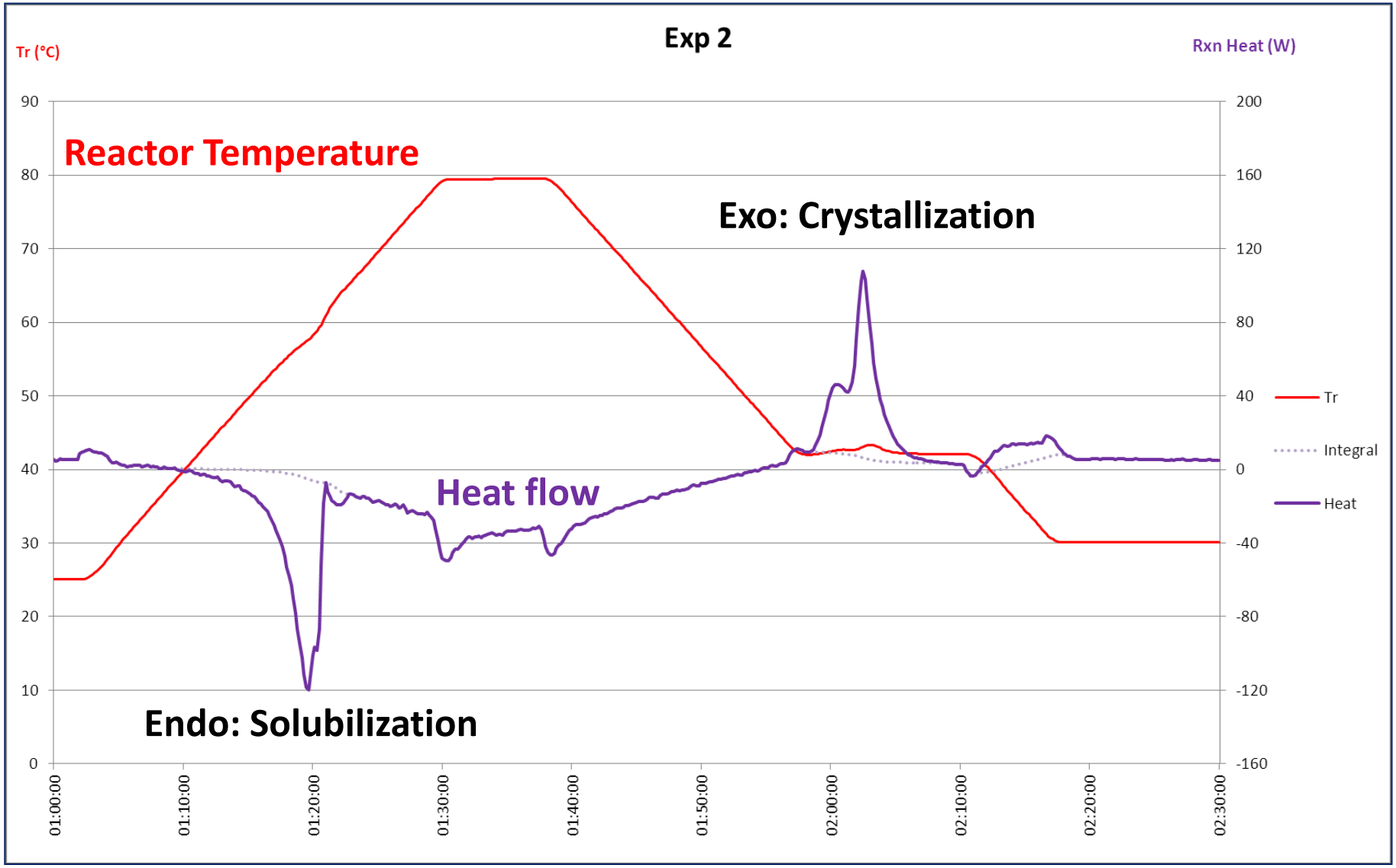
ON-LINE	OFF-LINE
Calorimetry (RC1)	PSD (Laser diffraction)
Particle Size (FBRM)	XRPD (X-Ray diffraction)
	SEM (Scanning electron Microscope)

On-Line control by calorimetry (RC1)

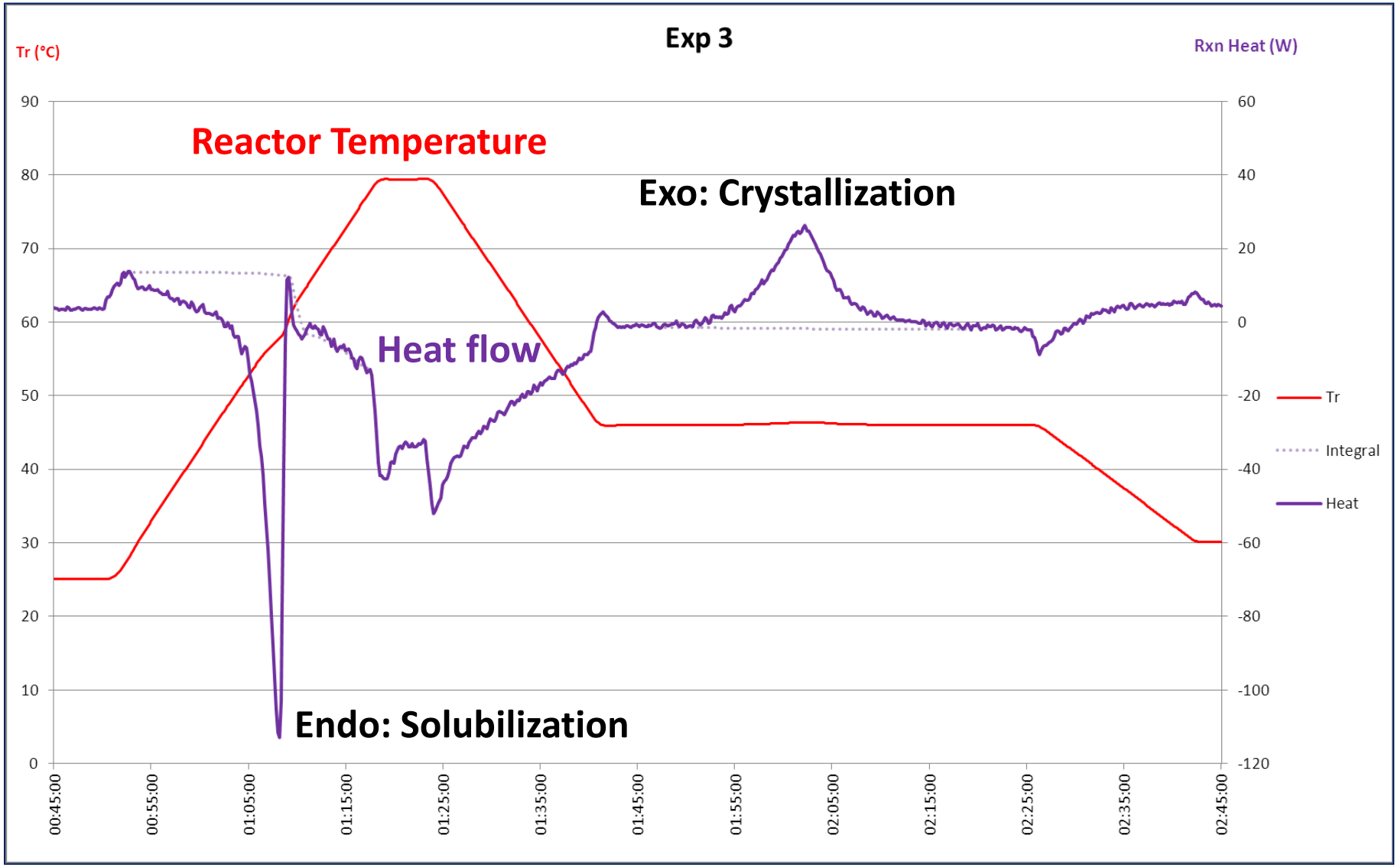
First Trial



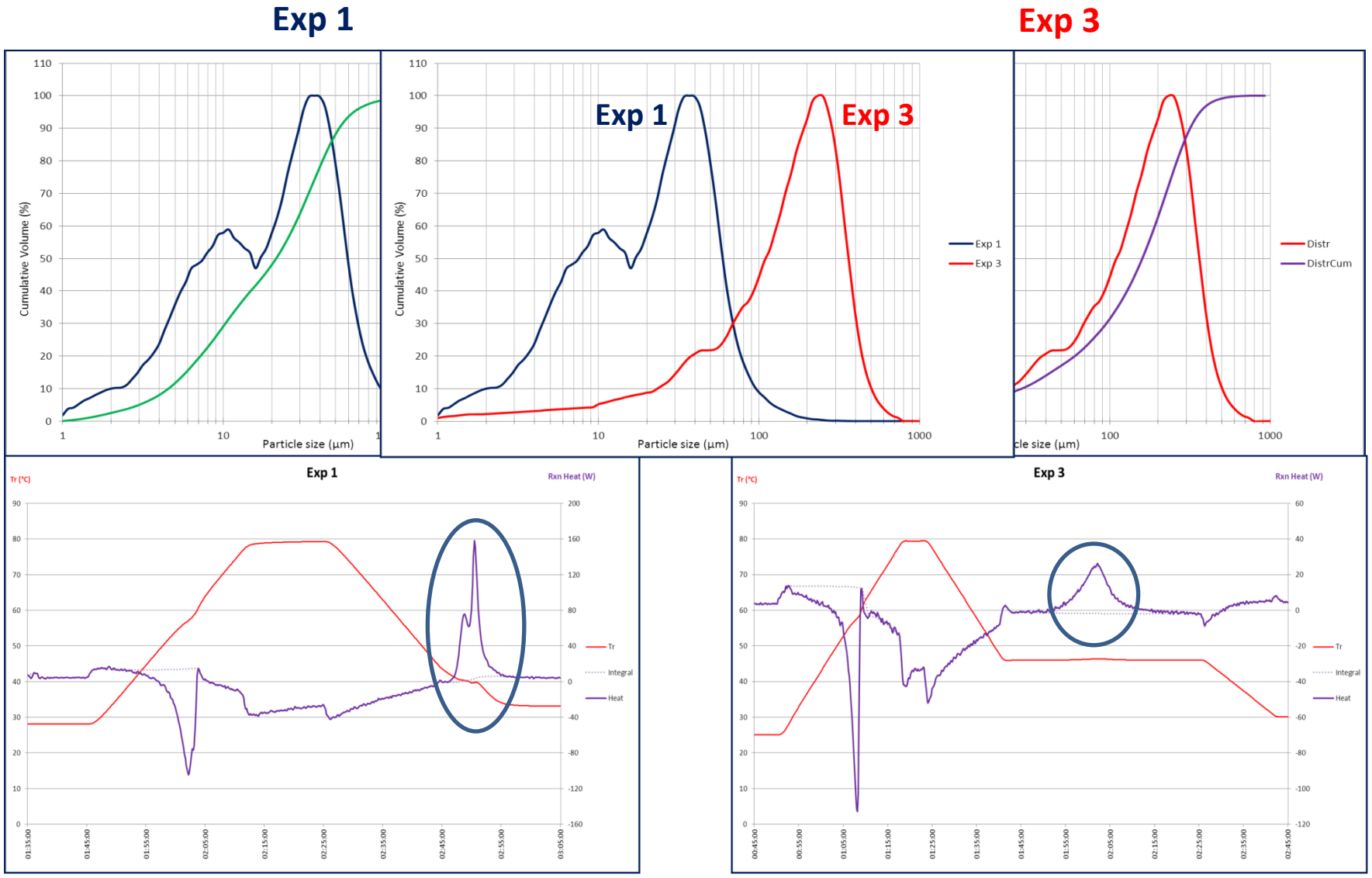
Second Trial



Third Trial

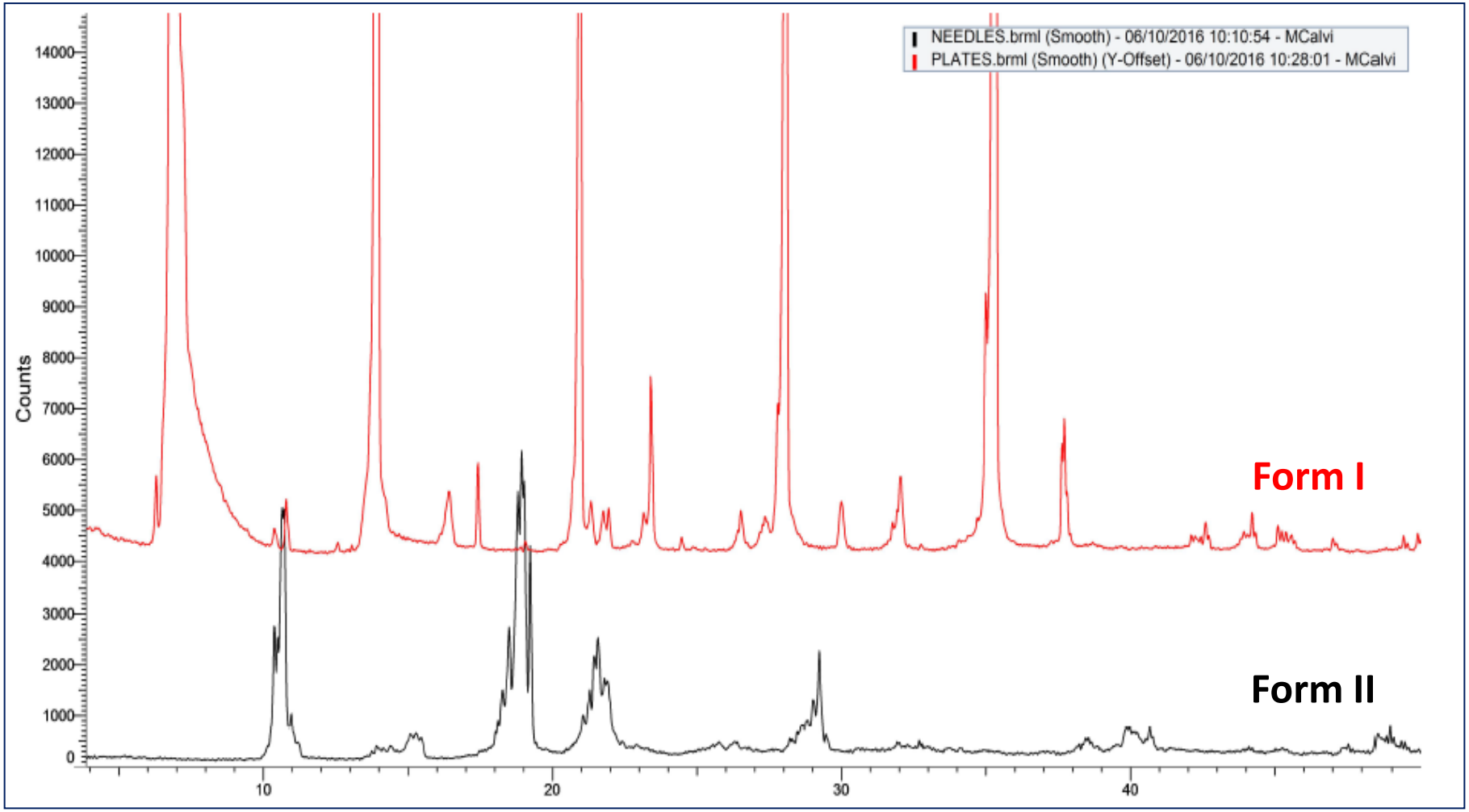

Exp 3
Tr (°C)
Rxn Heat (W)
Reactor Temperature
Exo: Crystallization
Heat flow
Endo: Solubilization
90
80
70
60
50
40
30
20
10
0
60
40
20
0
-20
-40
-60
-80
-100
-120
00:45:00
00:55:00
01:05:00
01:15:00
01:25:00
01:35:00
01:45:00
01:55:00
02:05:00
02:15:00
02:25:00
02:35:00
02:45:00
Tr
Integral
Heat

Comparison of Calorimetry and PSD data of the trials



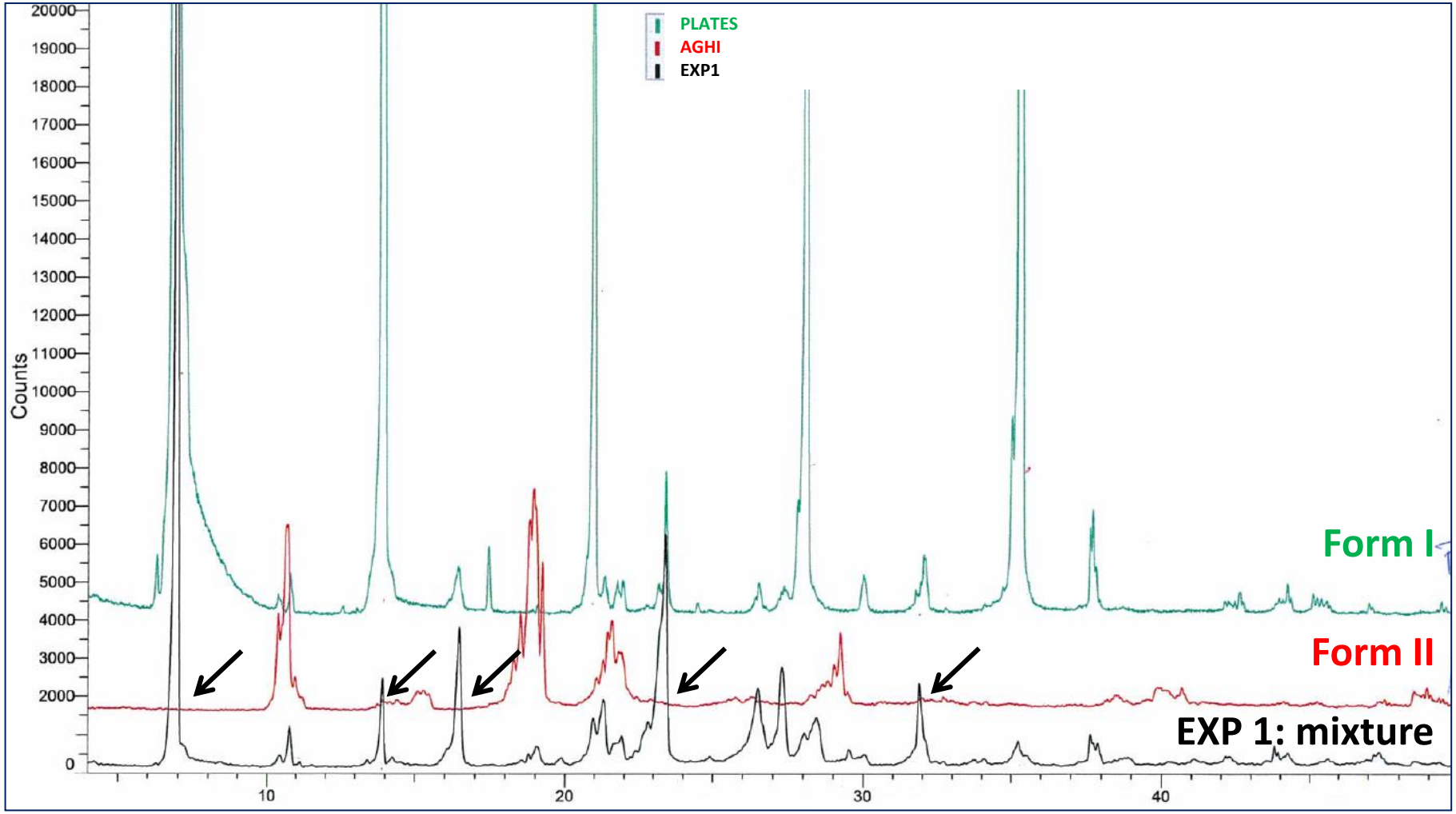
Off-Line Analyses - Polymorphism

XRPD – X-RAY POWDER DIFFRACTION



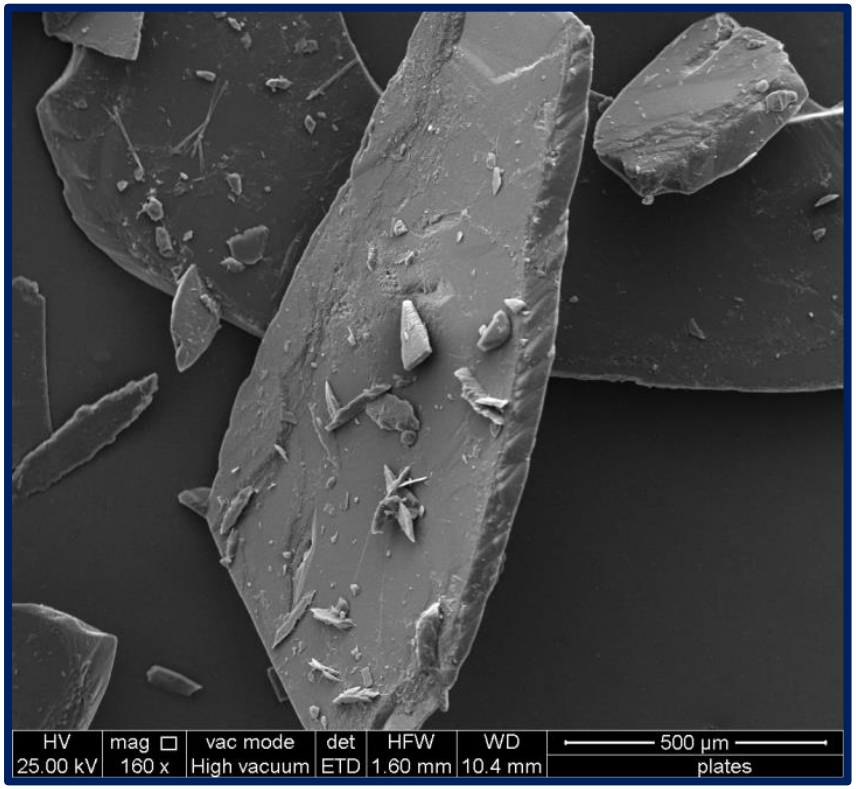
Polymorphic Mixture of solid froms Test 1

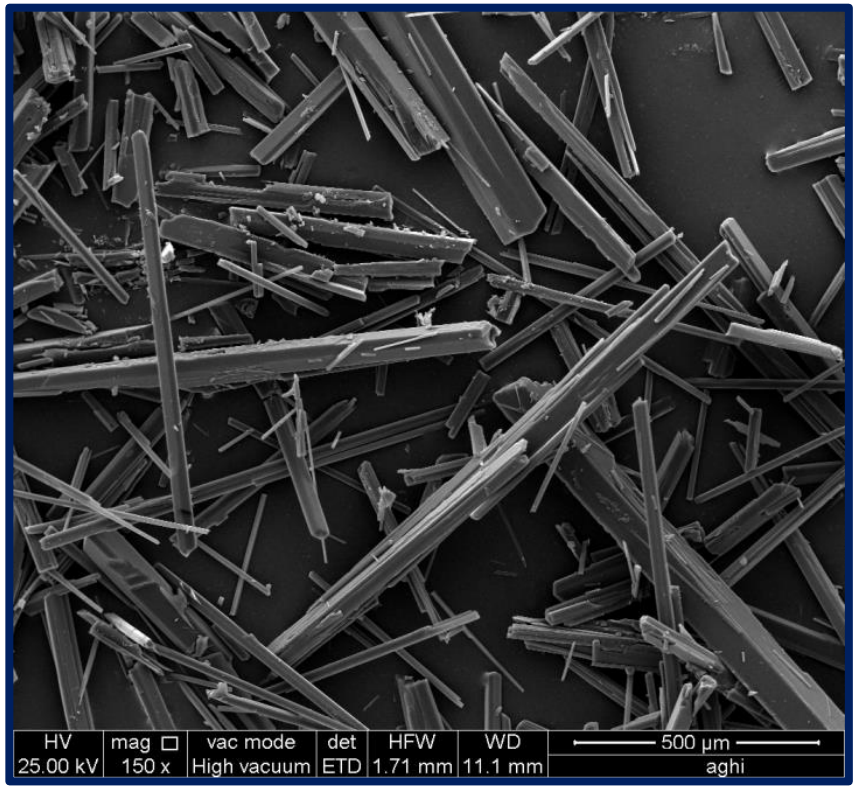
XRPD – X-RAY POWDER DIFFRACTION



Crystal Morphology of different polymorphs

SEM – SCANNING ELECTRON MICROSCOPE





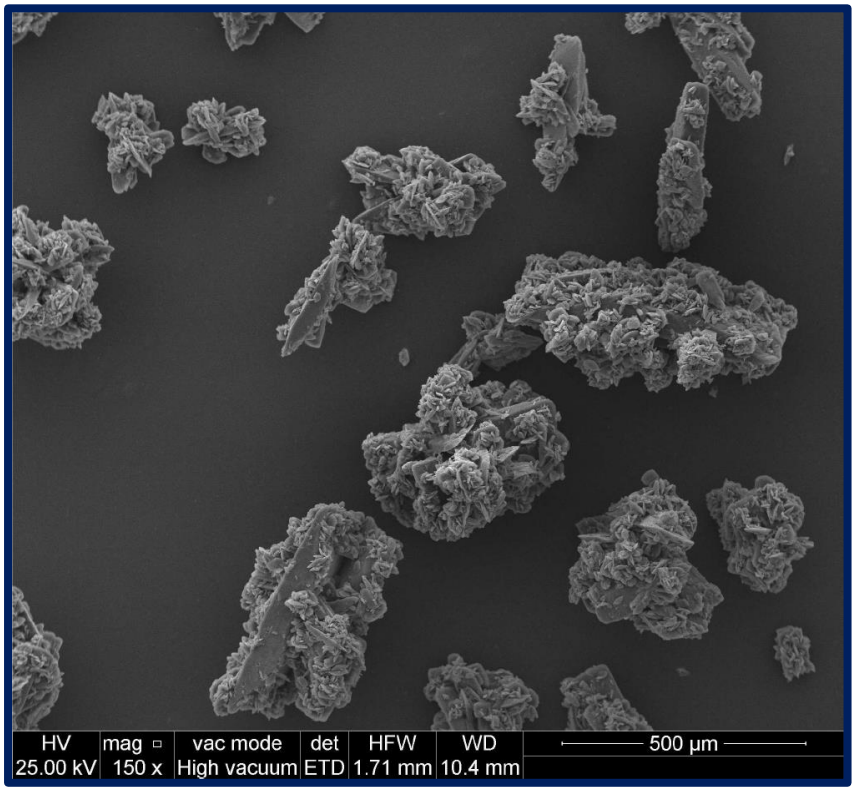
FORM 1 - PLATES

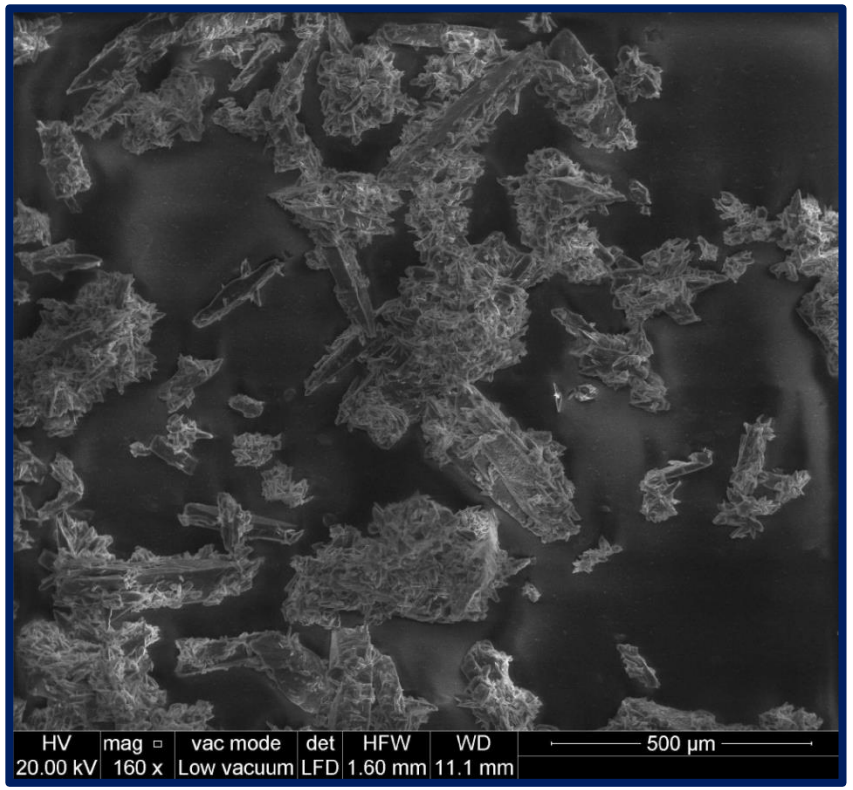
FORM 2 - NEEDLES

STANDARD FORMS

Crystal morphology of the polymorphic mixtures

SEM – SCANNING ELECTRON MICROSCOPE



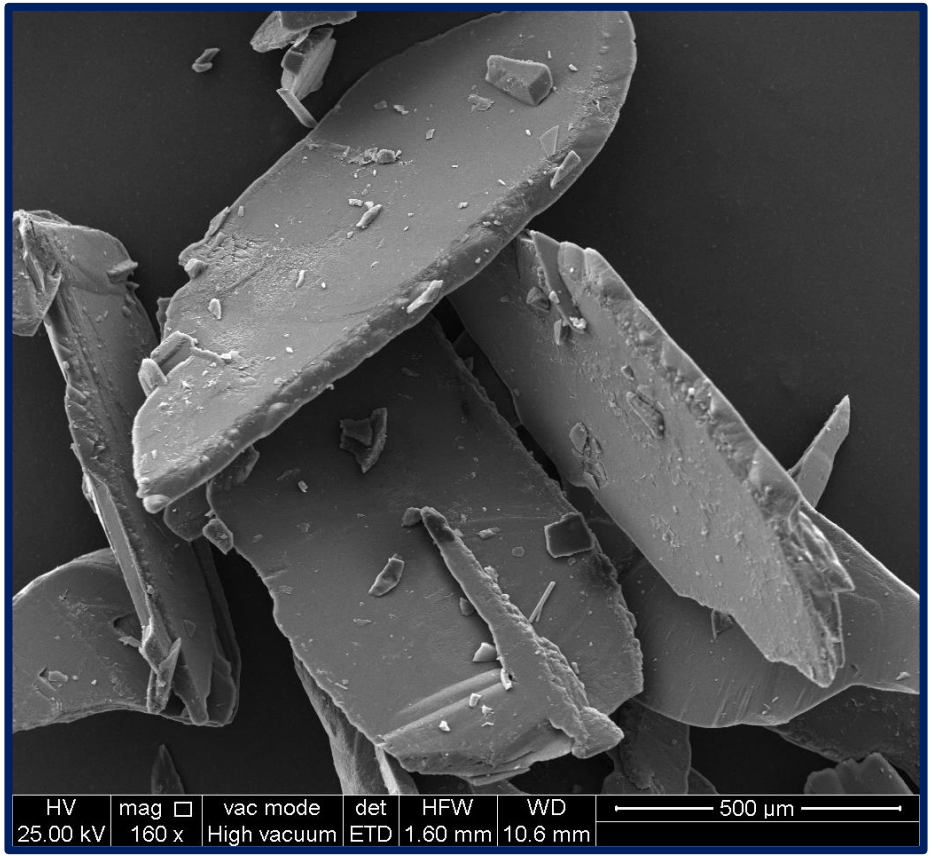


EXP 1 **EXP 2**

Mixture of POLYMORPHIC FORMS and amorphous

Crystal Morphology of Trial 3

SEM – SCANNING ELECTRON MICROSCOPE

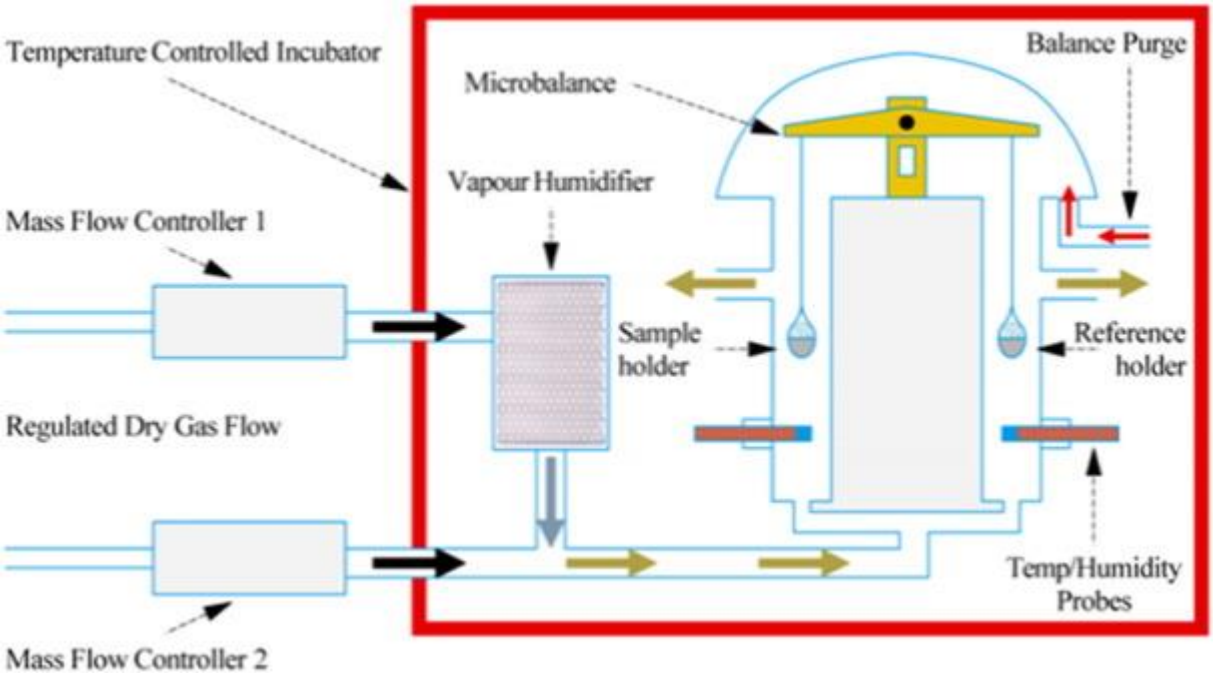


EXP 3

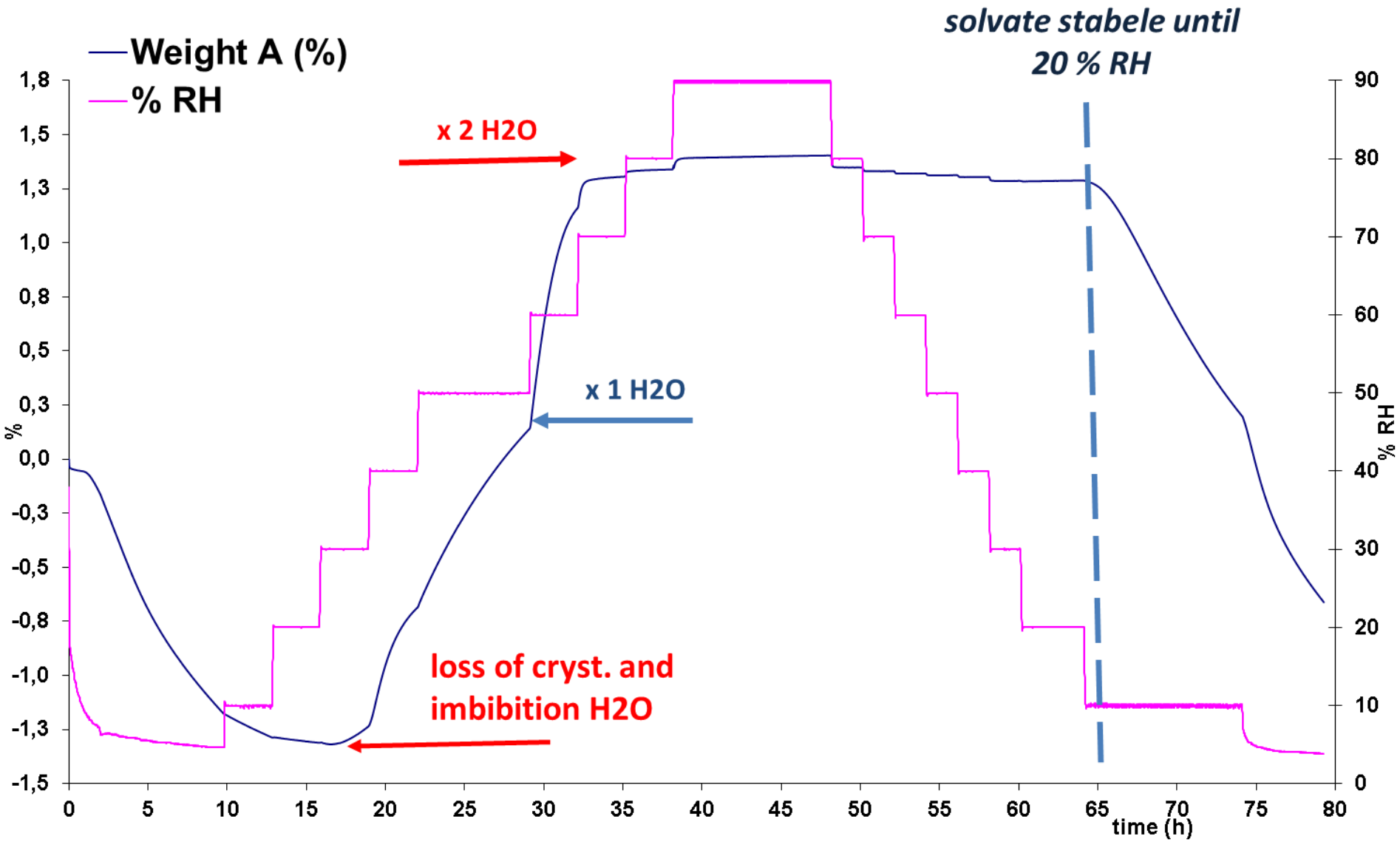
TARGET: FORM I

Crystal Solvate formation predict and characterized by
Dynamic Vapor Sorption

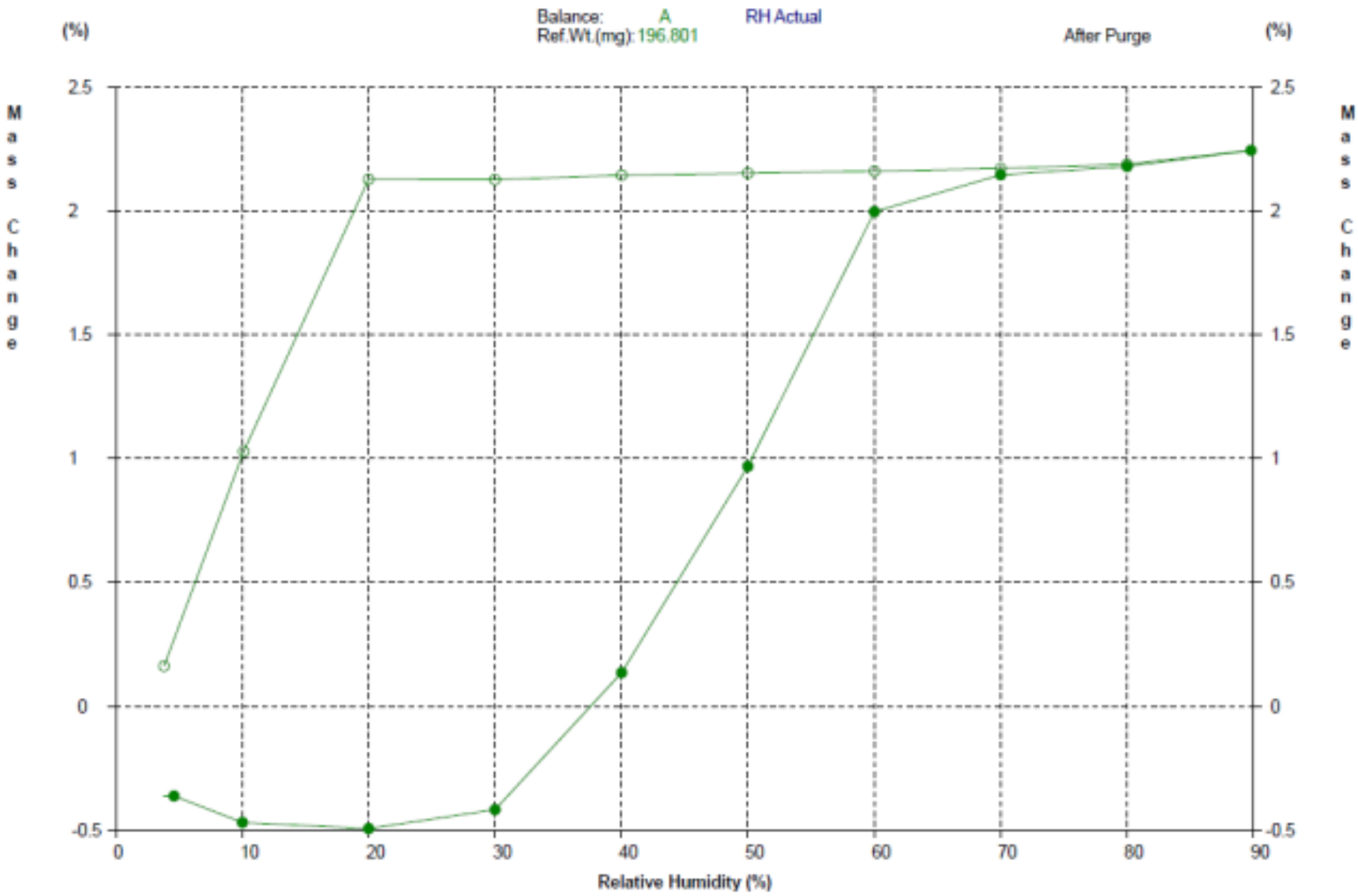
Dynamic vapor sorption (DVS) is a **gravimetric** technique that measures how quickly and how much of a solvent is absorbed by a sample: such as a dry powder absorbing water.
It does this by varying the vapor concentration surrounding the sample and measuring the change in mass which this produces



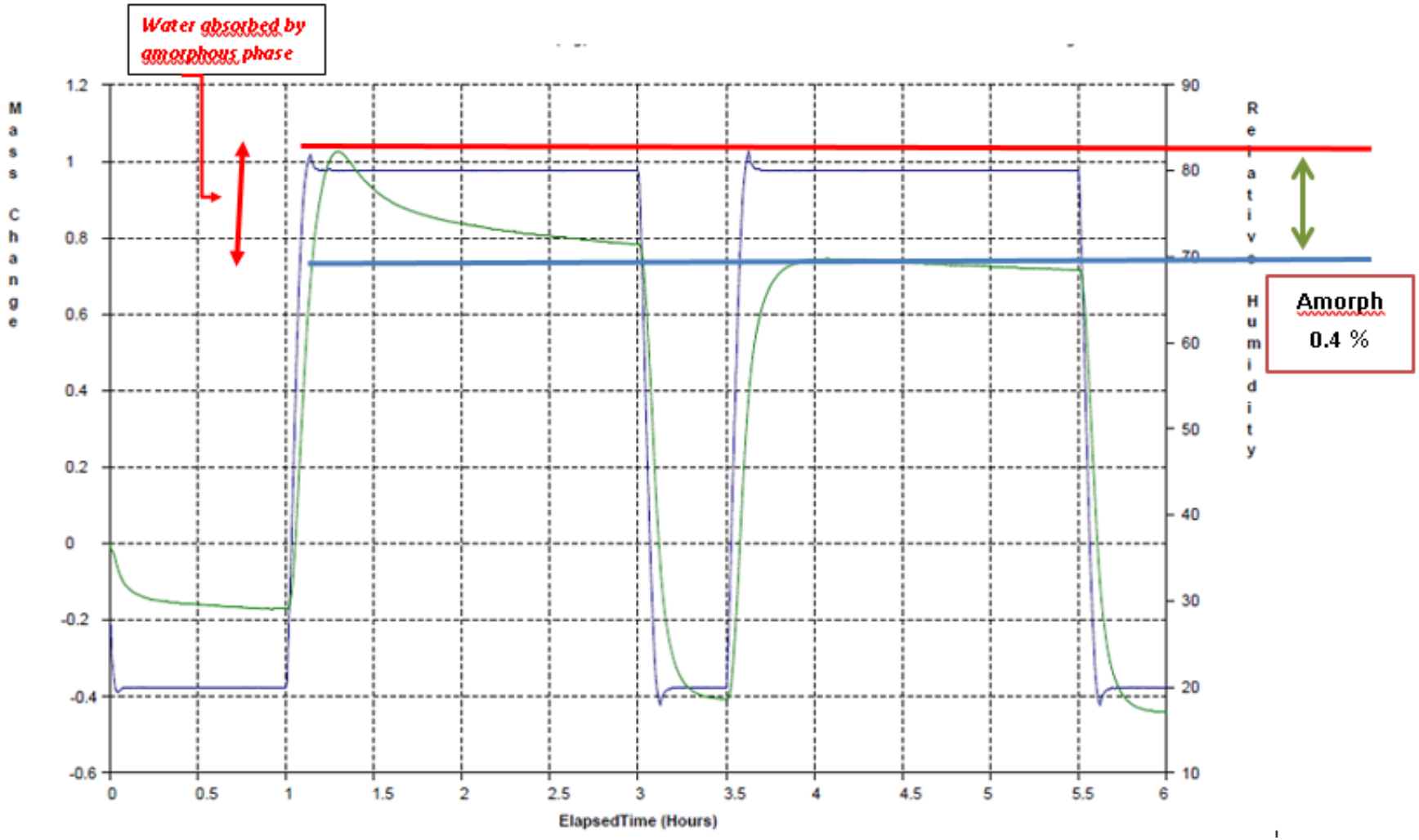
Hygroscopicity of API



De-hydration and Hydration profile of the API



Quantisation of Amorphous phase in crystalline compound by DVS



Particle Coalescence phenomenum due to Surface Energy

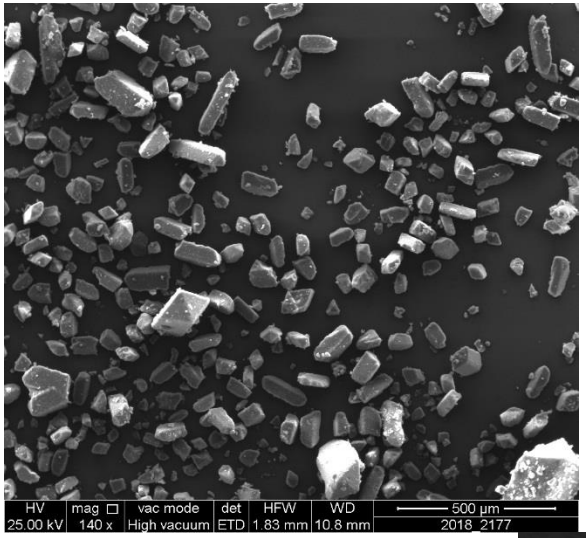
Root cause

- Environmental Humidity
- Storage of API (temperature, time, etc.)
- Energy aquired during the milling
- Drying process
- After micronization

Pharmaceutical Implication

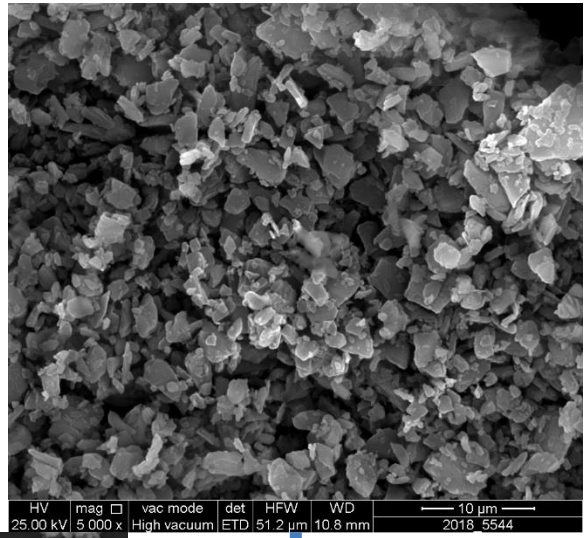
- Particle Size Distribution
- Dissolution Rate
- Electrostatic Charges
- Crystal phase modification (amorphous into crystalline phases)

Morphology modification
(after micronization)

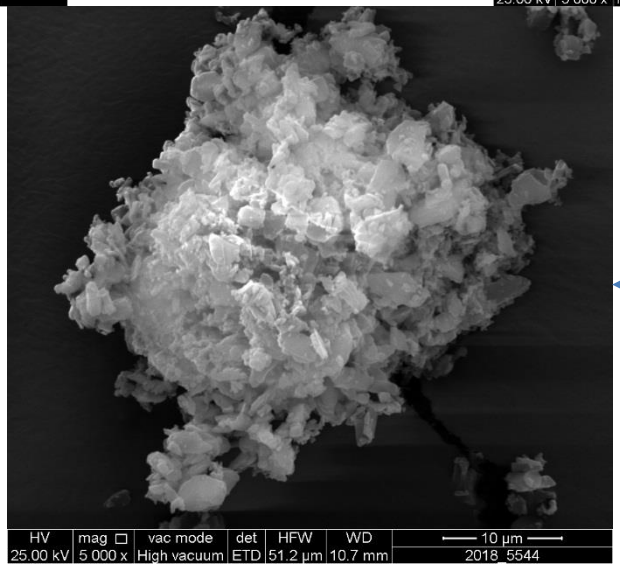


500 um

Micronization



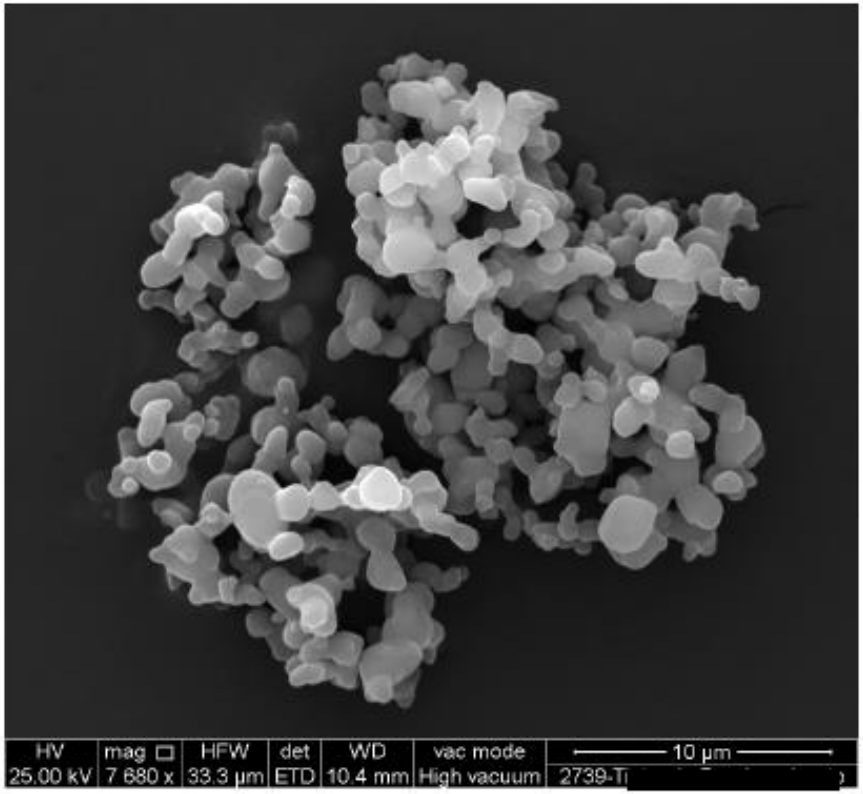
50 um



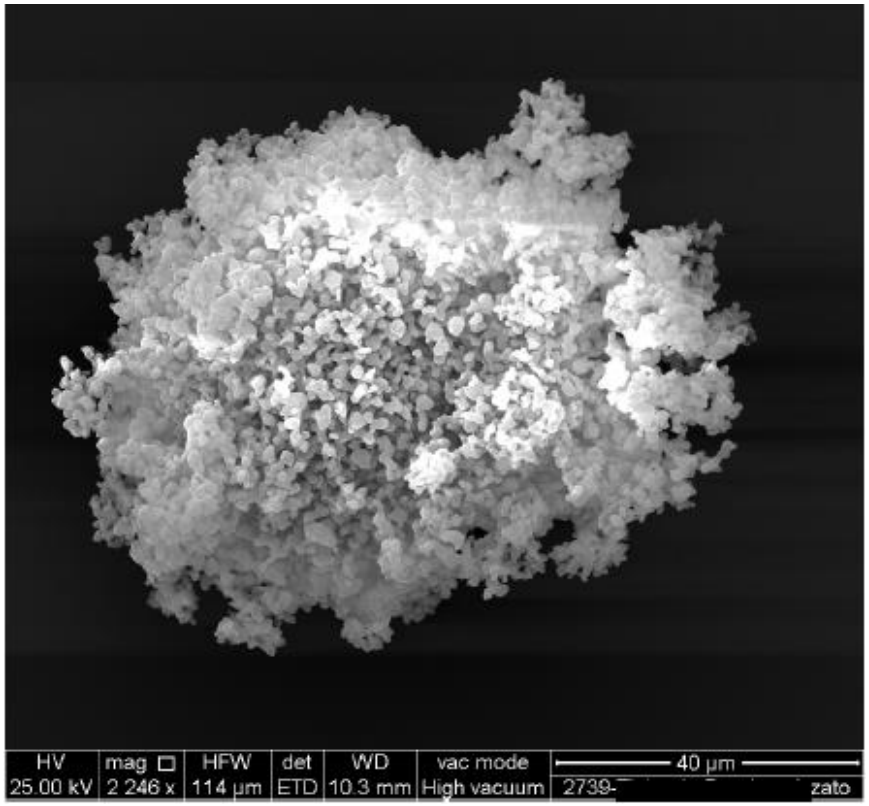
Bulk storage

10 um

Coalescence of micronized powder

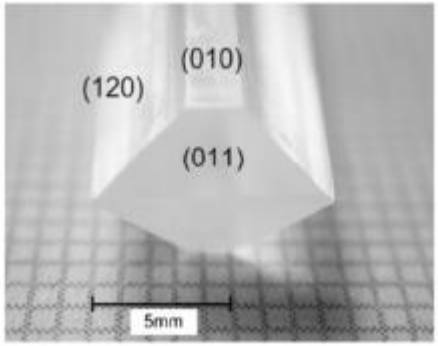


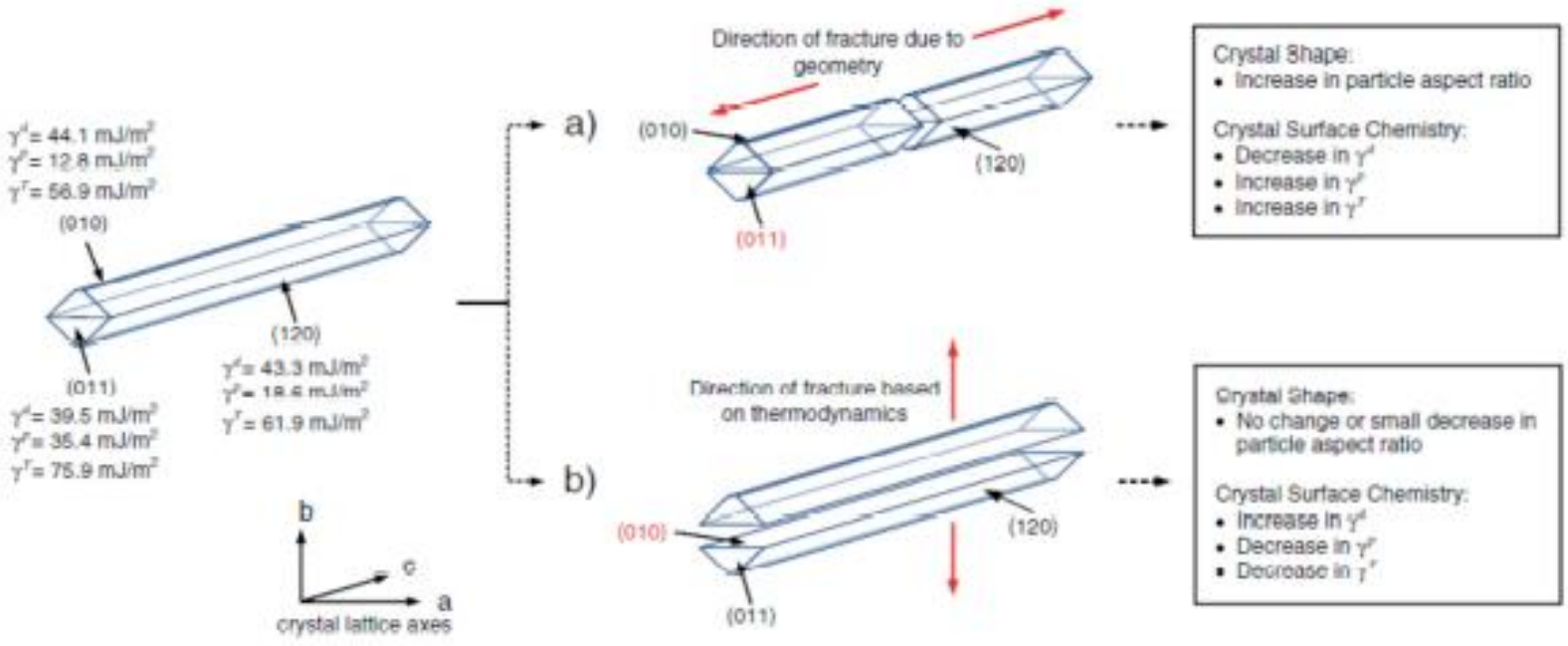
Time 0



After storage of 6 months

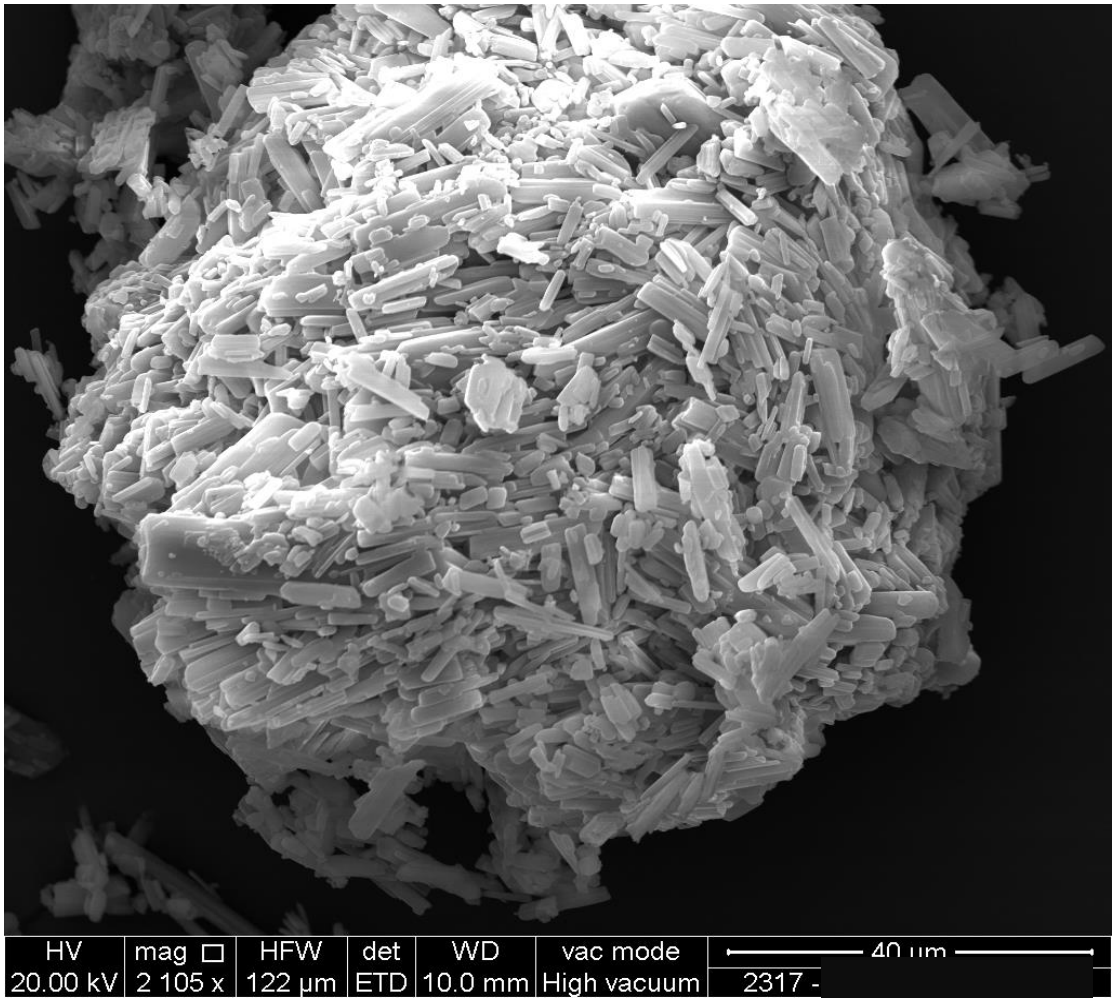
Particles morphology on Surface Energy





Crystal Morphology

(aggregates before coalescence)



Assessment of Surface Energy by Inverse Gas Chromarography (IGC)

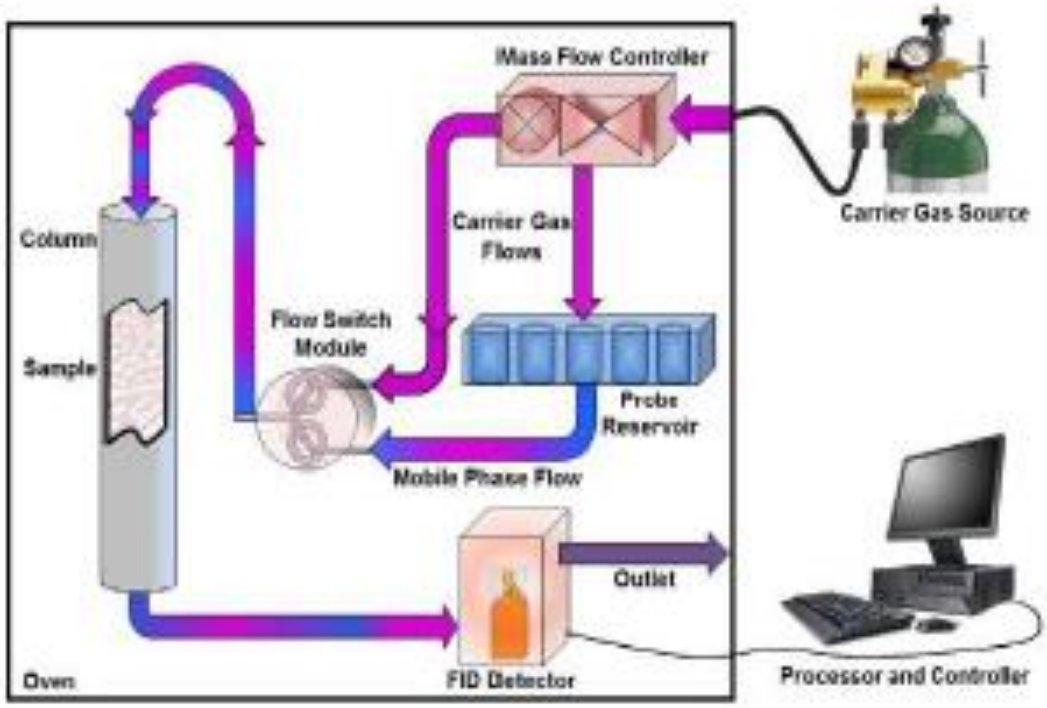


Fig. 1. Schematic illustration of a typical inverse gas chromatography (IGC) analyser.

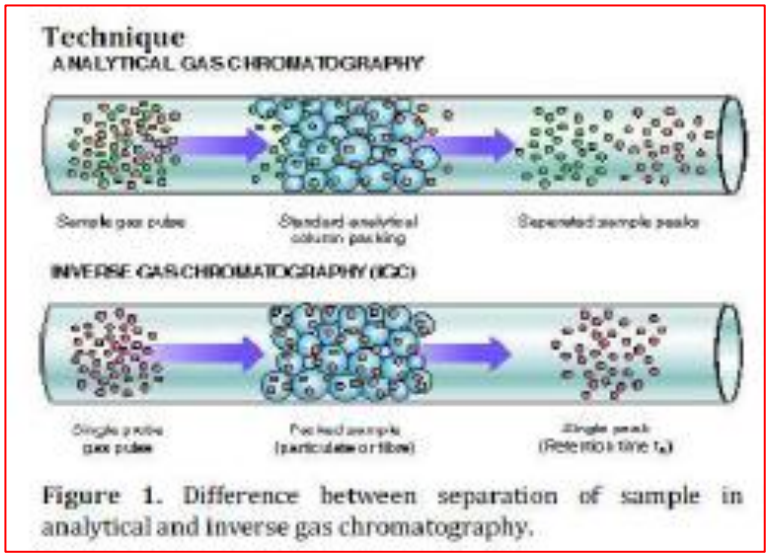


Figure 1. Difference between separation of sample in analytical and inverse gas chromatography.

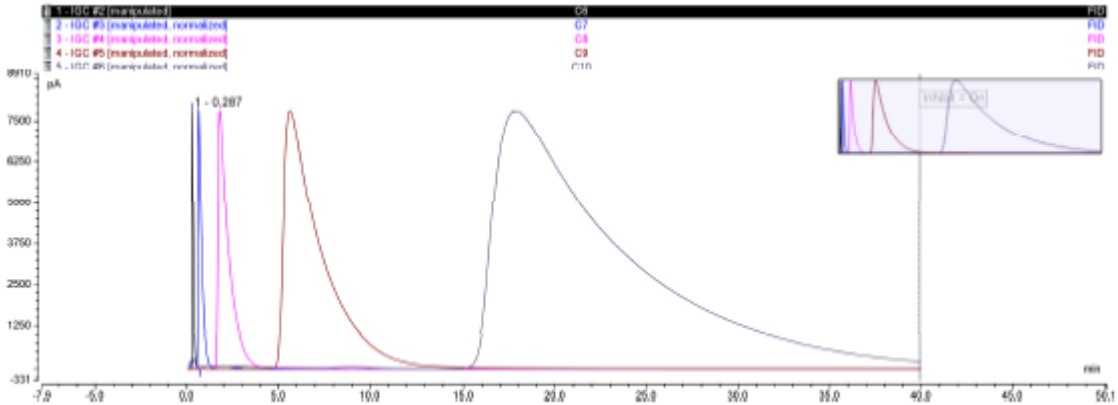
Thermodynamic Parameters defined by IGC

- *Cohesion power between particles*
- *Acid and base properties of particles surfaces*
- *Glass transition*
- *Crystalline and amorphous surface properties*

The termodynamic parameters define by different solvents "PROBE".

1.	**Apolar Probes**	**(normal alkenes da C6 to C10)**
2.	**Acid Probes**	**(dichloromethane chloroform,etc.)**
3.	**Basic Probes**	(ethyl acetate, toluene, etc,)
4.	**Anfoters Probes**	(acetone, acetonitrile)

Data evaluation by retention time and properties of the probes



CROMATOGRAMMA ESEMPLIFICATIVO DEI n-ALCANI C6-C10

$$-\Delta G = 2Na\left(\sqrt{\gamma_S^+\gamma_L^-} + \sqrt{\gamma_S^-\gamma_L^+}\right) = RT\ln(V_N) - \Delta G^D$$ Descirzione di Van Oss

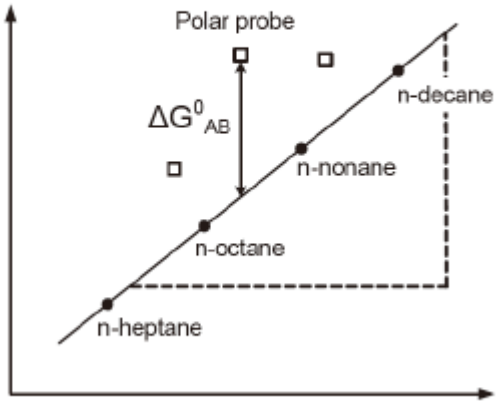
$$-\Delta G = 2Na\left(\sqrt{\gamma_S^+\gamma_L^-}\right)$$ probe basica — Approccio di Owens and Wendt

$$-\Delta G = 2Na\left(\sqrt{\gamma_S^-\gamma_L^+}\right)$$ probe acida — Approccio di Owens and Wendt

$$\gamma^{TOT} = \gamma^D + 2\cdot\sqrt{\gamma^+\cdot\gamma^-}$$

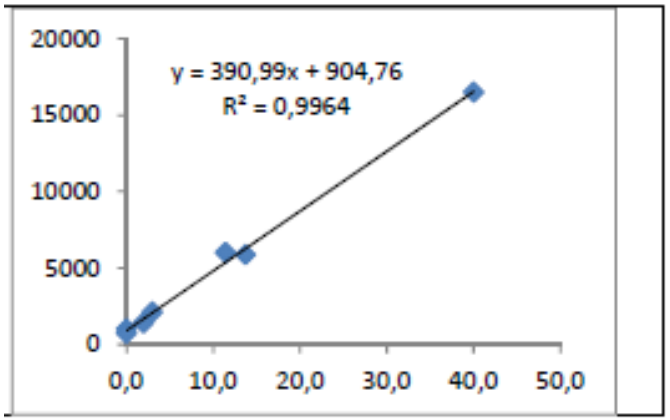
$$\Delta G = \Delta H - T\Delta S \approx \Delta H \text{ quindi } -\Delta H_{AB}^0 = K_A DN + K_B AN^*$$

$$\gamma^{TOT} = \gamma^D + 2\cdot\sqrt{\gamma^+\cdot\gamma^-}$$



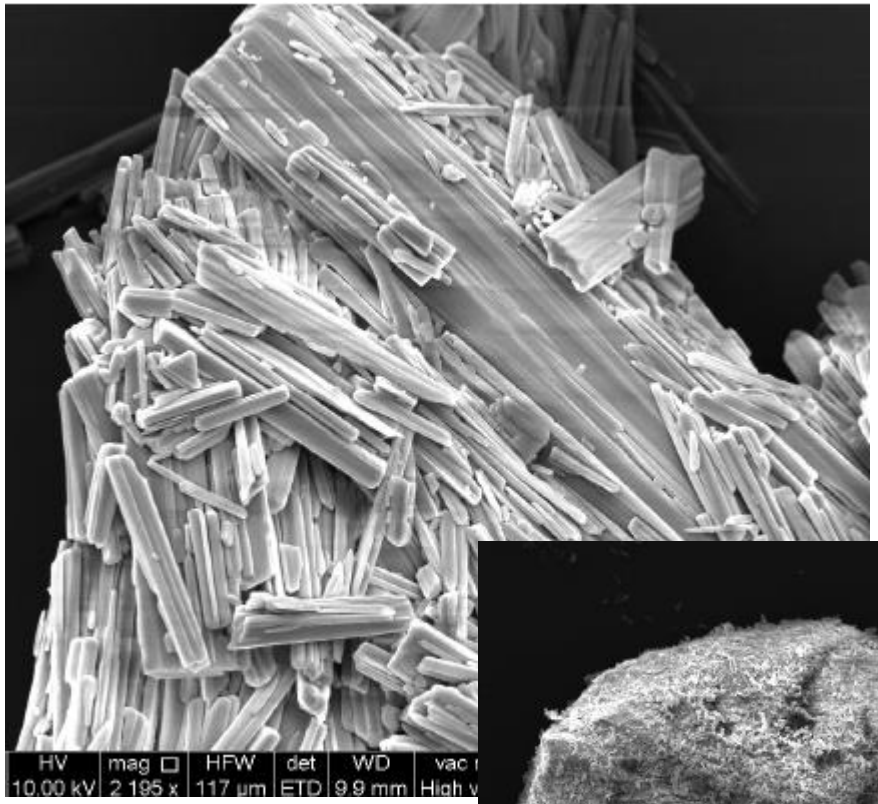
Definition of ratio between K_A and K_B

$$\frac{-\Delta H^0_{AB}}{AN^*} = K_A \frac{DN}{AN^*} + K_B$$



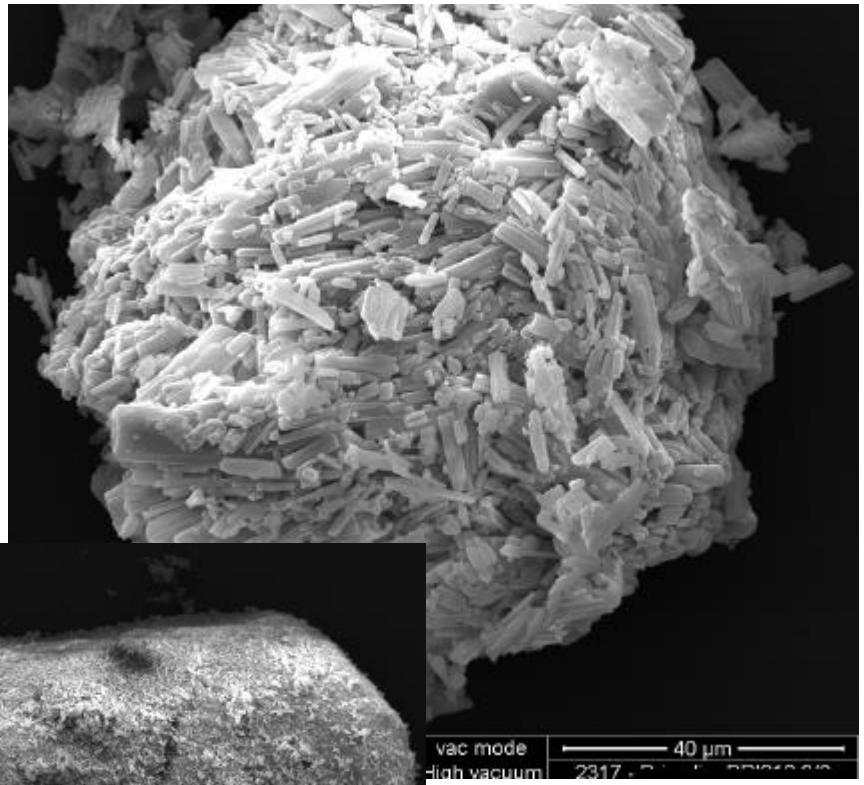
$K_A / K_B < 0.9$	basic surface
$0.9 < K_A / K_B < 1.1$	neutral surface or anfoter
$K_A / K_B > 1.1$	acid surface

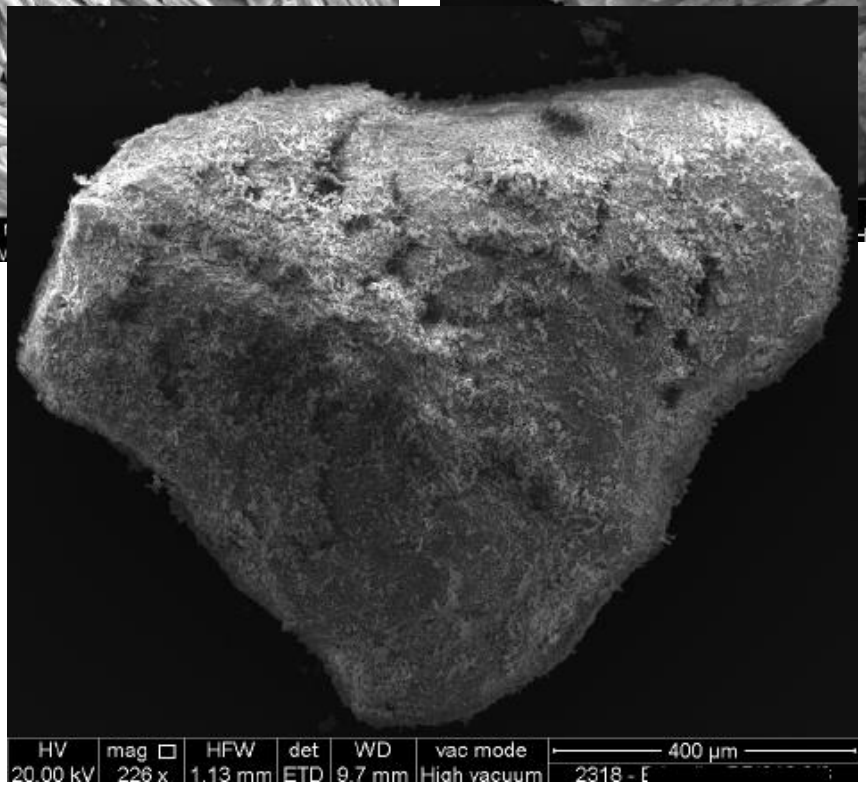
Bulk



40 micron

grounded





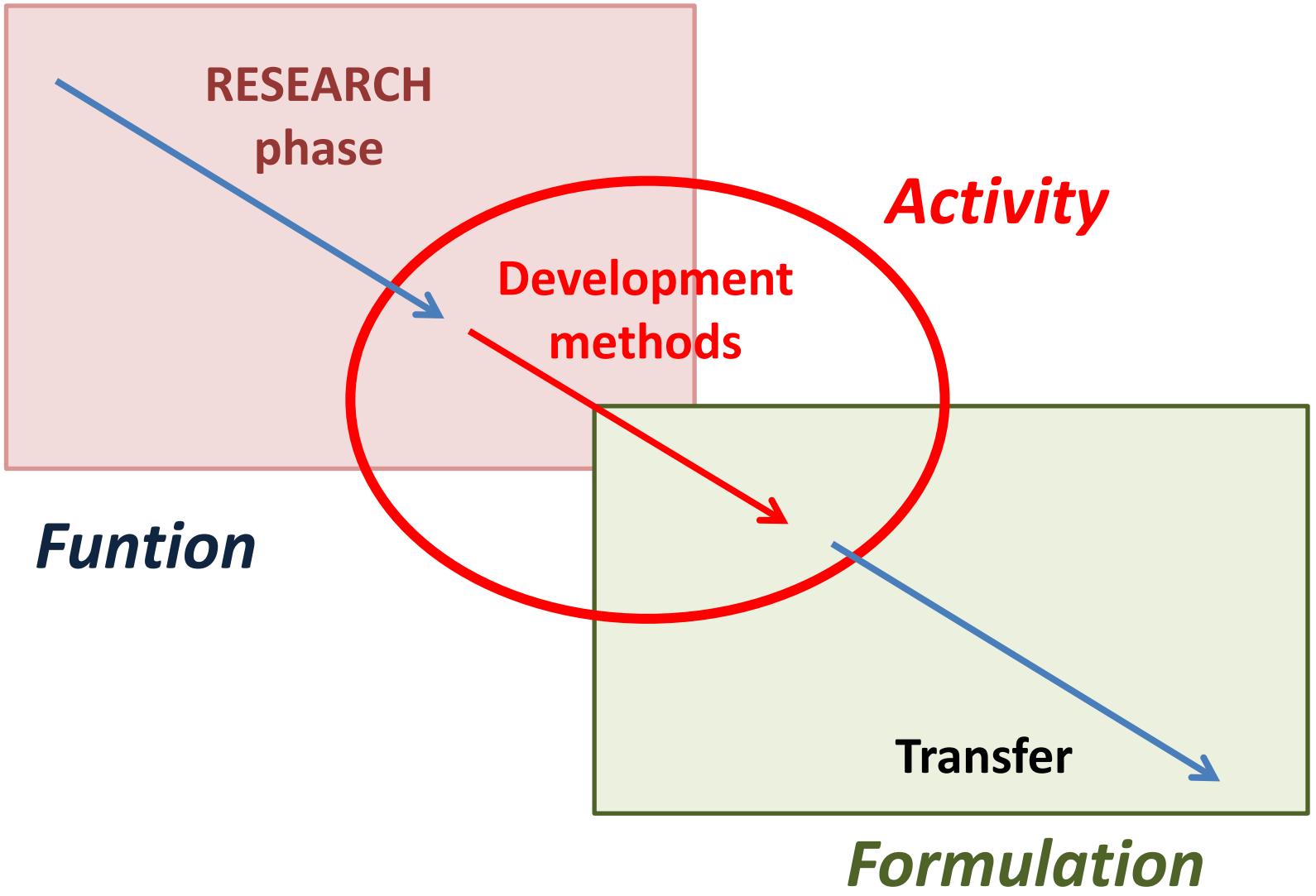
Stored at ta for 2 months

400 microns

Example of Surface Energy determination to predict the coalescence phenomenum

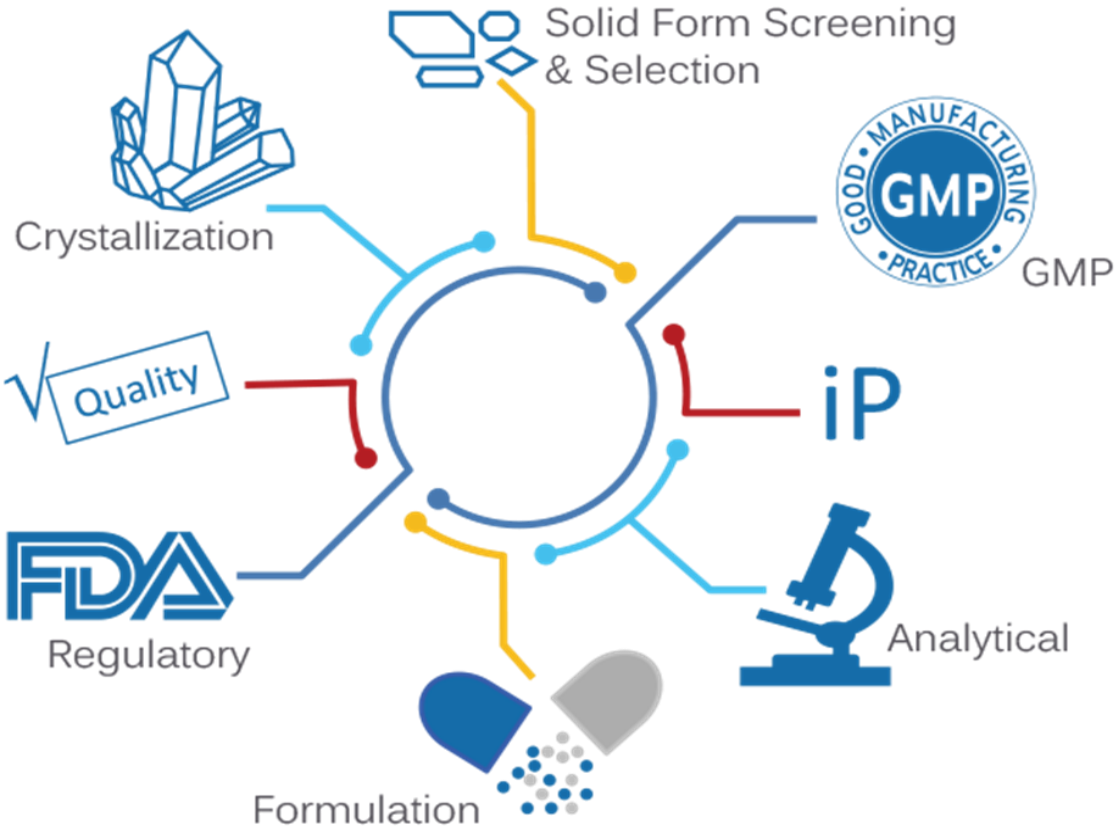
Batch	γ^D mJ/m^2	γ^{SP*} mJ/m^2	γ^{TOT} mJ/m^2	K_A/K_B
As such	37.5	26.1	63.6	0.9
Micronized	38.7	23.1	61.9	1.8
Conditioned at 40°C	38.1	30.8	68.9	1.2
Conditioned under 30% RH	39.6	31.3	70.9	1.2
Conditioned under 60% RH	40.9	30.2	71.1	1.0

Scale-up strategy - Development activities



CONCLUSION

Crystallization- and - Regulatory



Thanks for your attention

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Pavia – 23 Nov.2018