THERMAL ANALYSIS

Analytical Sciences 1 - TU 09

MASTER
Pharmaceutical sciences, drug innovation and health products

Caroline Aymes-Chodur
Associate Professor (Caroline.aymes-chodur@universite-paris-saclay.fr)

Applications Related to Pharmaceuticals

FIELD	APPLICATION	
Active pharmaceutical ingredients (API)	Polymorphism, melting point, glass transition, moisture effect, existence of solvates, purity analysis,...	
Formulations	Compatibility of excipients, thermal degradation, moisture determination,…	
Plastic materials	Identification of multilayer packaging, thermal stability, moisture determination,…	

Course outline

- Reminder on state domains
- Reminder on orders in macromolecules
- Different thermal analytical techniques
- Calorimetric techniques
    - First-order transition
    - Second-order transition
    - DSC Equipment (calibration and preparation)
    - Other applications
- Gravimetric techniques
    - Equipment
    - Calibration
    - Examples
    - Coupled techniques

Reminder on state domains (especially for polymers)

VITREOUS (Glassy) ⇄ RUBBERY STATE ⇄ MELTED

- Solid state
- Stiff
- Brittle
- High elastic modulus

- Ductile (as rubber)
- Amorphous phases are suitable
- Random coil

Reminder on state domains (especially for polymers)

Softening ——— Melting ⟶ T° ↗ (Heating)

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Reminder on state domains (especially for polymers)

Softening → Melting → **T° ↗** (Heating)

VITREOUS (Glassy) ⇄ RUBBERY STATE ⇄ MELTED

← Vitrification (Glazing) ← Crystallization ← **T° ↘** (Cooling)

- Solid state
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Reminder on orders in macromolecules

Amorphous state

Crystalline state

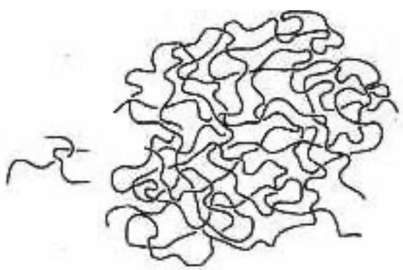
Reminder on orders in macromolecules

Amorphous state

Crystalline state

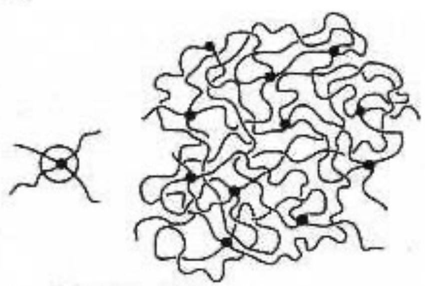
- No order to a large distance
- Random coil configuration,
- Entanglement ± important
- Viscosity ↗ with cooling

without entanglement



ex. : PVC, PS, PMMA, SAN

with entanglements



ex. : NR, SBR, PUR

Reminder on orders in macromolecules

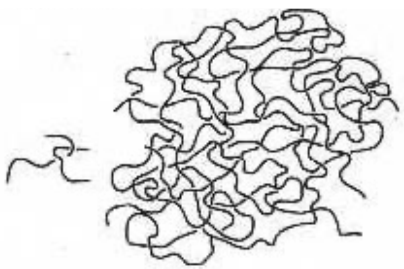
Amorphous state

- No order to a large distance
- Random coil configuration,
- Entanglement ± important
- Viscosity ↗ with cooling

Crystalline state

- Orderly arrangement,
- Compact design folded in the crystal seeds,
- Preferential conformation as crystalline lamellae

without entanglement



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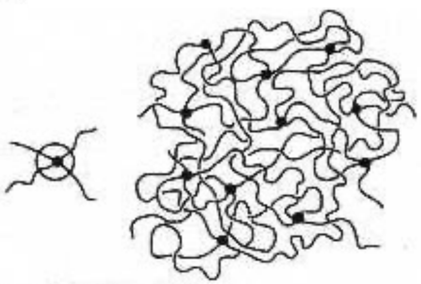

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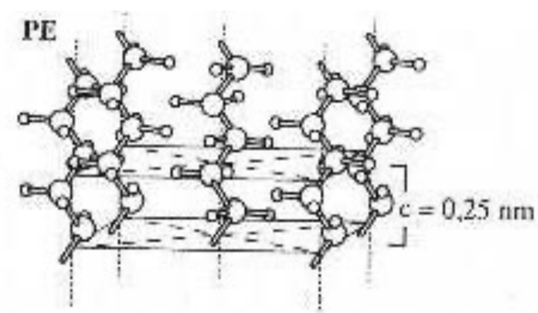
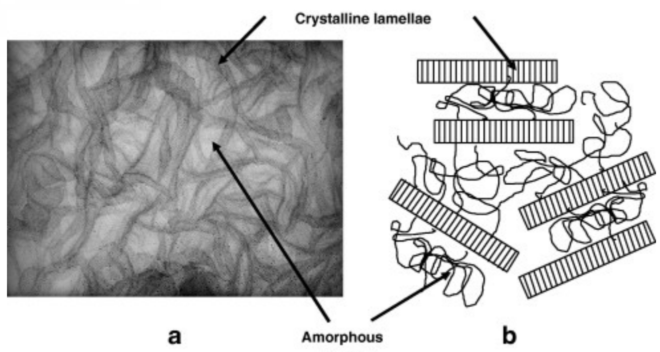


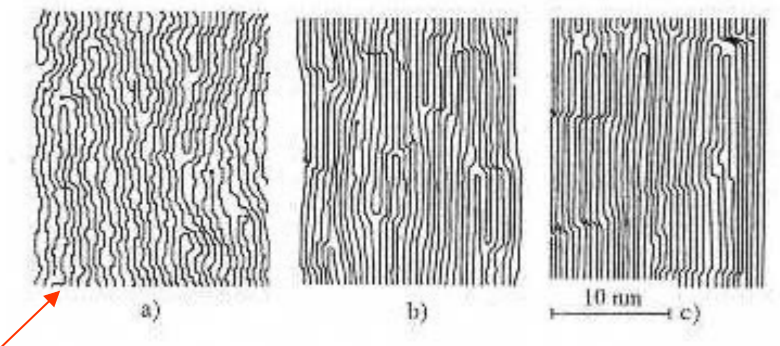


From « Hoffman, 1976. Treatise on Solid State Chemistry. Plenum, New York ».

Reminder on orders in macromolecules

Crystalline state

T° ↘ : viscosity ↗

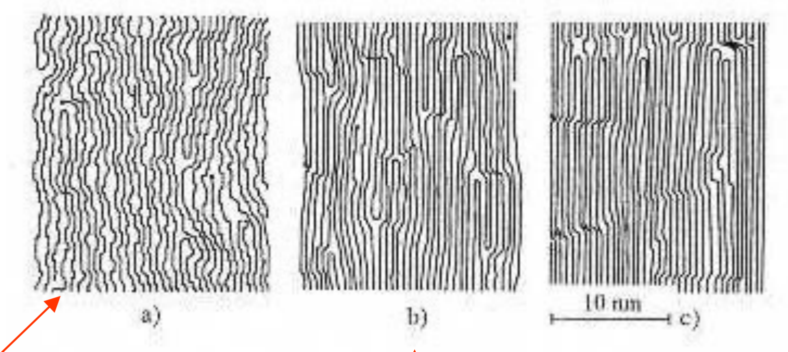


Molten matter

Reminder on orders in macromolecules

Crystalline state

T° ↘ : viscosity ↗



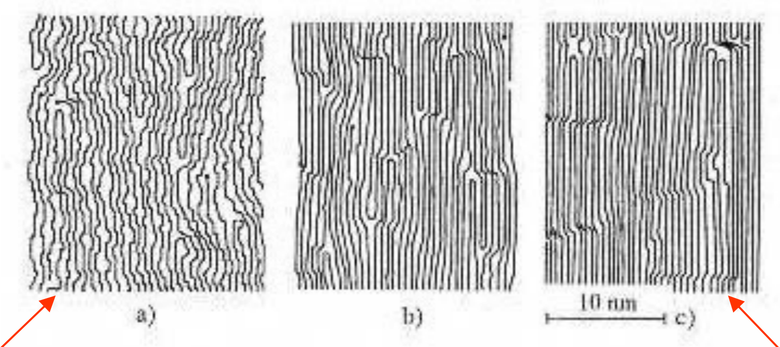
Molten matter

T° just < T°cristallization

Reminder on orders in macromolecules

Crystalline state

T° ↘ : viscosity ↗



Molten matter

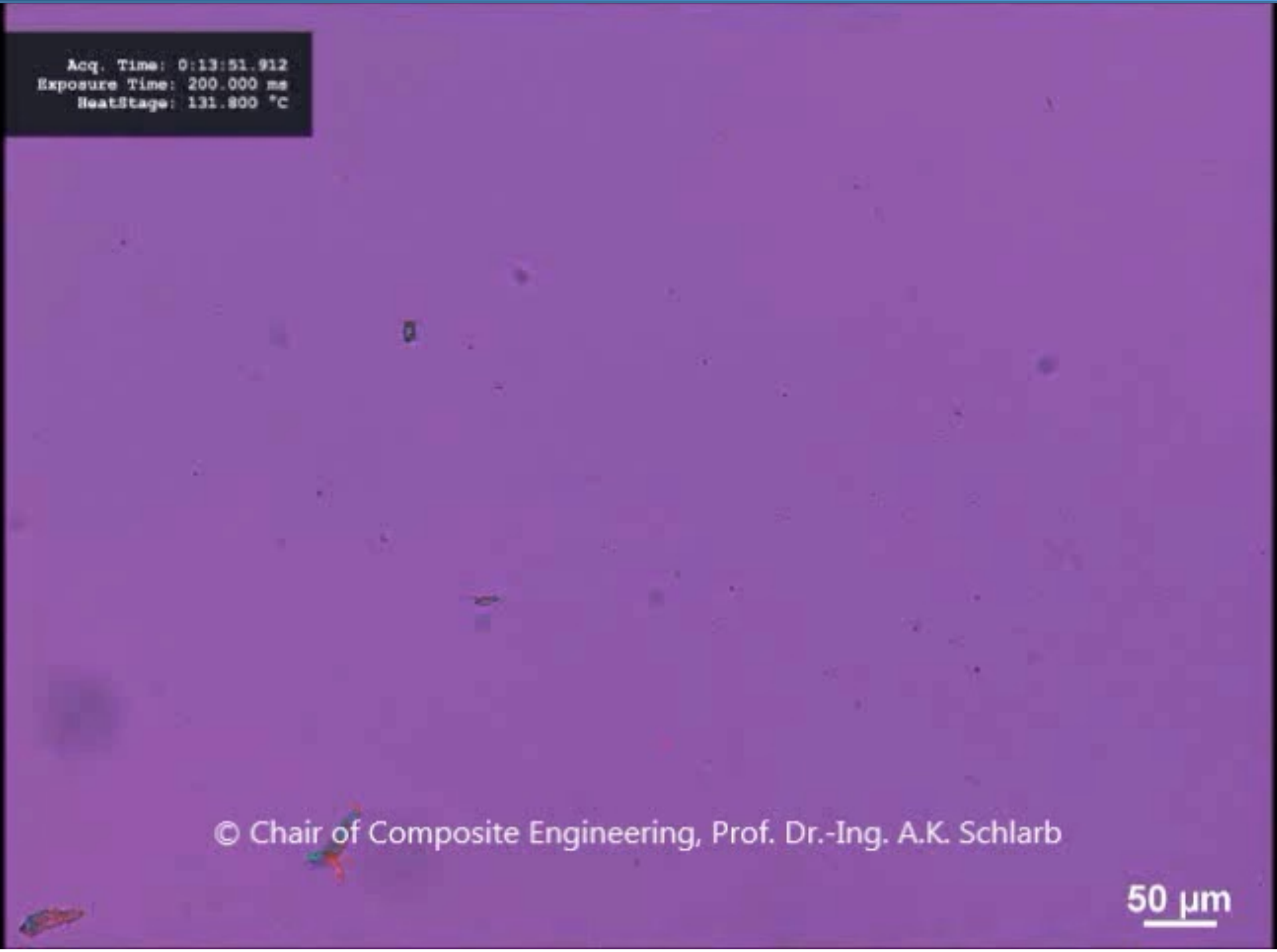
T° near T°cristallization

Crystalized matter
(↗ parallel arrangement)

crystal nucleation and growth

Lamellae , fibers, spherulites, formation …

Link to the video "**Spherulite Growth of Polypropylene »** https://www.youtube.com/watch?v=G4FjhP4aXBI&feature=youtu.be

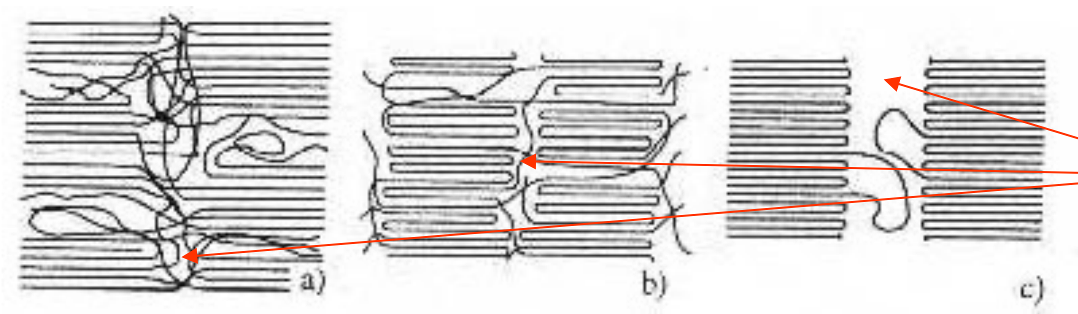


The growing of spherulites measured by polarized light microscopy

Reminder on orders in macromolecules

Crystalline state

- Length of the macromolecule >> lamellae thickness
- Alternation of the amorphous /crystalline areas



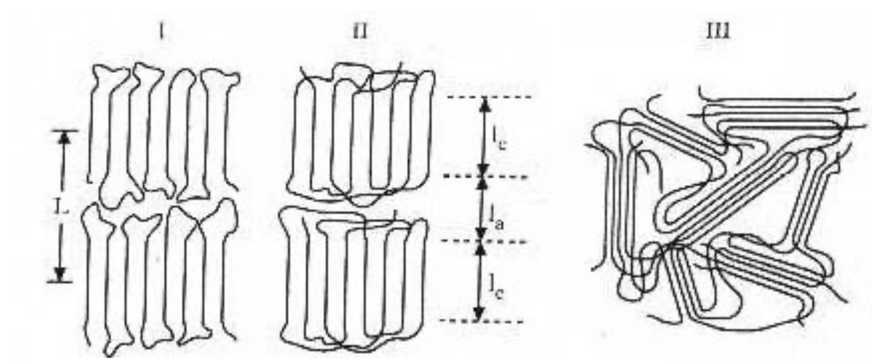
Inter-crystallites amorphous areas

Chains crossing from one cristallite to another

Loops formed by the folding chains

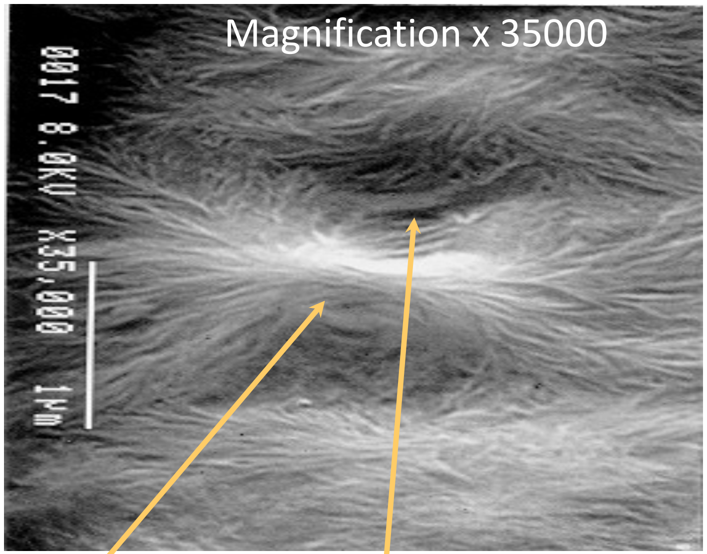
Crystalline areas

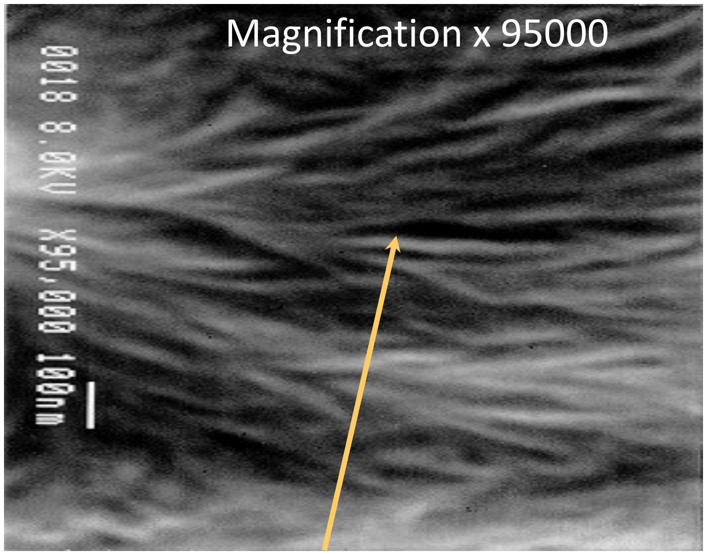
Folding : - I : regularly
- II : random
- III : lamellae

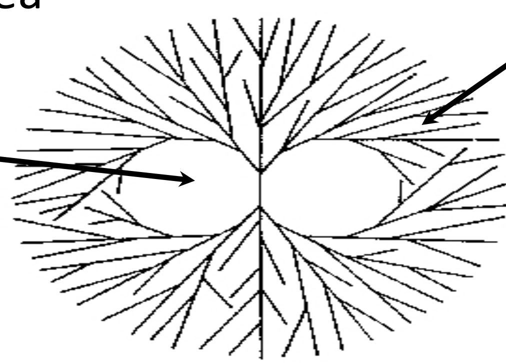


l_c : thickness of the lamellae
l_a : thickness of the amorphous zones
l_e : long period

Study of the surface morphology by SEM

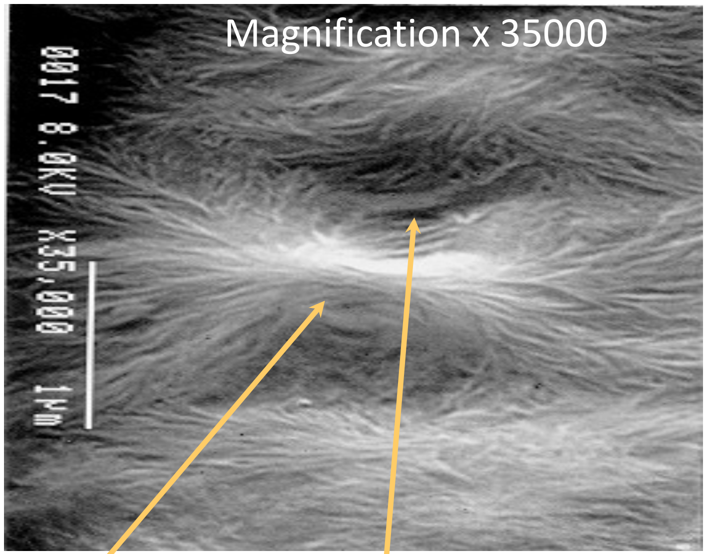


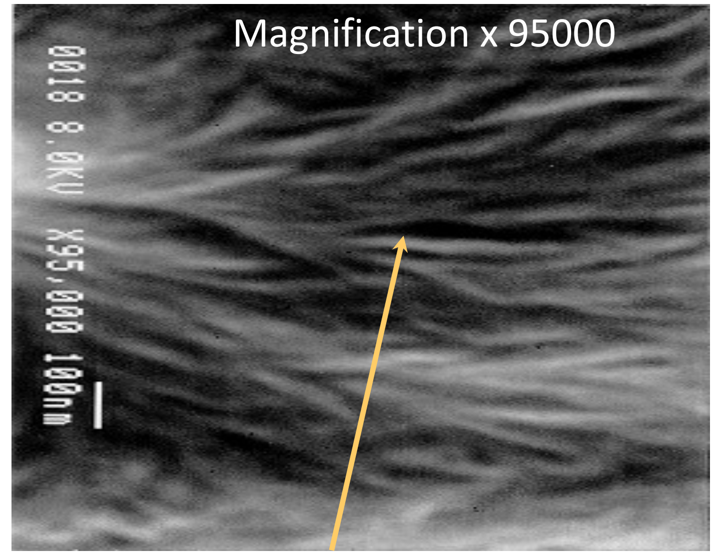




Spherulite structure

Study of the surface morphology by SEM

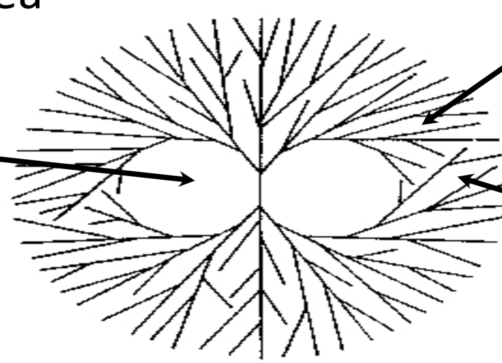


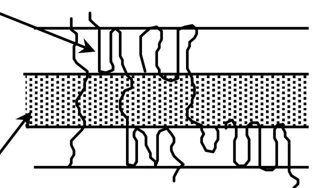


Inter-crystallites amorphous area

Crystalline lamellae

Heterogeneous nucléation site





Intra-crystallites amorphous area

Spherulite structure

PE Spherulites observed by Polarised Light Microscopy (PLM). L. Douminge

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Different thermal analytical techniques

A group of techniques in which a property of the sample is monitored against time or temperature while the temperature of the sample, in a specified atmosphere, is programmed.

CALORIMETRIC analysis

DTA, DSC

Temperature measurement and absorbed/desorbed heat flow

THERMOGRAVIMETRIC analysis

TGA :

Mass loss monitoring

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CALORIMETRIC analysis

DTA, DSC

Temperature measurement and absorbed/desorbed heat flow

THERMOGRAVIMETRIC analysis

TGA :

Mass loss monitoring

European Pharmacopea

THERMOMECANIC

TMA, DMA :

dimensions , stiffness

OTHERS

TSC : *dipolar molecules*

DEA : *dielectric permittivity*

DOA : *optical properties*

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Calorimetric techniques

Effect of the temperature on the state change, macromolecular reorganization, degradation, …

CALORIMETRY : measure of the absorbed heat flow (endothermic phenomenon) or released (exothermic phenomenon) by the sample.

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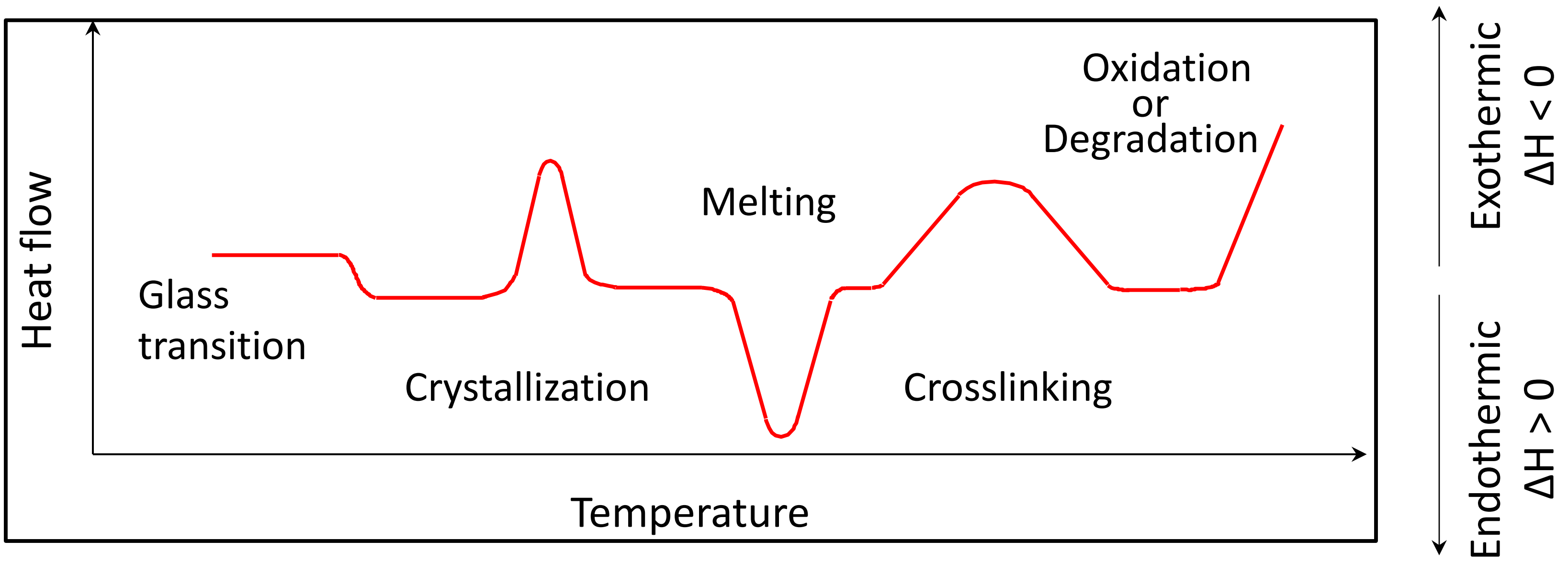

Heat flow and heating capacity

$\Delta H = Cp \times \Delta T$

or

$d(\Delta H)/dt = Cp \times d(\Delta T)/dt$

with : Cp = heating capacity (J/°C)

T = temperature (°C)

H = heat (J)

$\Delta H/dt$ = Heat flow (J/min)

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FIRST-ORDER TRANSITION : Peak (endo- or exothermic) : enthalpy variation is *proportional to the area under the peak (melting, crystallization, ...)*

SECOND-ORDER TRANSITION : Jump of the baseline : No enthalpy variation but Cp variation (Tg, Oxydation, ...)

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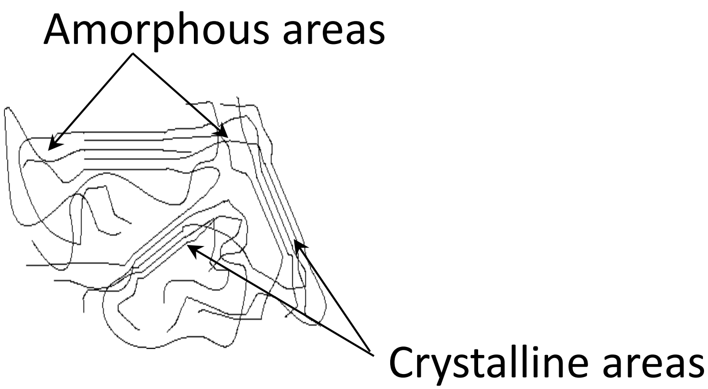
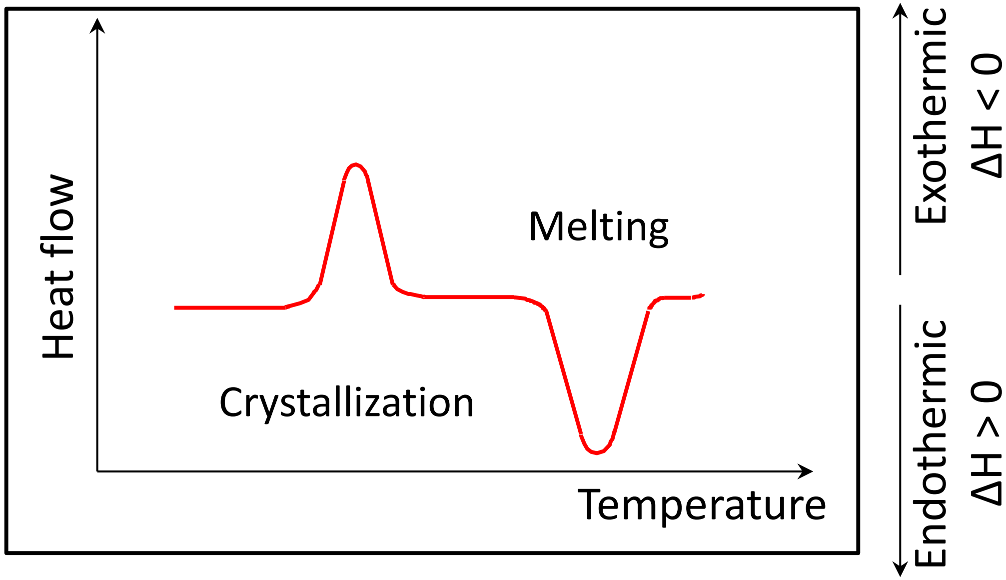
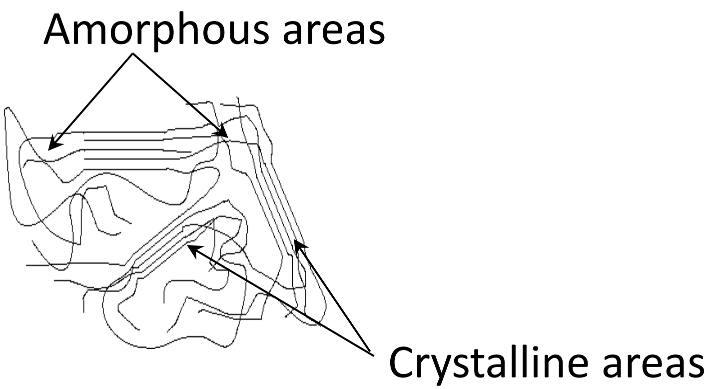
FIRST-ORDER TRANSITIONS

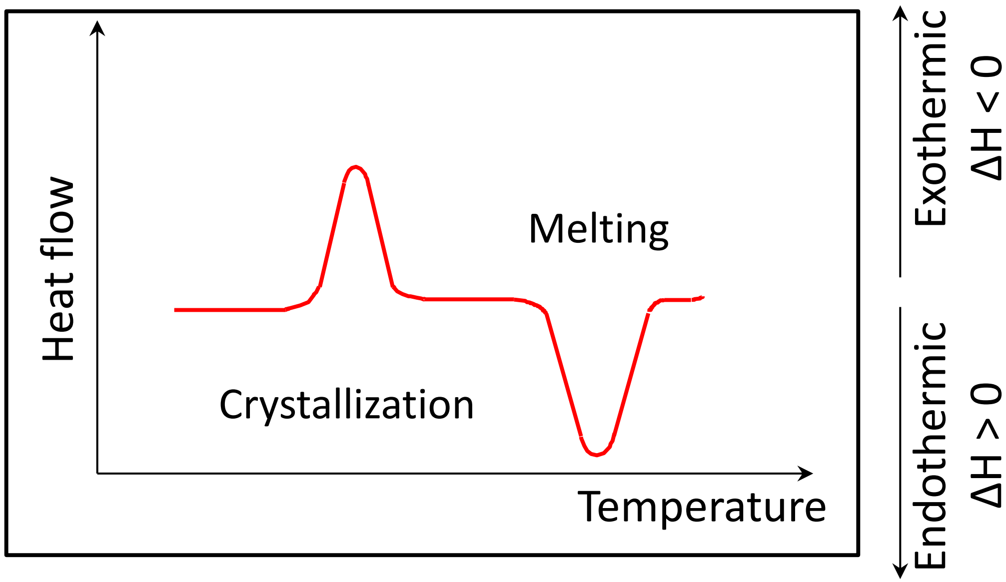




MELTING : crystalline solid state (order) → liquid state (→ molten polymer).

FIRST-ORDER TRANSITIONS





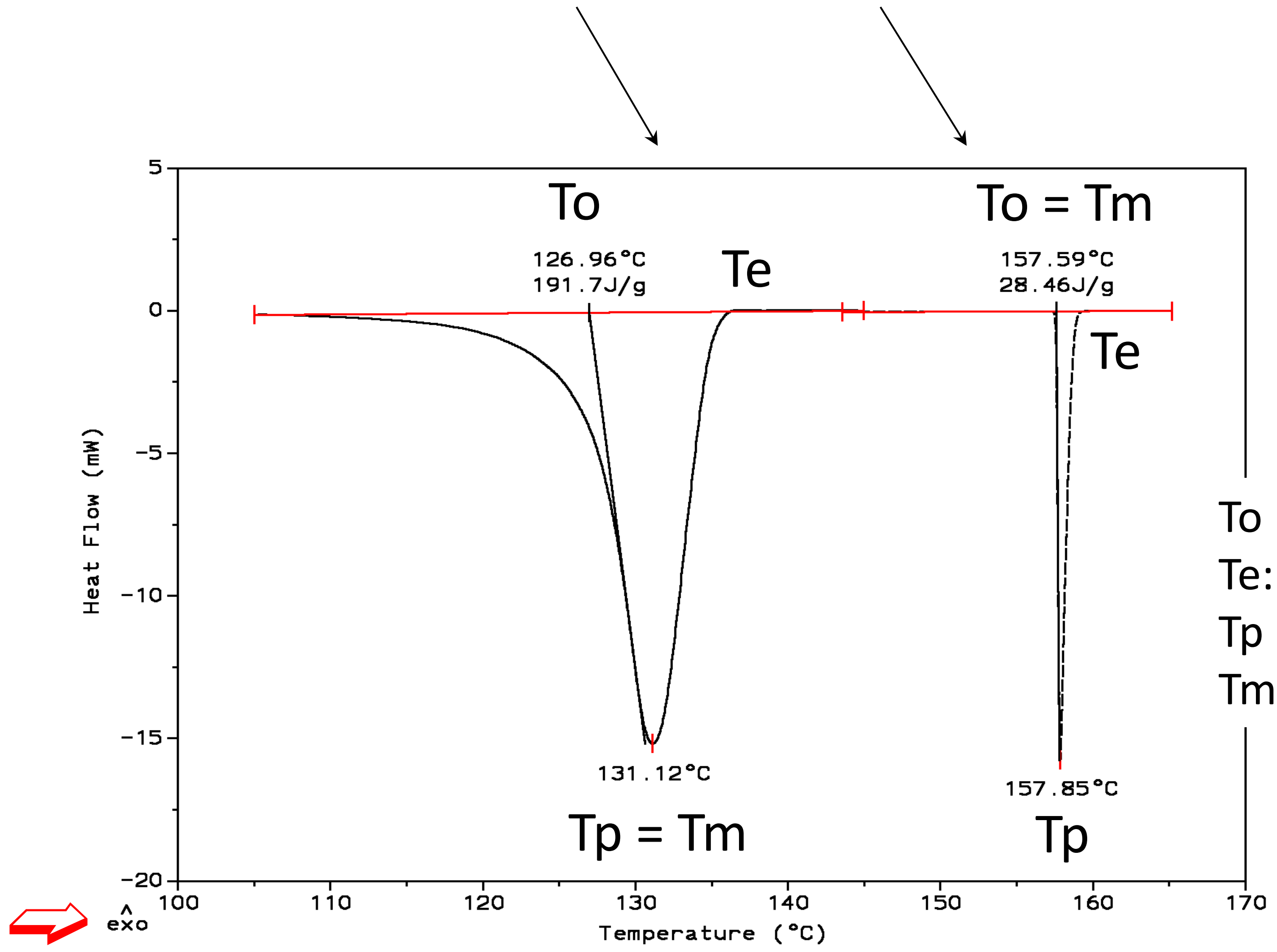
MELTING : crystalline solid state (order) → liquid state (→ molten polymer).

CRYSTALLIZATION : reverse phenomenon : reorganization of the crystalline domains.

Crystallization depends of the cooling rate.

It sometimes appear when heating the sample and is then called "cold crystallization".

<u>Ex</u> : Melting of Polyethylen and Indium (pure metal)



To : Onset temperature

Te: End temperature

Tp : Peak temperature

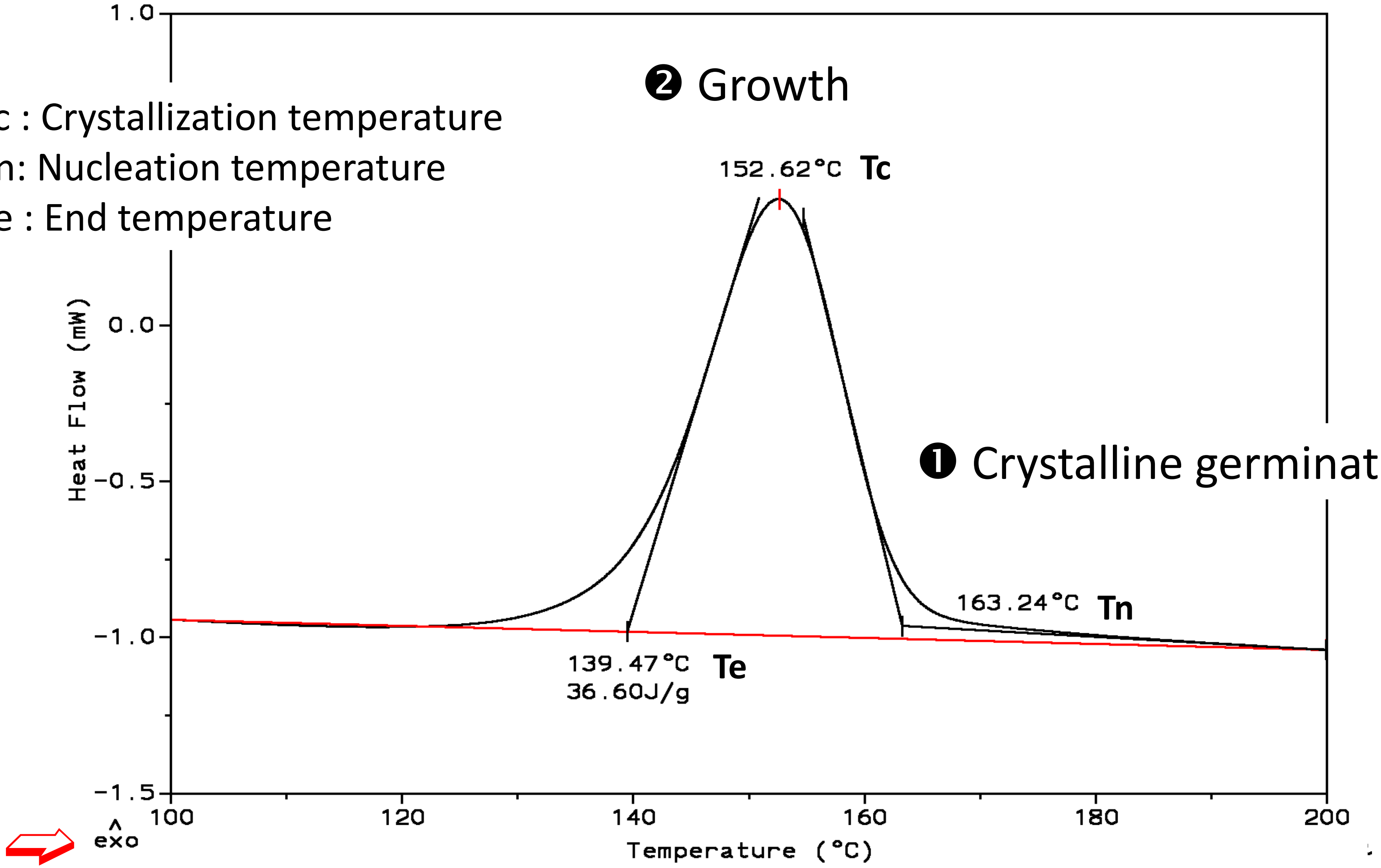
Tm : Melting temperature

Ex : Crystallization of PE HD

Tc : Crystallization temperature

Tn: Nucleation temperature

Te : End temperature



Examples of application for first-order transition :

- Crystallinity percentage

Be carefull :

The sample but be constituted of a pure material (no copolymer nor additivated polymer).

Melting enthalpy of the 100 % crystalline sample must be known ($\Delta H_{lit.}$).

$$\% \text{ crystallinity} = 100 \times \Delta H_f / \Delta H_{lit.}$$

Calorimetric techniques

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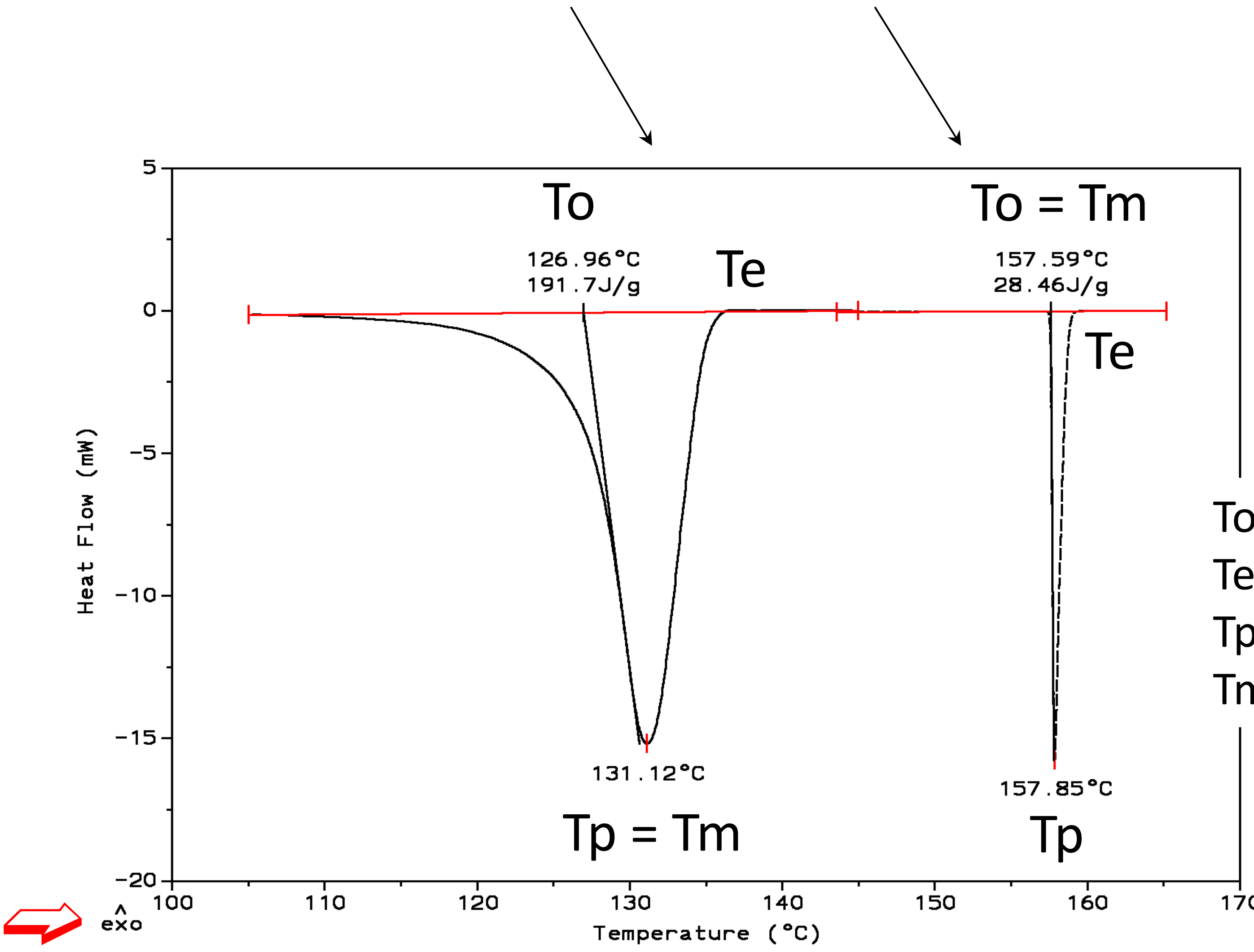

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Ex : % crystallinity of PE = 100 x 191,7 / 290 = 66 %

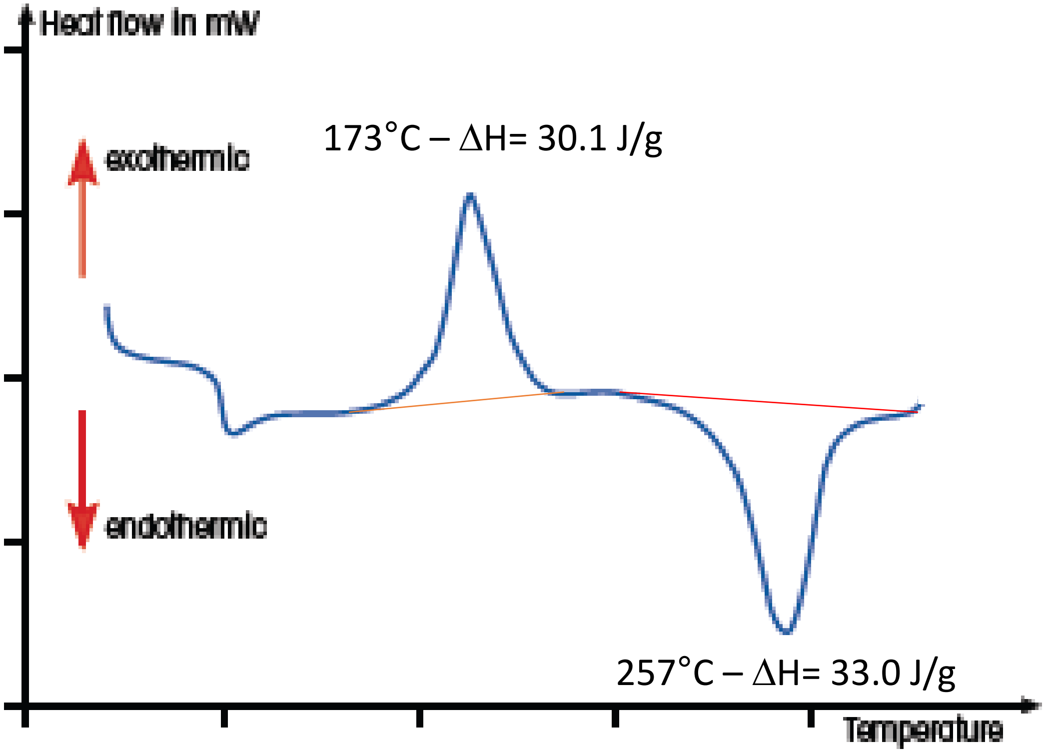
In the case of cold-crystallization :

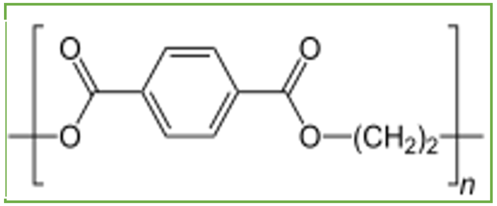
$$\% \text{ crystallinity} = 100^* (\Delta H_f - \Delta H_C) / \Delta H_{lit.}$$

Calorimetric techniques

EX : PET analyzed by DSC

1- Comment the DSC curve.
2- What kind of thermal history had this sample ?
3- Calculate the crystallinity yield with ΔH_{lit}= 140.1 J/g.





Thermogramm obtained under N_2 at 10°C/min with DSC (1st increase of temperature)

Calorimetric techniques

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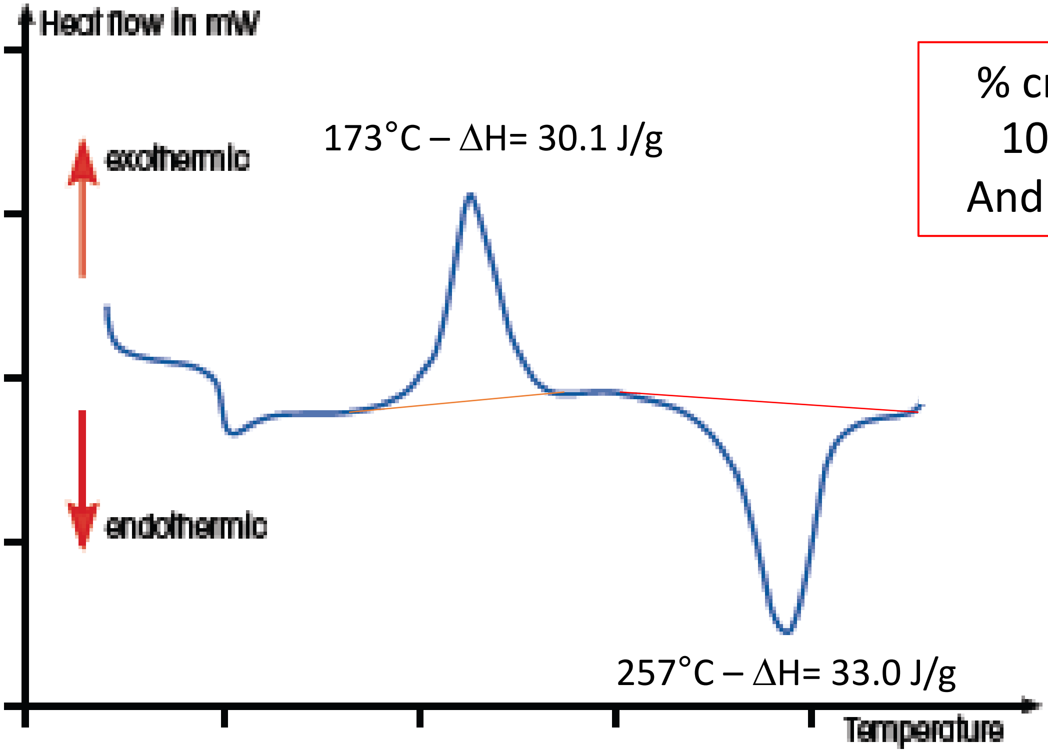
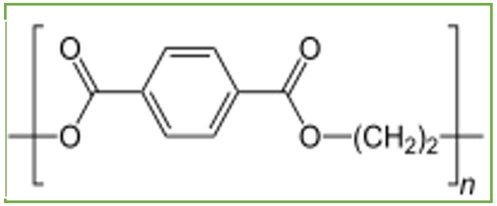


% crystallinity of **quenched** PET =
100 x (33,0-30,1) / 140,1 = 2 %
And NOT : 100 x 33 / 140,1 = 23 %



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Examples of application for first-order transition :

- Polymorphism study

POLYMORPHISM : is the ability of solid materials to exist in two or more crystalline forms with different arrangements or conformations of the constituents in the crystal lattice.

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Effects on:

- the physicochemical properties (dissolution and solubility, chemical and physical stability, flowability and hygroscopicity).
- drug efficacy, bioavailability, and even toxicity.

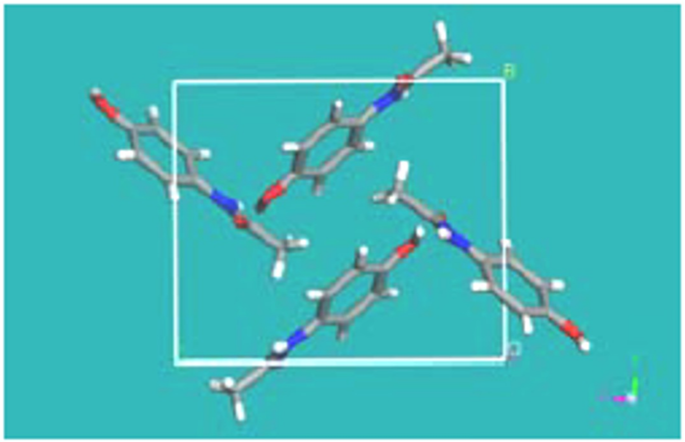
Polymorphic studies are important as a particular polymorph can be responsible for a particular property which might not be exhibited by any other form.

Pseudo-polymorphism appears when water molecules are trapped in the crystalline structure

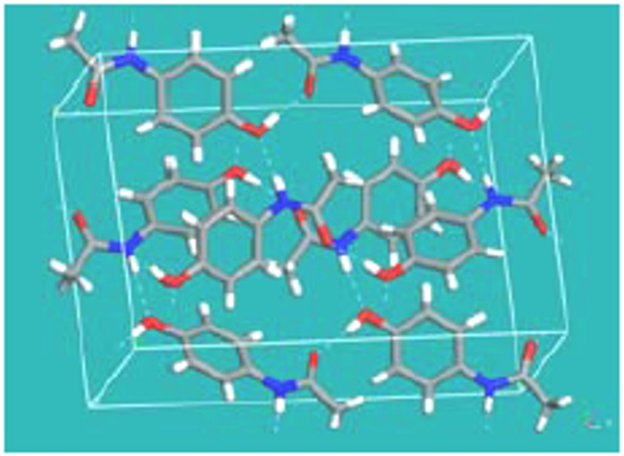
Calorimetric techniques

<u>Example 1</u> : Two polymorphs of paracetamol

Highlighting the two crystalline forms by DSC



Crystal lattice of
form 1 of Paracetamol



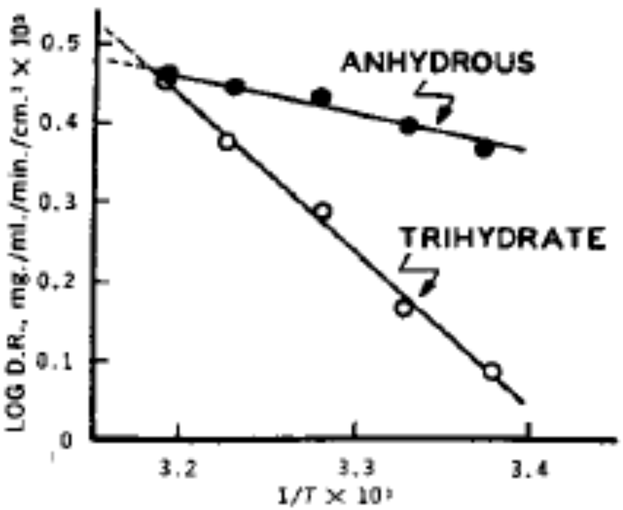
Crystal lattice of
form 2 of Paracetamol

STERIC HINDRANCE ≠

⇨ REACTIVITY ≠

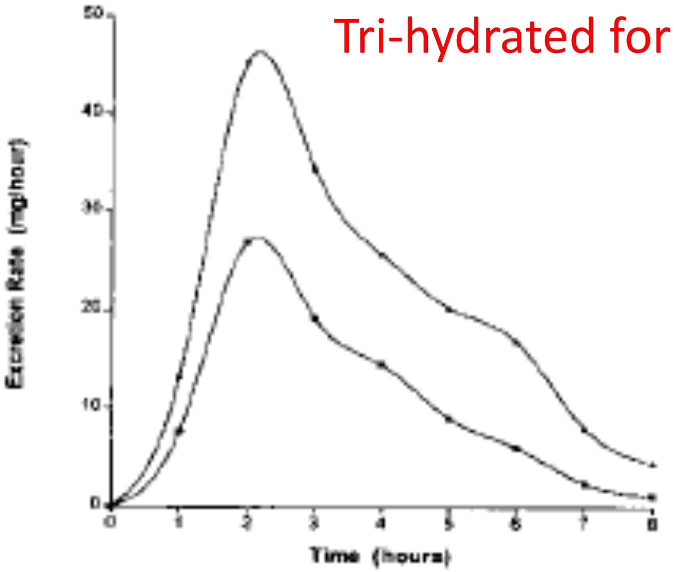
Calorimetric techniques

<u>Example 2</u> : Ampicilin used to treat bacterial infections



G-T diagramm :
log dissolution as a f (1/T) for both formes

Anhydrous form
Tri-hydrated form



Urinary excretion rate after administration of both forms crystalline

⇨ Effect on the bioavailability of the Active Principle according to the form

Calorimetric techniques

Example 3 : MHBA : m-hydroxybenzoïc acid

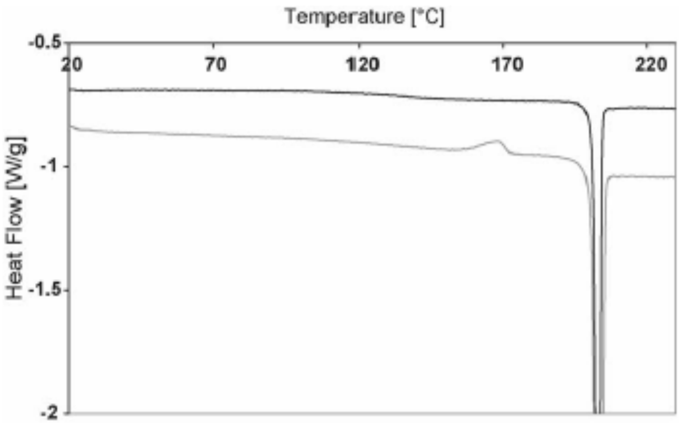


Fig. 2 – DSC thermograms of monoclinic (upper) and orthorhombic (lower) MHBA at 2 K/min.

Exists as 2 polymorphs monoclinic (more stable) / orthorhombic

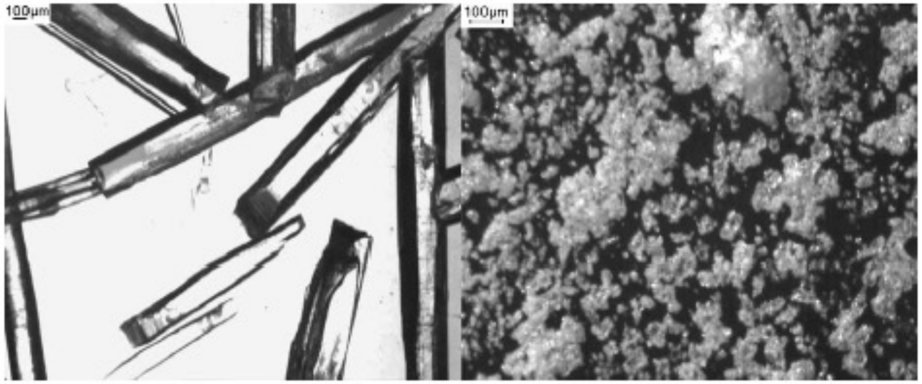


Fig. 5 – Crystals of the orthorhombic MHBA (left, magnified 40 times) and monoclinic MHBA (right, magnified 90 times), obtained through evaporation crystallization from ACN and MeOH, respectively, at 20 °C.

Summary on 1st order transition :

- **MELTING** : 1-step phenomenon
- **CRYSTALLIZATION** : 2-steps phenomenon : germination and crystalline growth
- Melting enthalpy can be used for crystallinity determination.
- Any process that promotes the organization of molecules increases the melting temperature.
- The phenomenon of polymorphism can be highlighted by DSC.

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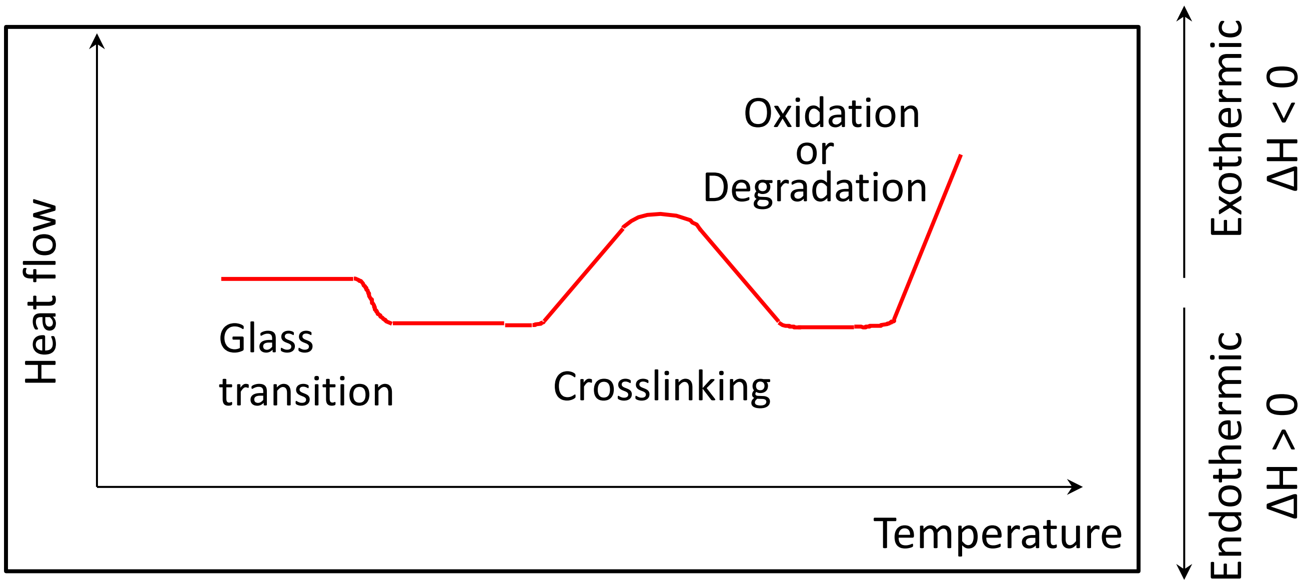
SECOND-ORDER TRANSITION



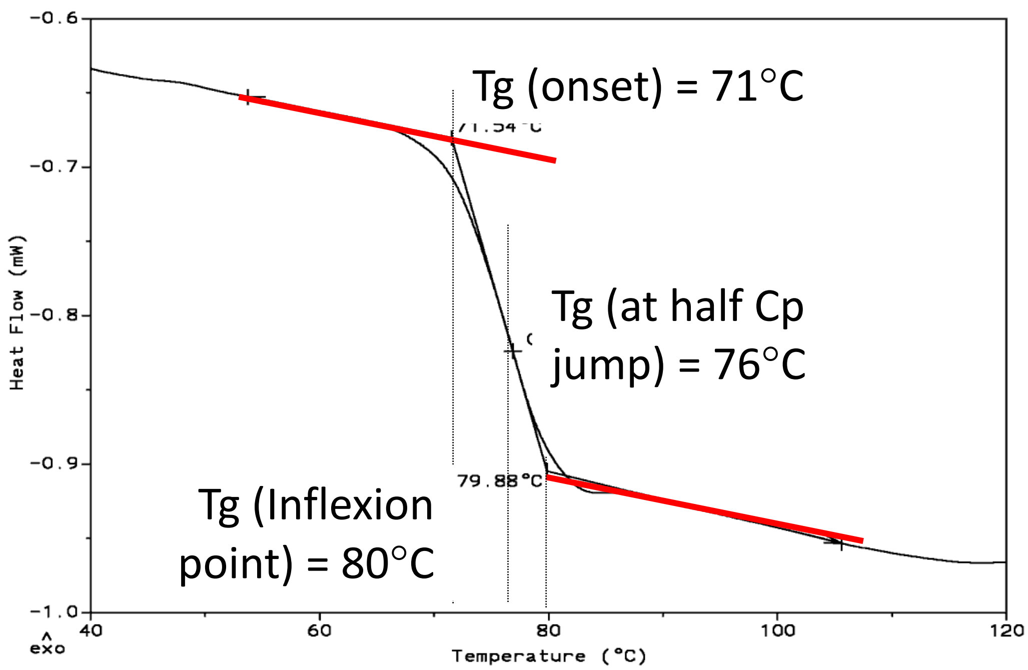
GLASS TRANSITION : reversible change of the amorphous phase of a polymer from a hard and relatively brittle form to a viscous or rubbery form.

The transformation is opposite when cooling.

It has a stair shape.

Calorimetric techniques

Ex : Tg of PET

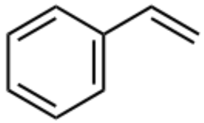


Tg : jump of Cp

Tg depends of :
- Scanning temperature
- Heating and cooling
- Ageing
- Plasticizers
- Charges
- Crystallinity
- Molecular Mass
- Copolymer
- Hydrogène bonds

MOLECULAR MASS EFFECT

Molecular mass (g/mol)	Tg (°C)
104	-138
524	- 40
2210	40
3100	62
15100	86
36000	94
170000	100



Tg ↗ when MM ↗

↳ Chains mobility more difficult

Calorimetric techniques

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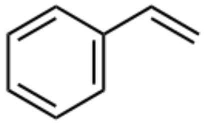
36000	94
170000	100



Tg ↗ when MM ↗

➩ Chains mobility more difficult

PLASTICIZERS EFFECT ON POLYAMIDE

Moisture content (%)	Tg (°C)
0.35	94
0.70	84
1.17	71
1.99	56
2.70	45
4.48	40
6.61	23
10.33	6

Tg ↘ when moisture content ↗

➩ Plasticizers effect : spread out the chains

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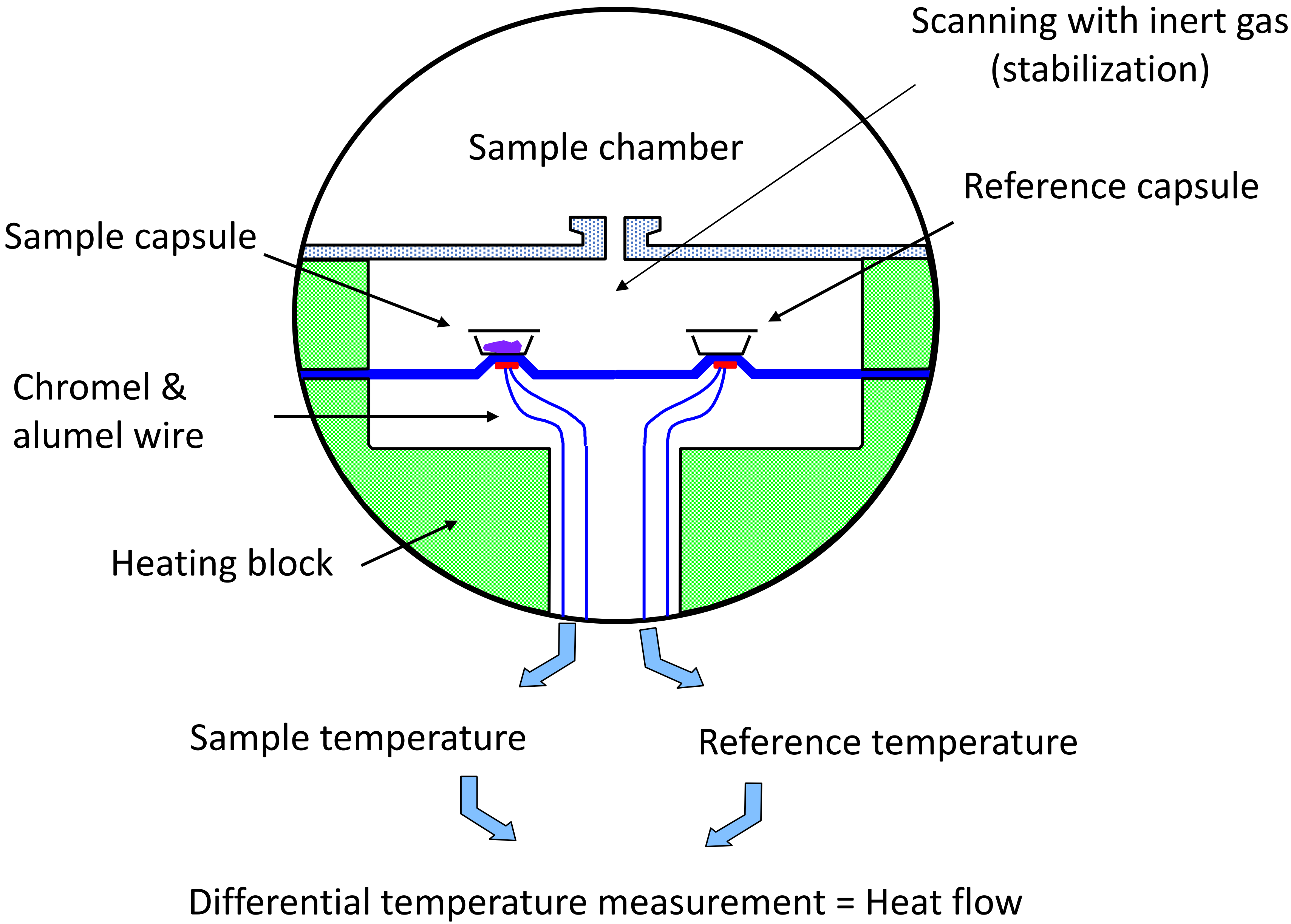
Calorimetric techniques

https://www.perkinelmer.com/fr/category/differential-scanning-calorimetry-dsc-instruments

https://www.netzsch-thermal-analysis.com/fr/produits-solutions/calorimetrie-differentielle-a-balayage/

https://www.tainstruments.com/products/thermal-analysis/differential-scanning-calorimeters/

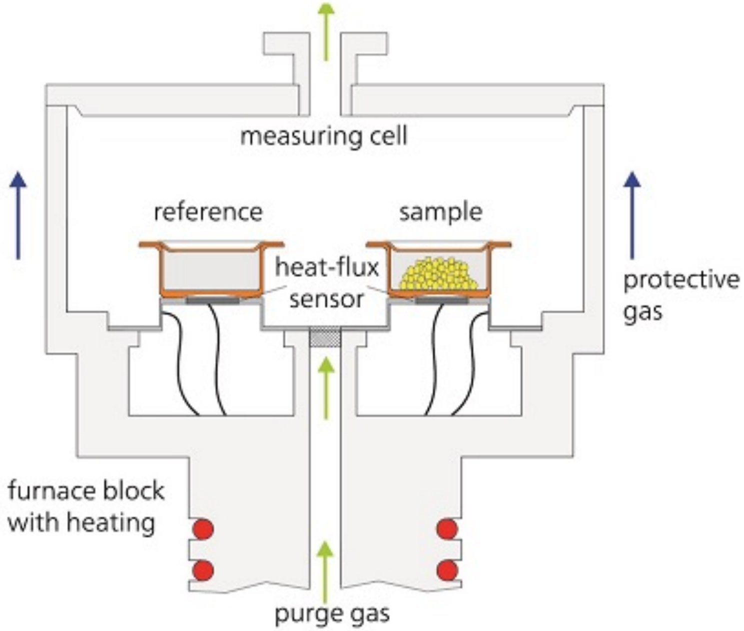
Calorimetric techniques



Calorimetric techniques

Three types of calorimeters

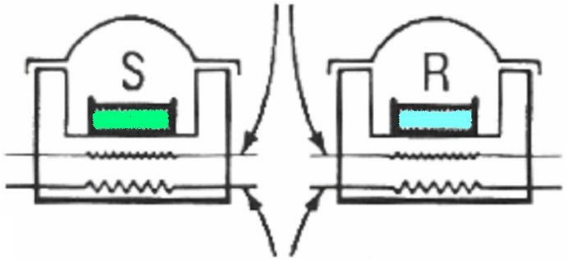
- Heat Flow measurement : Passive ΔT measurement



CONVENTIONAL DSC

- Power Compensation DSC : Readjustment of ΔT by supplying an electrical energy (active)

2 heating resistors



2 thermocouples : ΔT

Modulated DSC : same equipment than the "classical" one but the temperature variation is sinusoidal, instead of being linear as in conventional DSC.

"conventional" DSC

$$T = T_o + b \cdot T$$

$$dT/dt = b$$

Modulated DSC

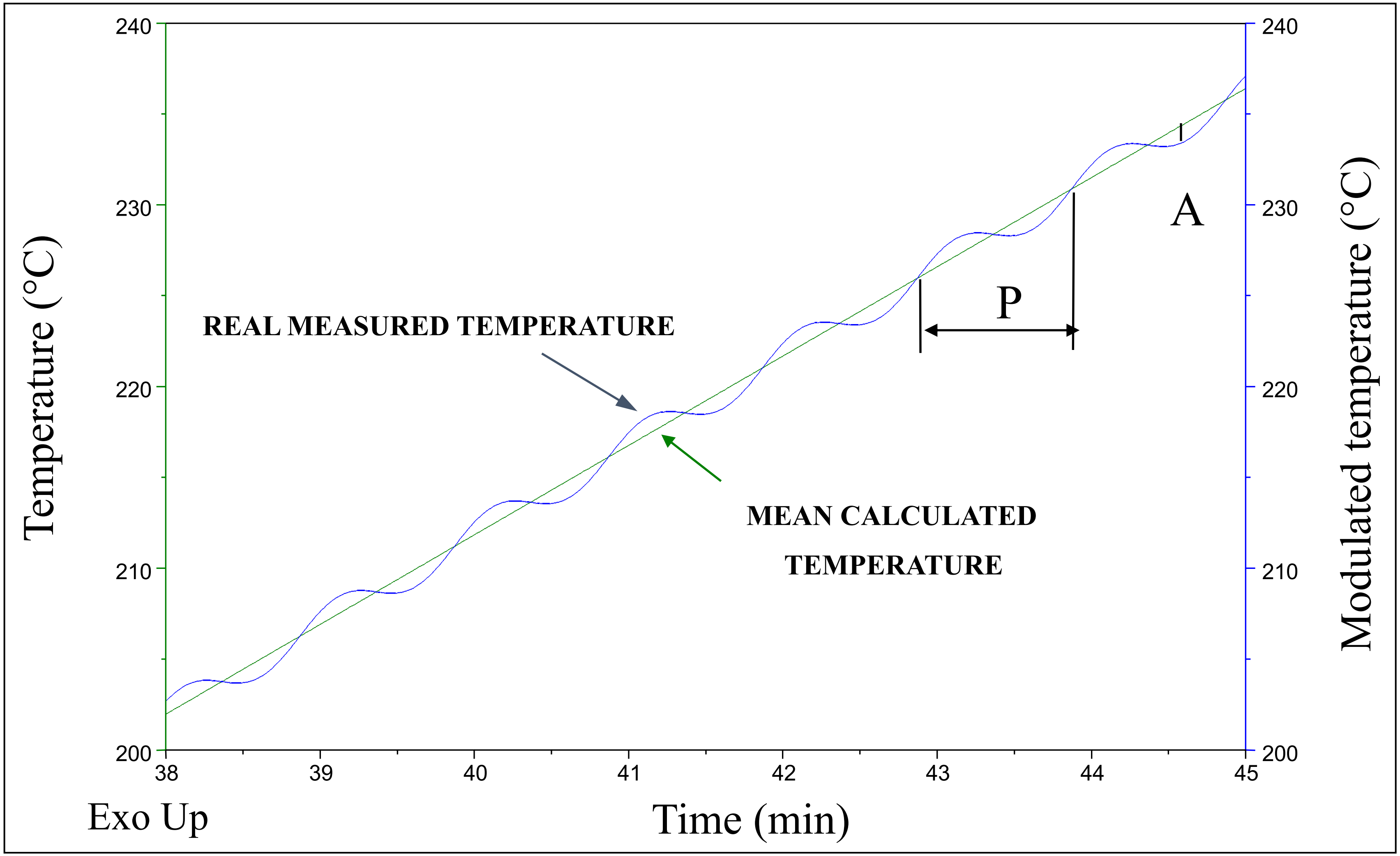
$$T = T_o + b \cdot t + A \cdot \sin(\omega \cdot t)$$

$$\omega = 2\pi / P$$

$$dT/dt = b + A \cdot \omega \cdot \cos(\omega \cdot t)$$

b : average heating rate
A : modulation amplitude
P : modulation period

Calorimetric techniques



AVANTAGES OF MODULATED DSC

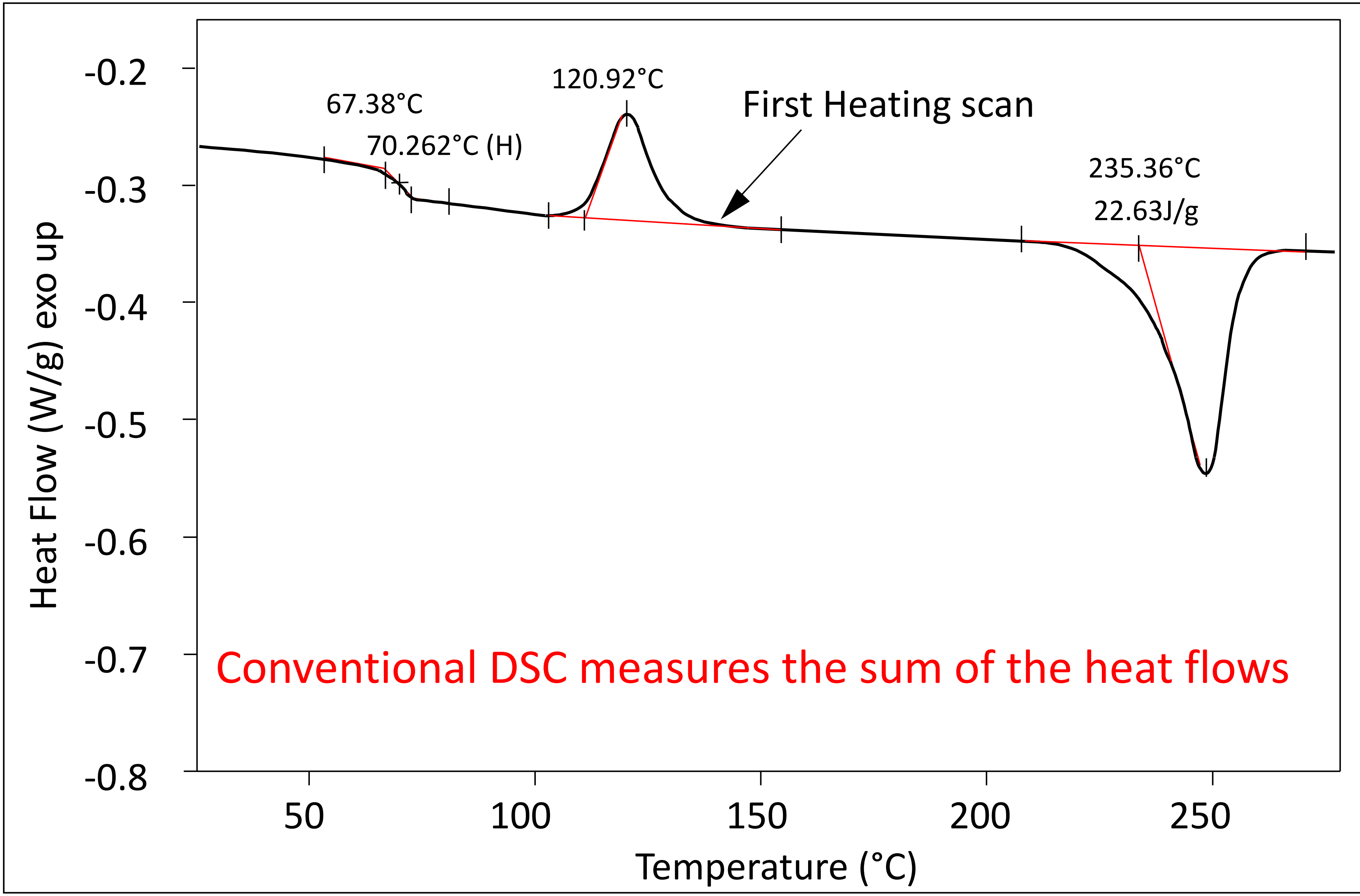
Separation of complex thermal events into the components of Calorific Capacity and Kinetic

TOTAL FLOW = CP part + KINETIC part

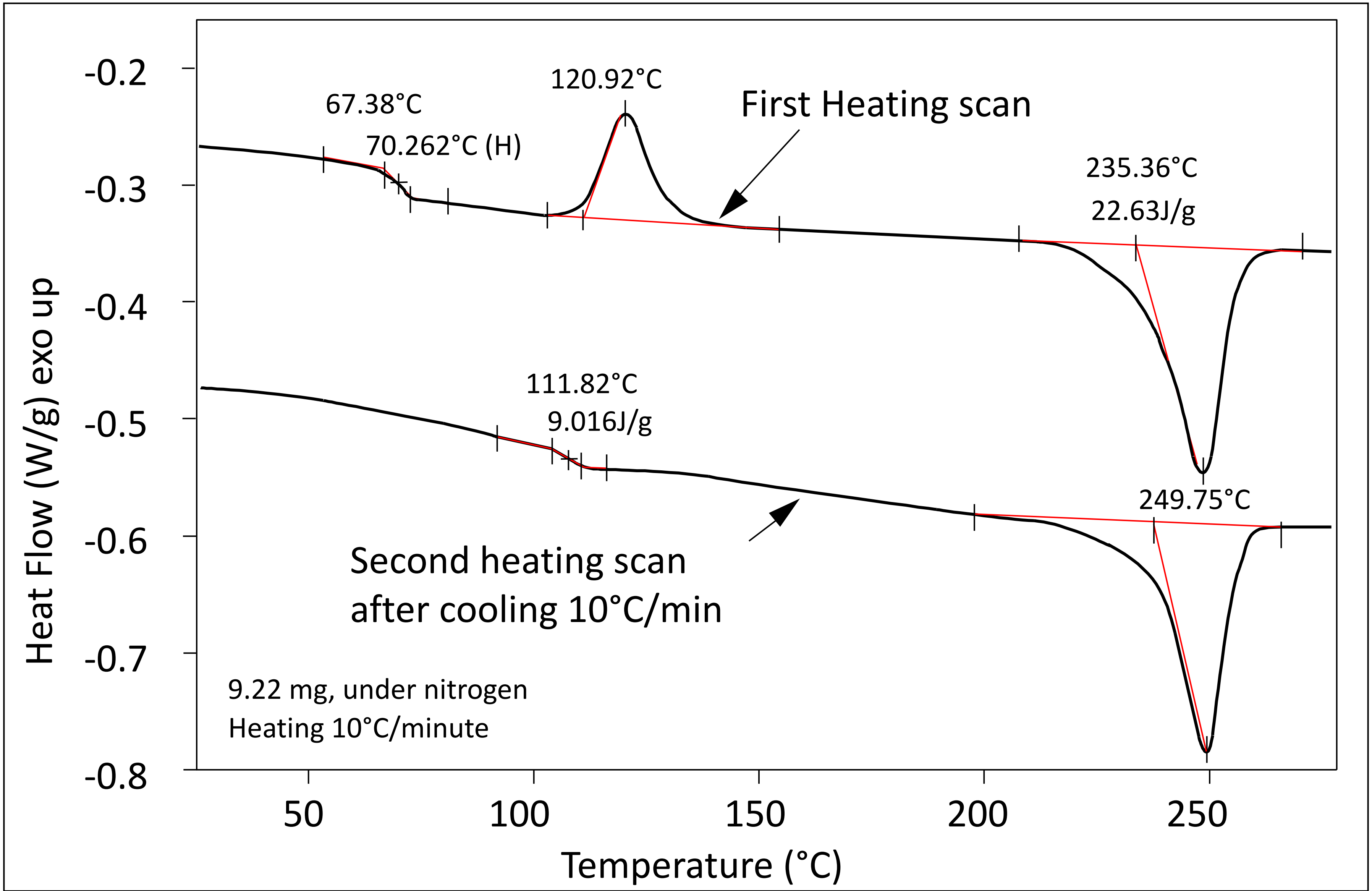
Reversible	**+**	**Non reversible**
- Glass transition		- Enthalpic relaxation
- Melting (sometimes)		- Evaporation
		- Crystallization
		- Degradation
		- Crosslinking

Calorimetric techniques

PET/ABS – Conventional DSC

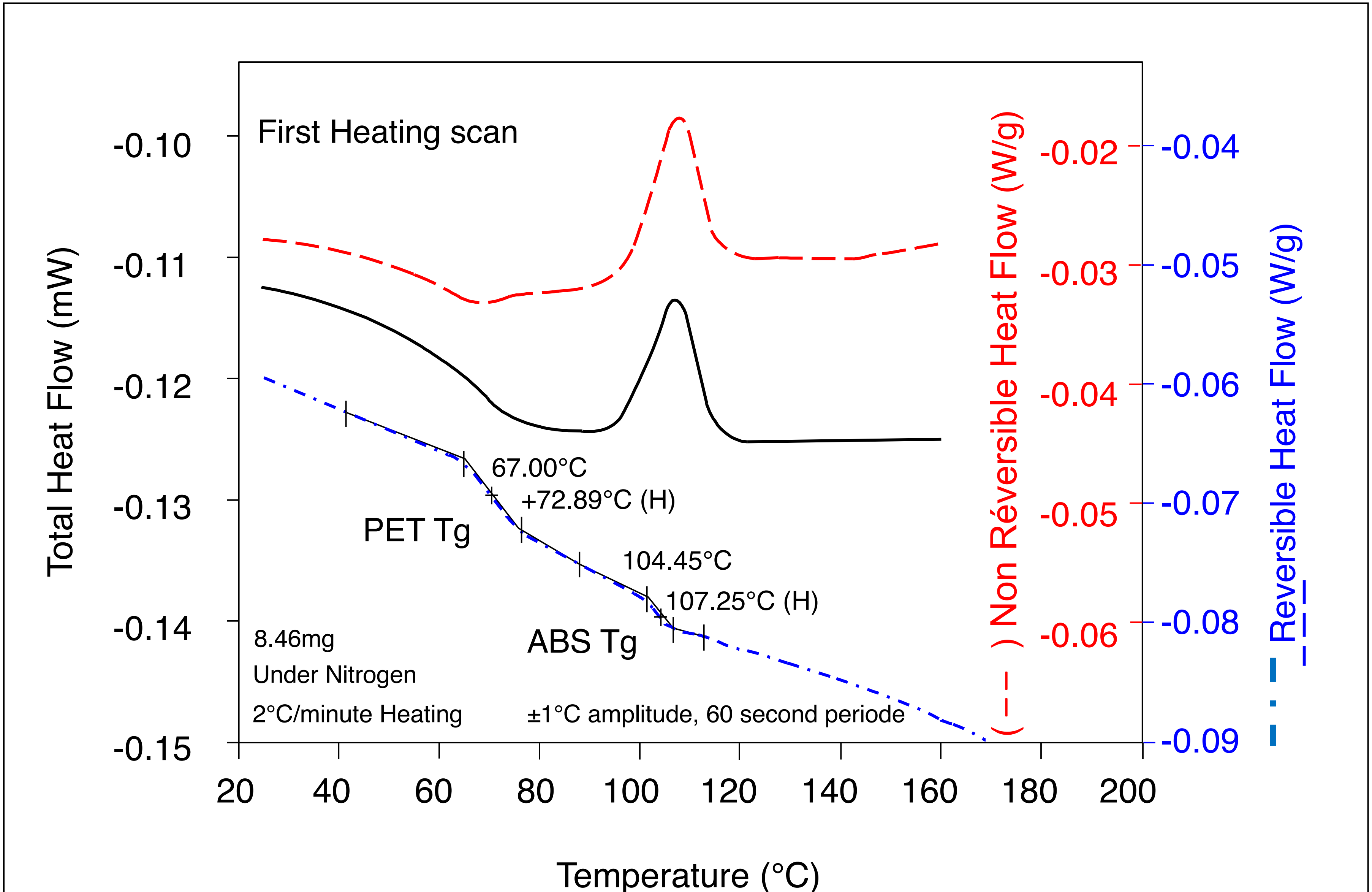


PET/ABS – Conventional DSC



Calorimetric techniques

PET/ABS – Modulated DSC : separation of the thermal events



DSC Calibration

- Calibration of the baseline

- Calibration of Heat and Temperature by certified materials

HEAT

Benzoic acide : 147.3 J/g
Urea : 241.8 J/g
Indium : 28.45 J/g
Anthracen : 161.9 J/g

TEMPERATURE (Tm)

Cyclopentane* -150.77°C
Cyclopentane* -135.09°C
Cyclopentane* -93.43°C
Cyclohexane# -83°C
Water # 0°C
Gallium# 29.76°C
Phenilic Ether # 30°C
p-Nitrotoluen~ 51.45°C
Naphthalen~ 80.25°C
Indium# 156.60°C
Tin # 231.95°C
Lead* 327.46°C

Samples preparation

Crimp the sample (~3-20 mg) into sealed or unsealed capsules using a crimping press.

Nature	Temperature limit
Aluminium	600°C
Copper	725°C (under N_2)
Gold	725°C
Graphite	725°C (under N_2)
Sealed Al	600°C (3 atm.)
Sealed Gold	725°C (6 atm.)
Platinum	725°C

Al Pt alumina Ni Cu quartz

Calorimetric techniques

The most important point for the sample preparation is to get the best thermal exchange between sample and thermocouple

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Sample :

- As thin as possible
- Quality of the contact capsule/sample
- Loss of sensitivity if low mass

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Scanning rate

- Better resolution at low scanning rate
- Better sensibility at high scanning rate

Calorimetric techniques

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Echantillon :

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– Quality of the contact capsule/sample

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Scanning rate

- Better resolution at low scanning rate

- Better sensibility at high scanning rate

Scanning gas

- Nitrogen : low thermal conductivity but good sensitivity

- Helium: good thermal conductivity and better resolution

In classical DSC a compromise is necessary between SENSITIVITY and RESOLUTION.

SUMMARY of DSC applications

- **Phase changes**

	Solid / Solid transitions:	- Glass transition
		- Polymorphism
		- Desolvatation
	Solid / Liquid transitions :	- Melting
	Liquid /Solid transitions :	- Crystallization

SUMMARY of DSC applications

- **Phase changes**

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- **Chemical composition changes**

Measurement of ΔH and temperatures in specific conditions : kinetics reaction, degradation; desolvatation

SUMMARY of DSC applications

- **Phase changes**

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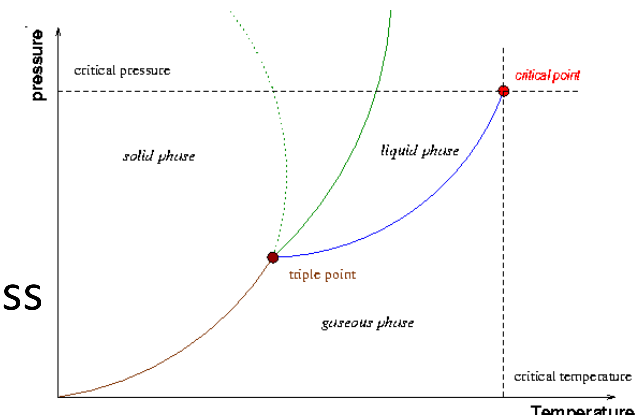
- **Chemical composition changes**

Measurement of ΔH and temperatures in specific conditions : kinetics reaction, degradation; desolvatation

- **Establishment of phase diagramms**

Important for the pre-formulation and freeze-drying process



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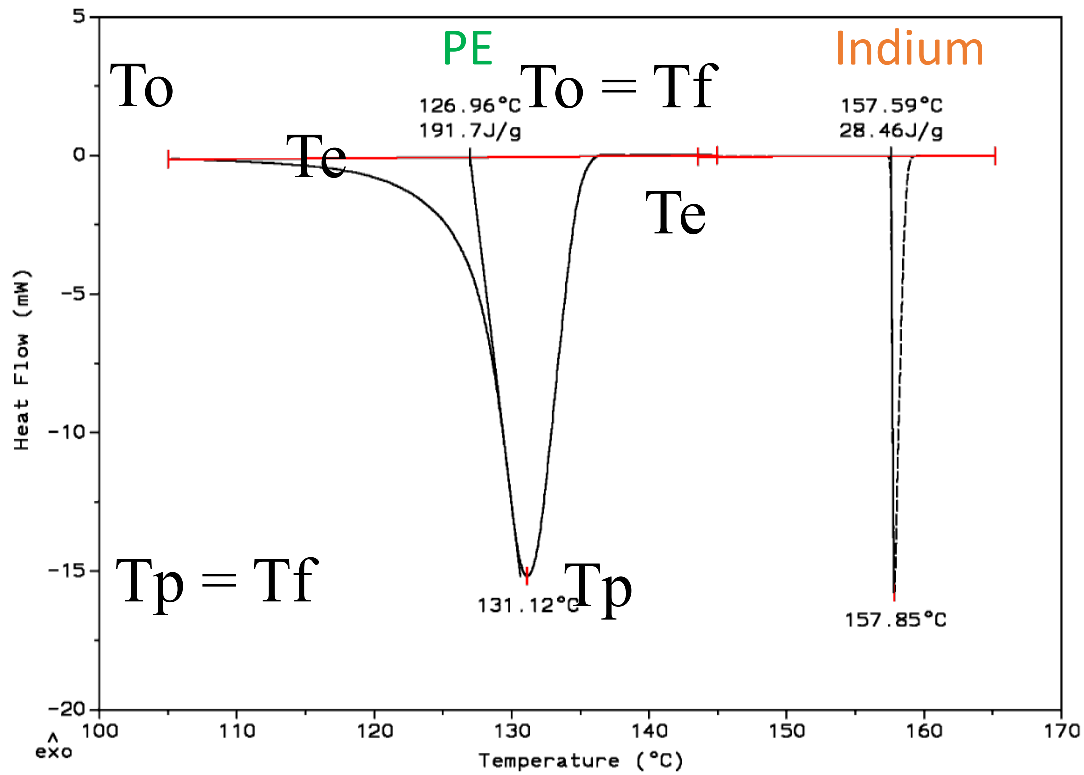
Calorimetric techniques

- **Purity determination**

Measurement of ΔH et Tm to get the impurity content :

Broadening of temperature range
Incurvation of the thermogram

} sensitive criteria for the detection of impurities



Calorimetric techniques

- **Purity determination : Van't Hoff equation**

$$T = T_o - \frac{RT_o^2}{\Delta H_f} \times x_2$$

T_o : Tm of a chemically pure substance (K)

R : cste of perfect gases ($J.K^{-1}.mole^{-1}$)

ΔH_f : melting molar enthapy (J)

X_2 : molar fraction of the molten impurity

F : molten fraction

$$X_2 = \frac{\text{Nbre of molecules in molten impurity}}{\text{Total nbre of molecules in the liquid phase (T)}} = \frac{x}{F}$$

Validity of Van't Hoff's equation :

The main component should have a purity of > 99.5 % (in mole)

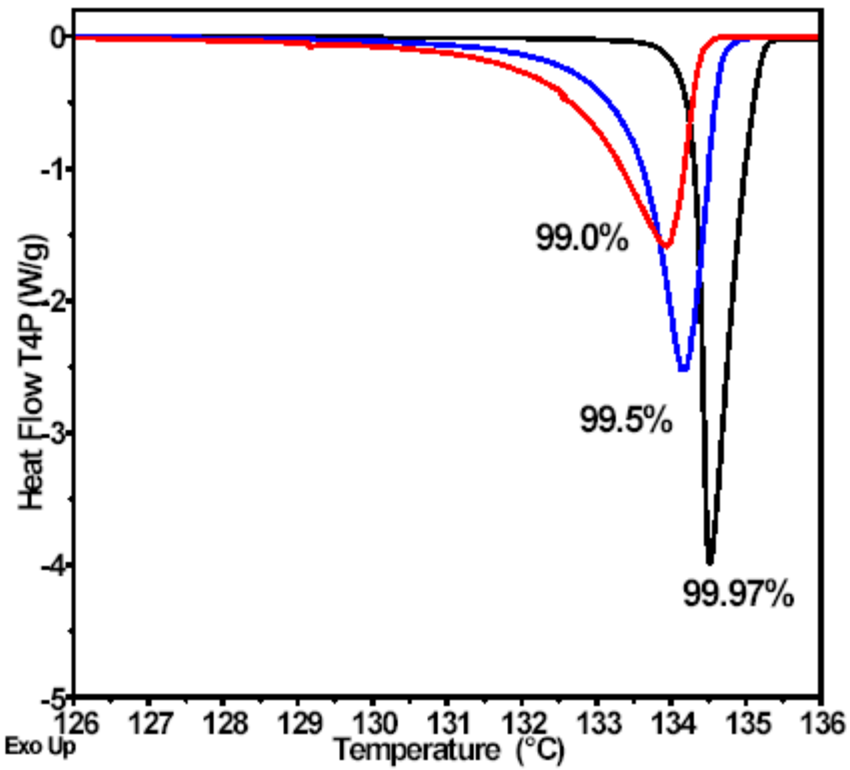
Impurities are generally secondary products whose identity can be determined using HPLC for example.

It is then necessary to prepare samples with known levels of impurities.

m1 (µg)	m2 (µg)	Added impurity (mol %)	Measured impurity (mol %)	Error (measured / added) (mol %)
3360	0	0.0	0.037	0.037
3610	12	0.465	0.526	0.061
5584	23	0.58	0.65	0.07
3224	36	1.55	1.45	-0.1
3868	94	3.30	2.77	-0.52

Calorimetric techniques

Thermal diagrams obtained as a function of the purity variation

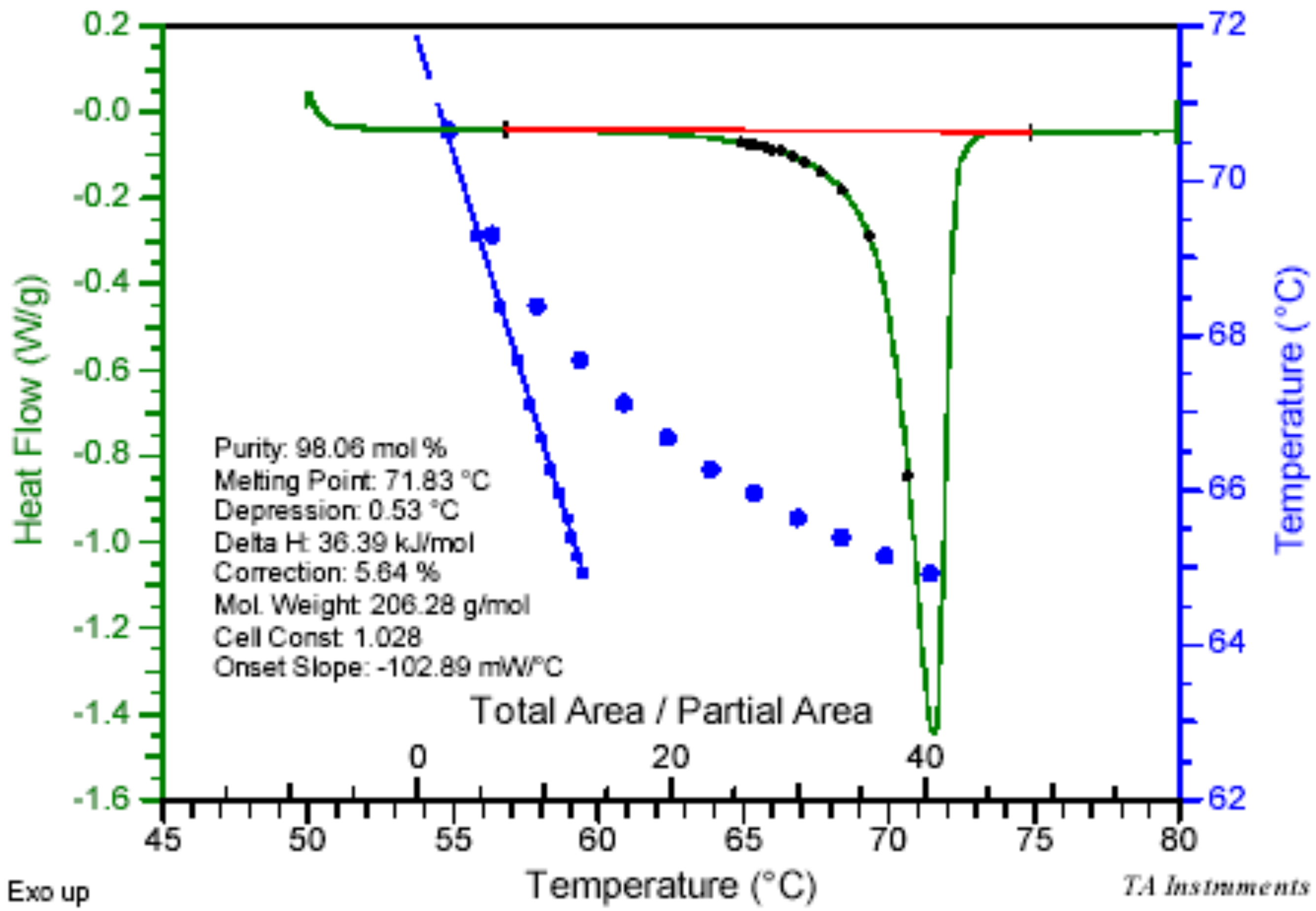


Example from Pharmacopea : Phenacetin in 3 different degrees of purity

Calorimetric techniques

Example from Pharmacopea : Determination of purity's degree of Ibuprofen®

Difficulty : - Low scanning rate (1°C/min)
- Good sensibility of the thermocouple



Calorimetric techniques

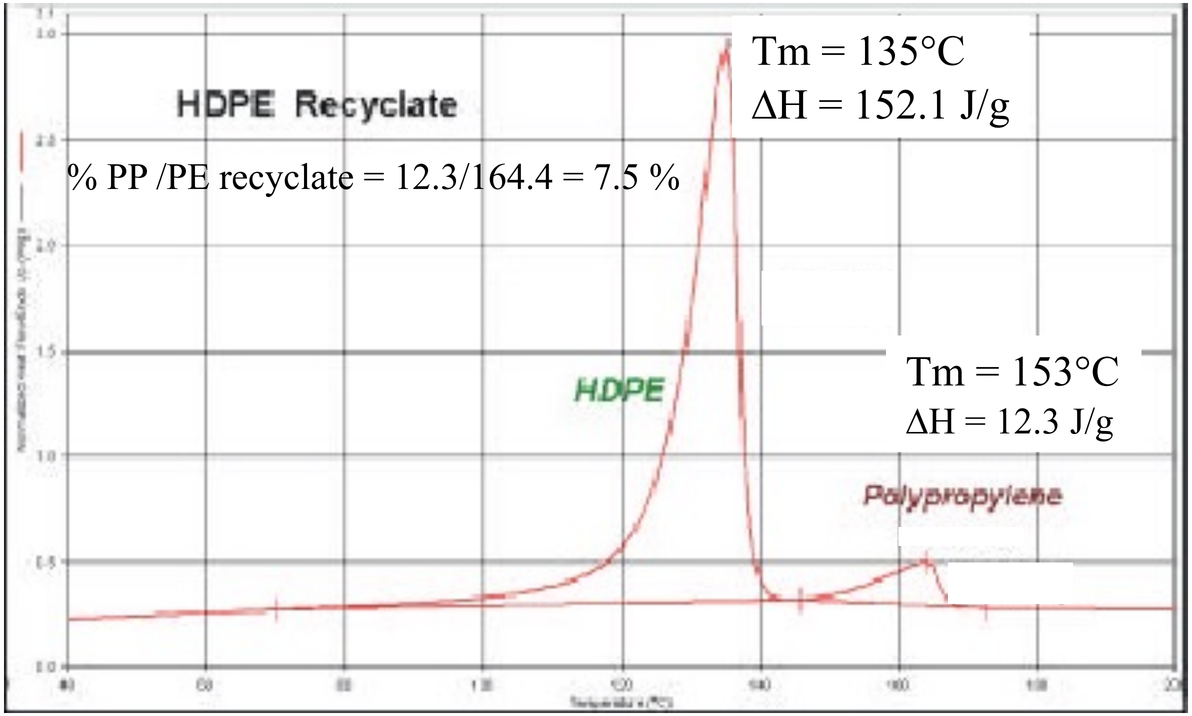
- **Miscibility/immiscibility**

Immiscibility between two compounds each having a melting peak

⇨ 2 endothermal peaks

Miscibility between the 2 components

⇨ 1 only endothermal peak intermediate between the 2 Tm



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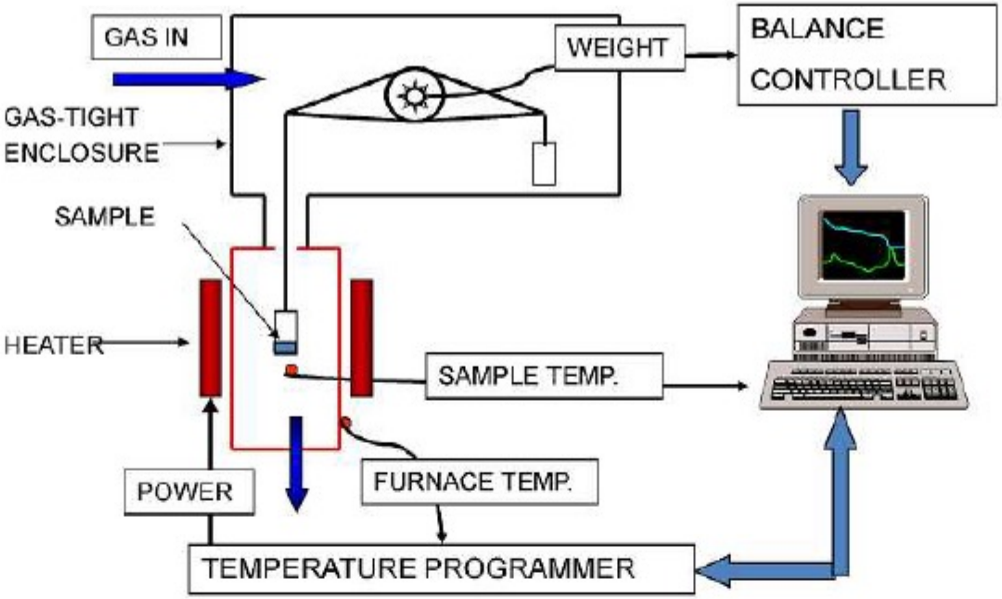
Thermogravimetric analysis

THERMOGRAVIMETRY : is a method of thermal analysis in which the mass of a sample is measured over time as the temperature changes and under a given atmosphere.

This measurement provides information about :

- Physical phenomena, such as phase transitions, absorption, adsorption and desorption;
- Chemical phenomena including chemisorptions, thermal decomposition and solid-gas reactions (e.g., oxidation or reduction);
- Identification des volatile products by coupling DSC/FTIR/MS.

Thermogravimetric analysis



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TGA calibration

- Calibration of MASS :

  ↳ Certified gold bead (static calibration)

  ↳ Copper sulphate (dynamic)

- Calibration of TEMPERATURE :

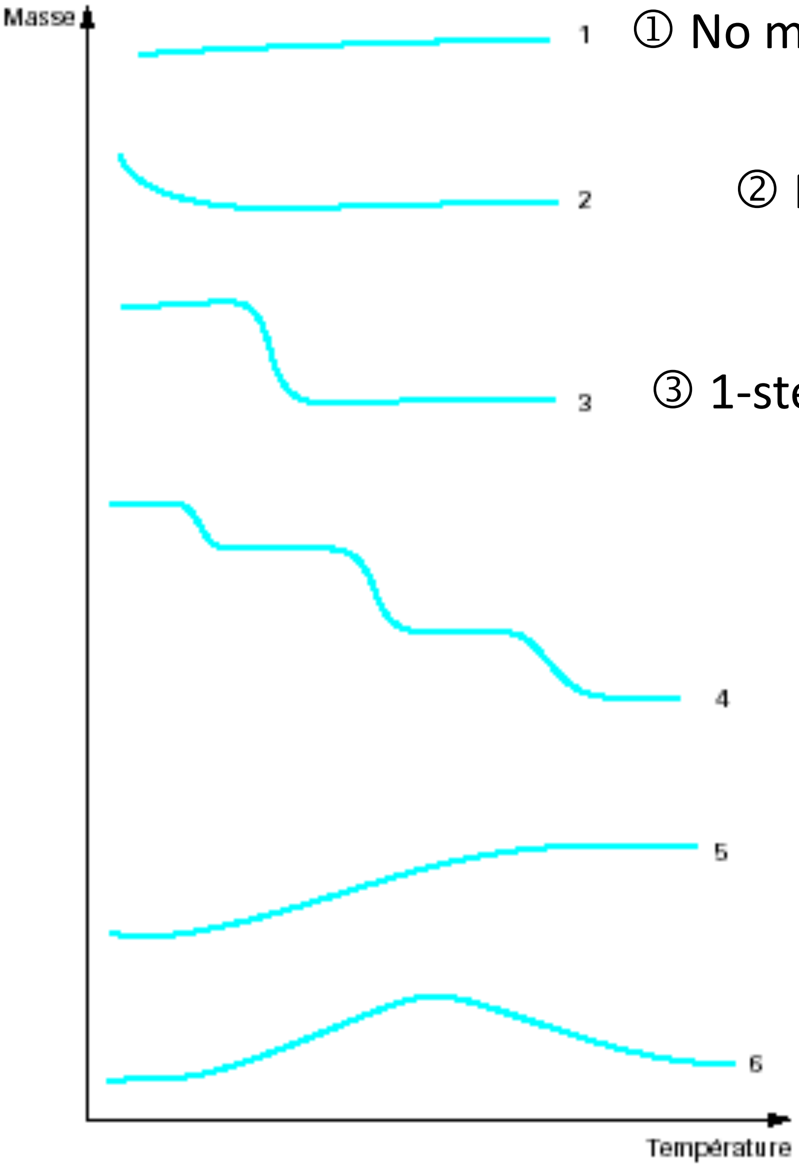
  ↳ Magnetic materials (Point de Curie) / Alumel

  ↳ Materials with a transformation at a known temperature

- Calibration of TIME

Thermogravimetric analysis

Different types of TGA curves



① No mass loss, no chemical decomposition

② Fast mass loss (evaporation)

③ 1-step decomposition : thermal stability

④ Several steps decomposition

⑤ Mass increase : formation of a non volatile product / oxidation

⑥ Mass increase and decrease : formation of a non volatile product that is degraded at higher temperature

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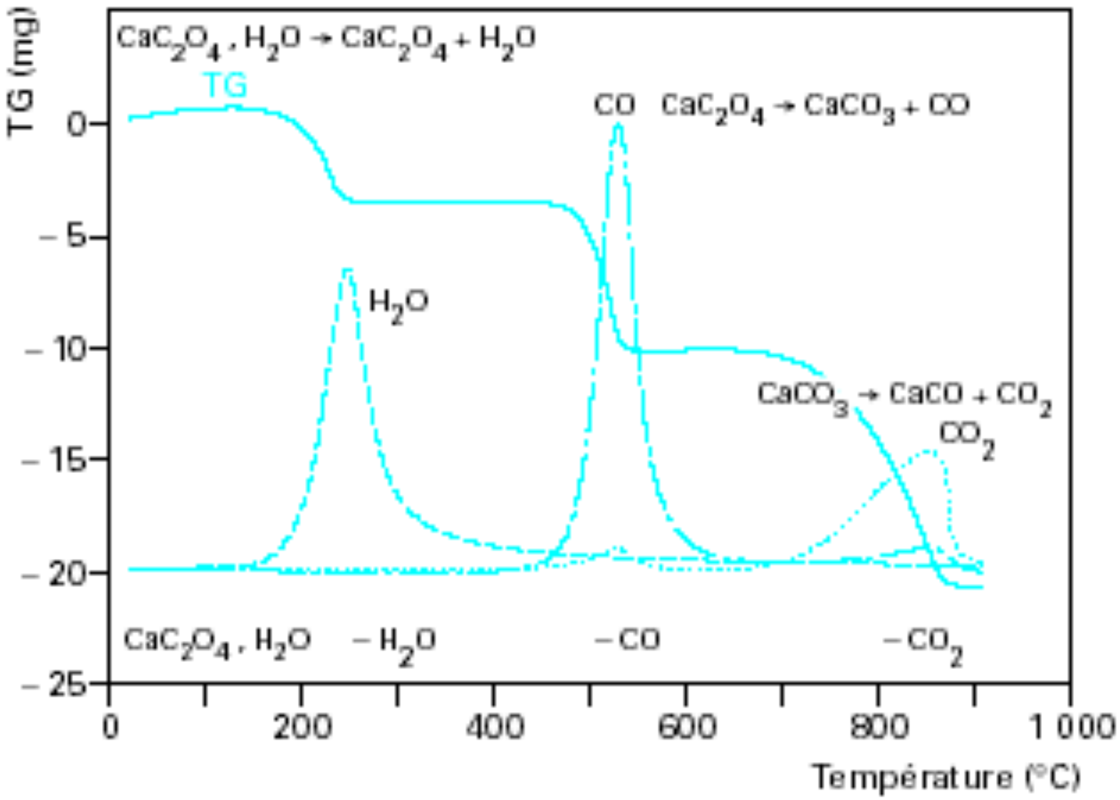
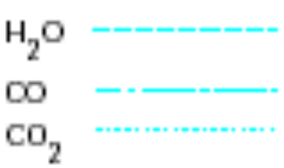
Thermogravimetric analysis

Example : decomposition of calcium oxalate

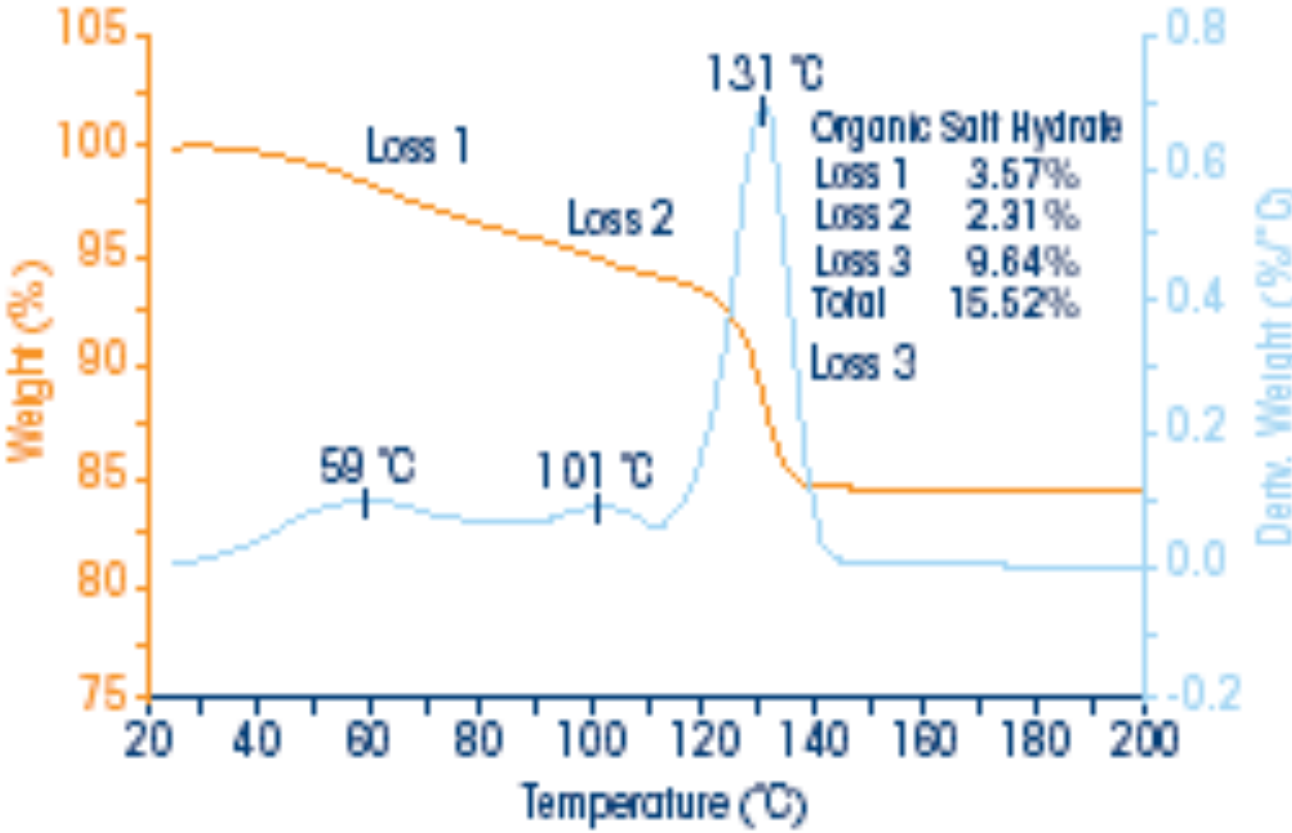


Procedure : from 20°C to 900°C (10°C/min)
Capsule : Alumine
Atmosphere : Helium



Thermogravimetric analysis

Example :
Moisture content of an organic salt



Thermogravimetric analysis

Adsorbed water / free

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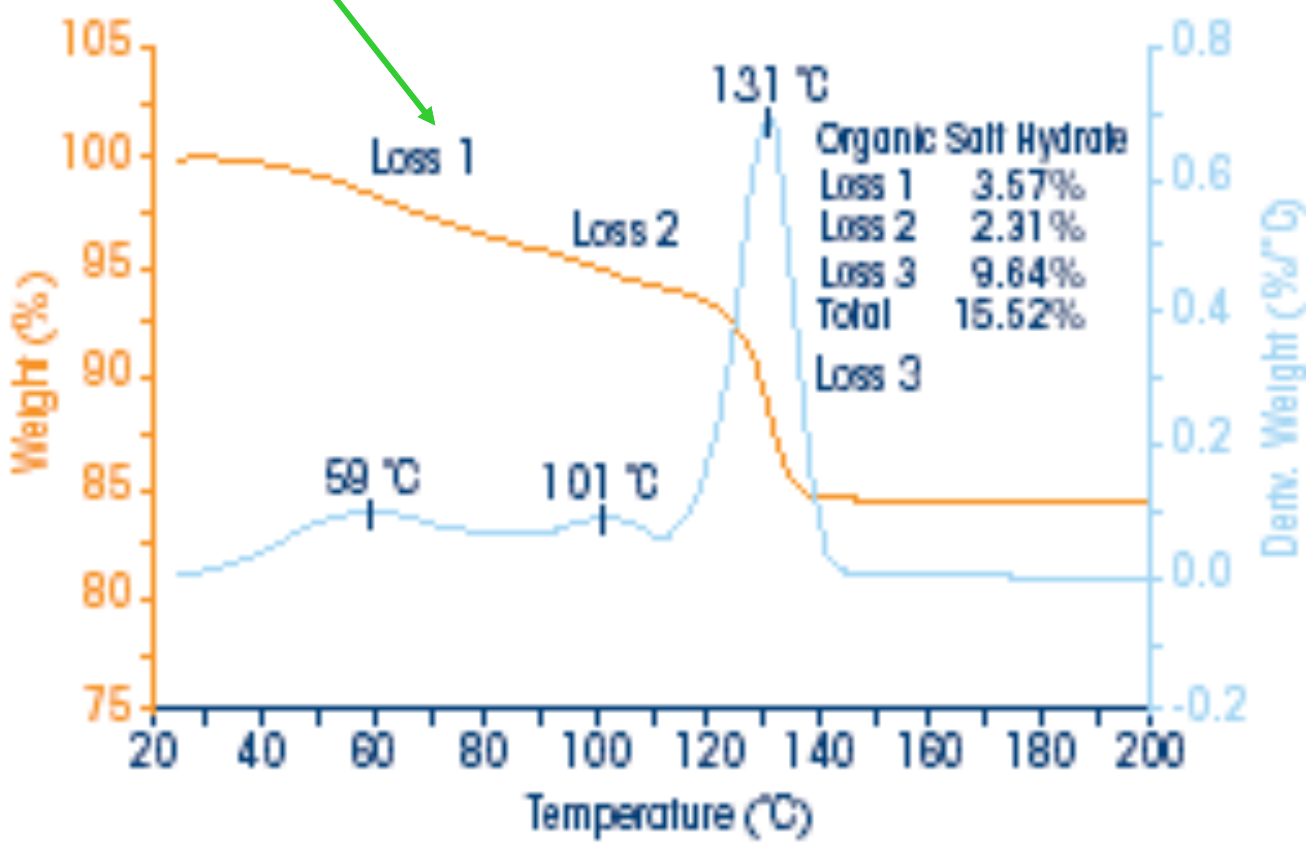

Thermogravimetric analysis

Adsorbed water / free

Absorbed water / weak bonds

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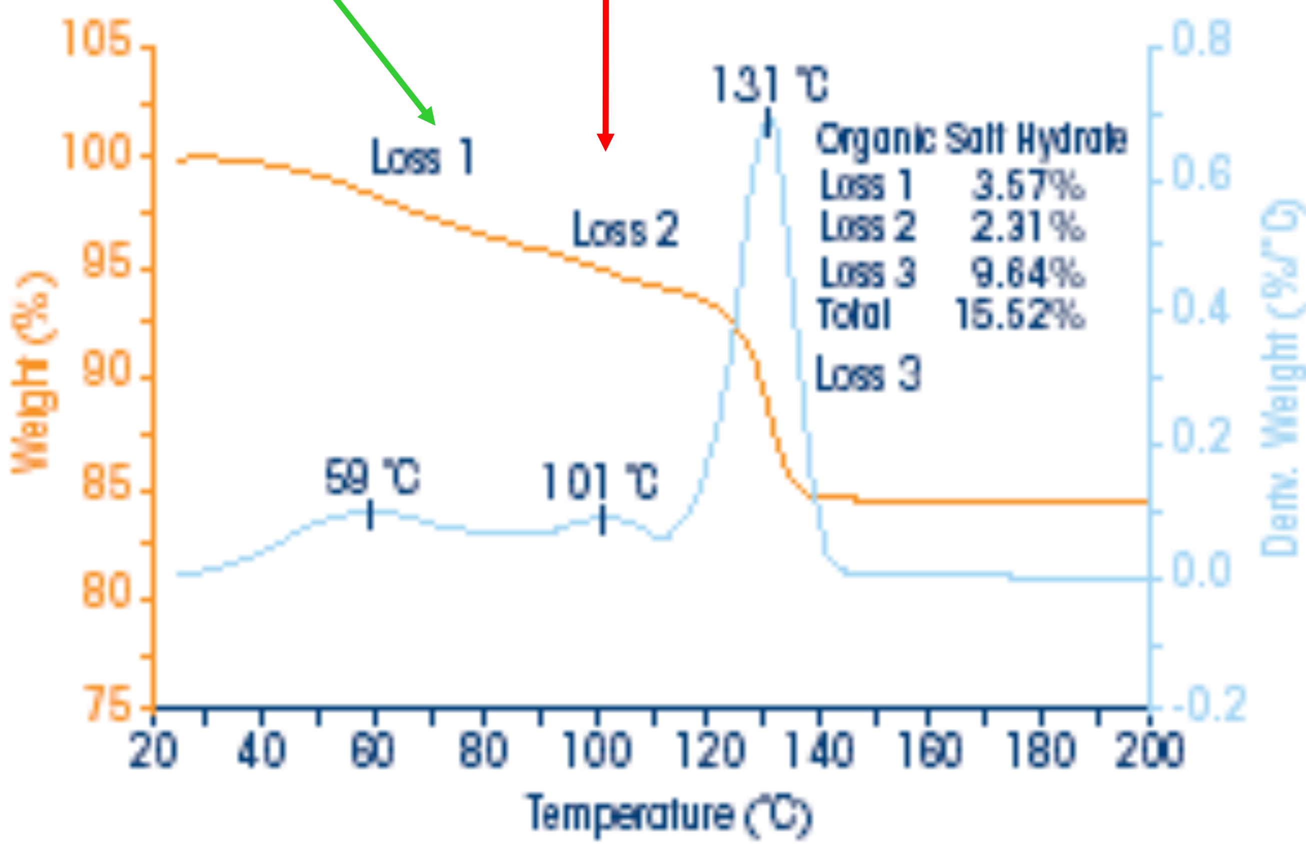

Thermogravimetric analysis

Adsorbed water / free

Absorbed water / weak bonds

Linked water

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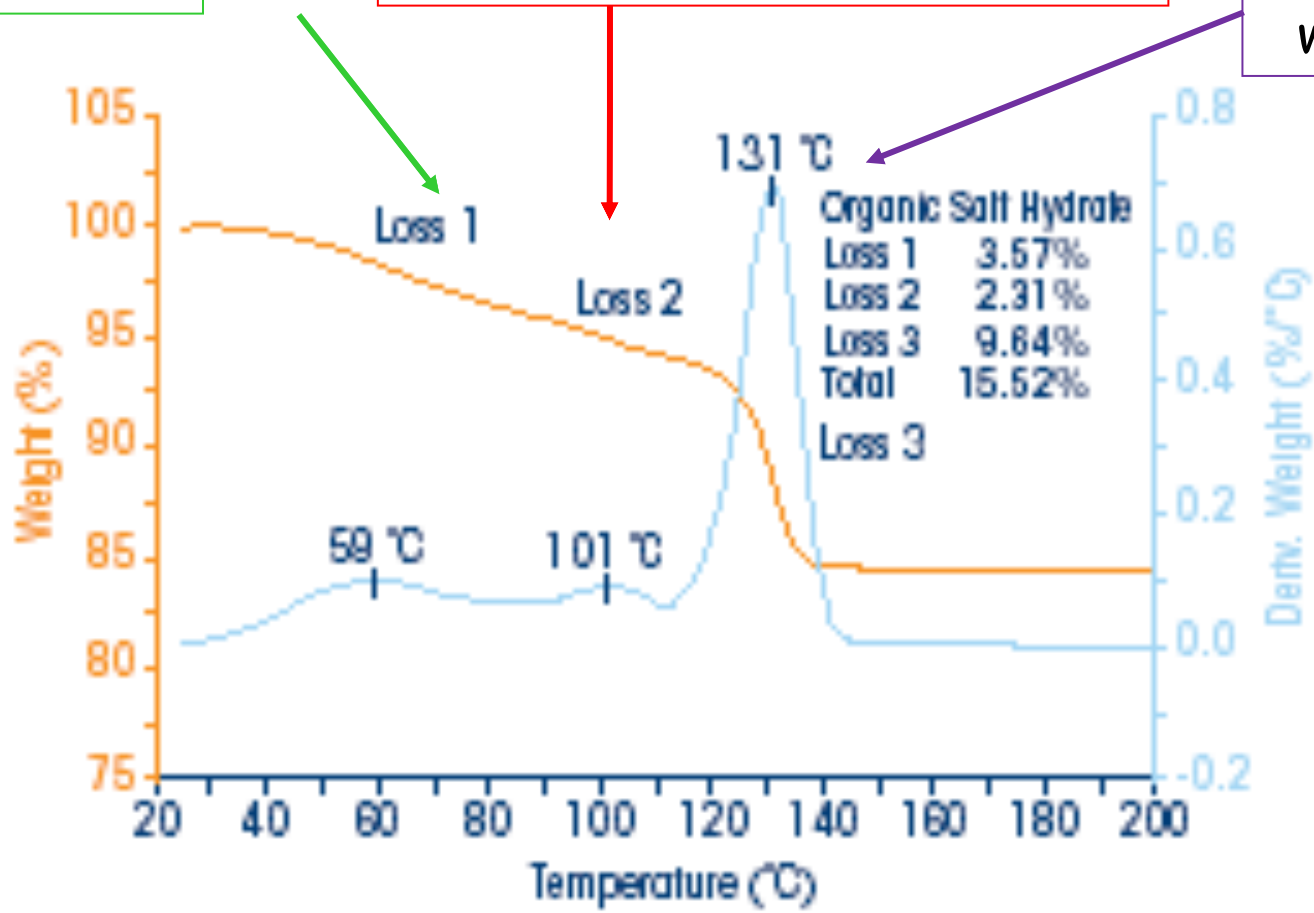
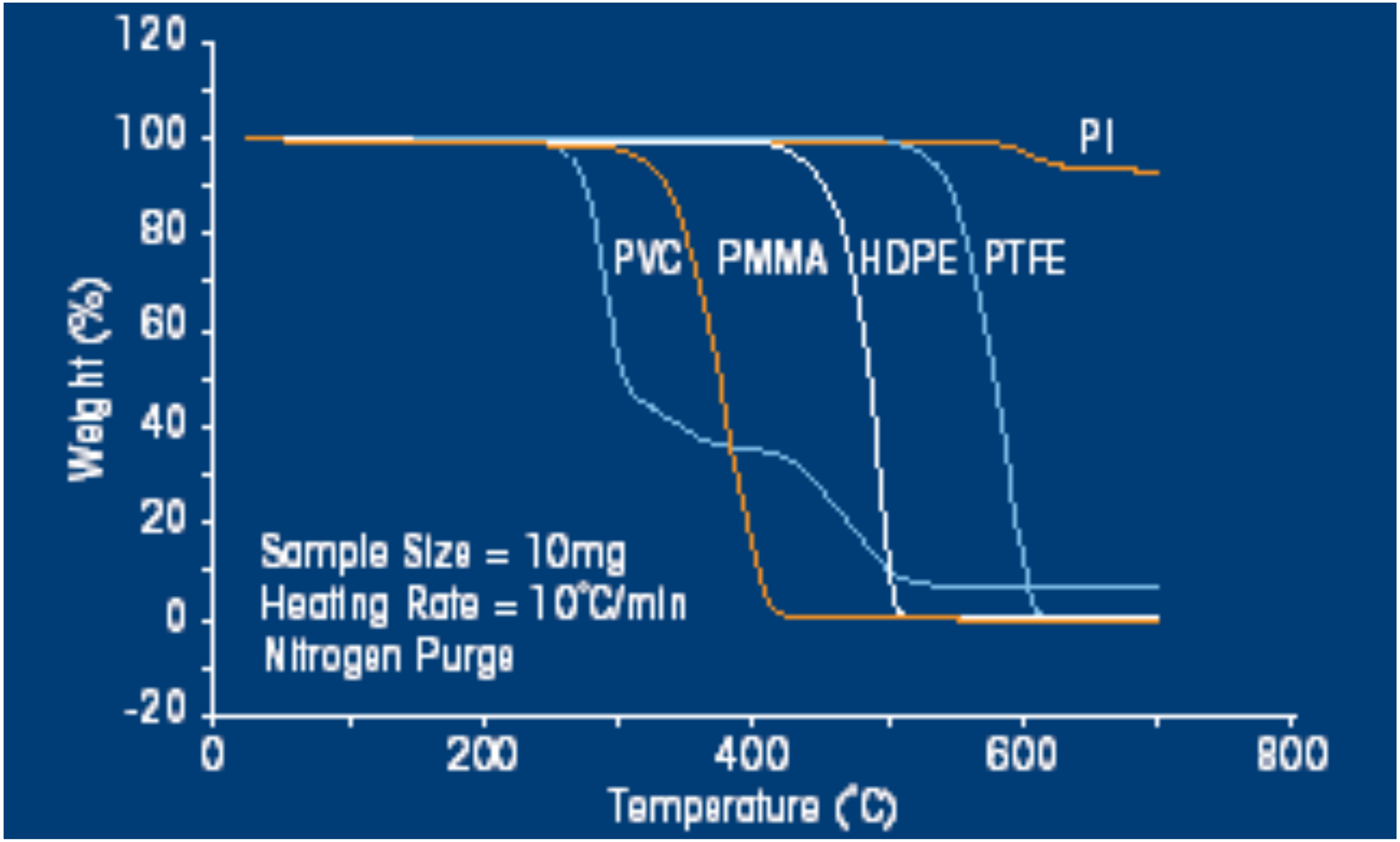


Thermogravimetric analysis



Example : Thermal stability PVC < PMMA < HDPE < PTFE

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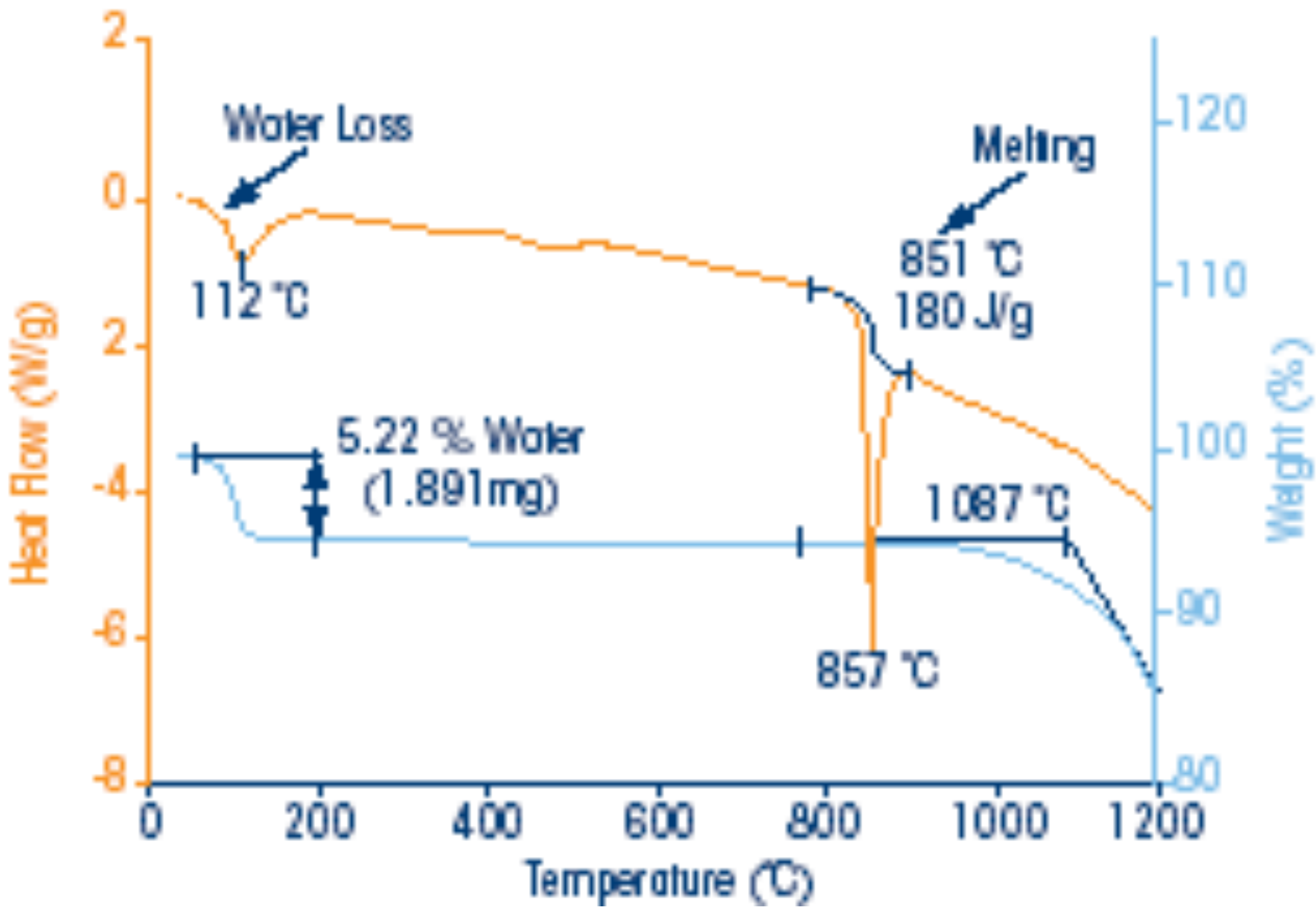
Thermogravimetric analysis

- **Coupling TGA / DSC**

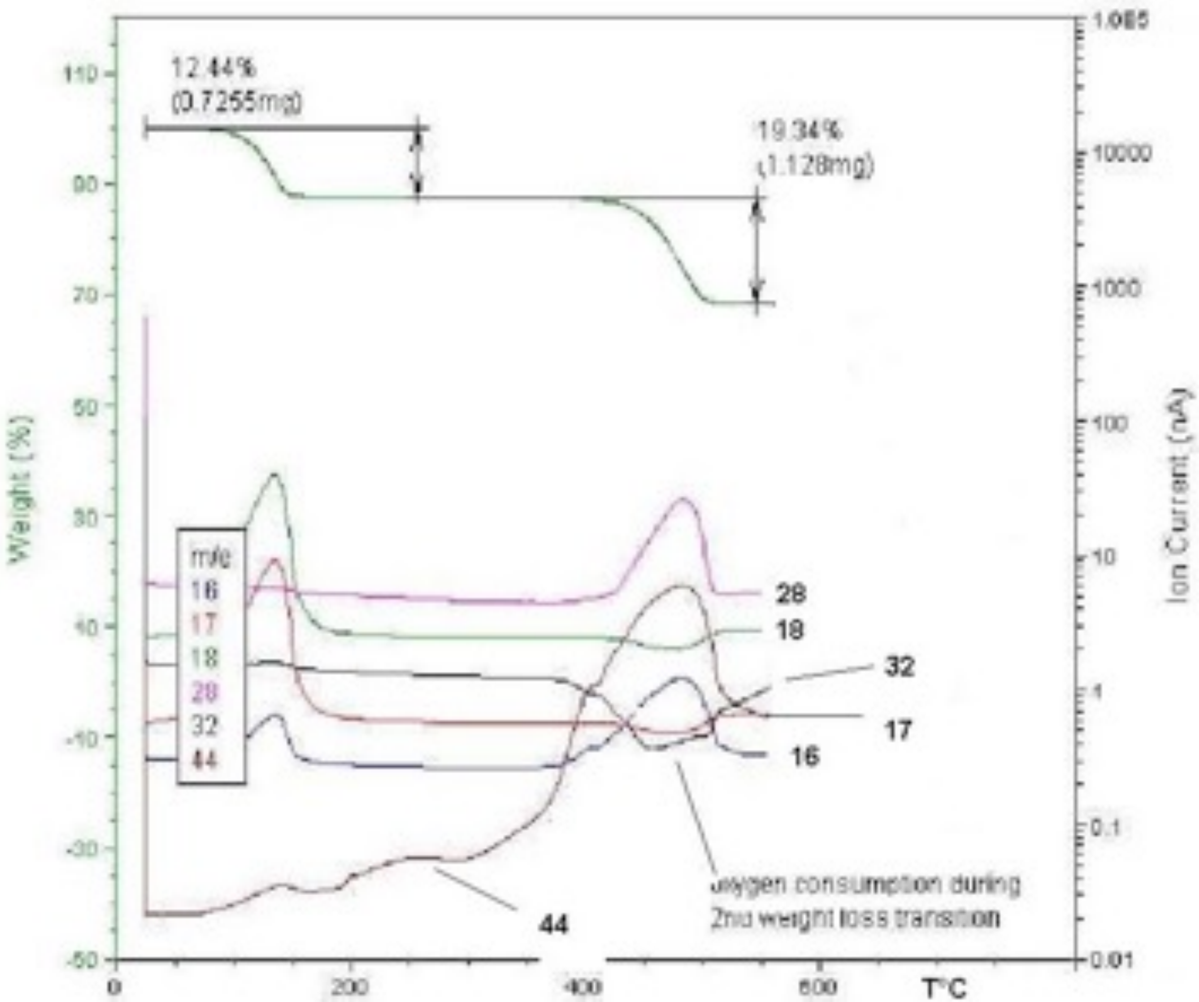
Ex : Soda in powder



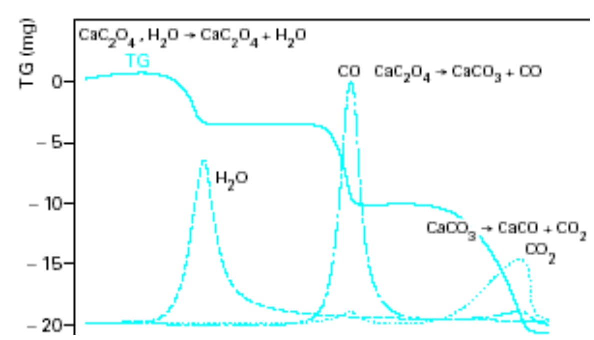
Thermogravimetric analysis

- **Coupling TGA / MS**

Mass spectrometry helps in identifying the volatile nature

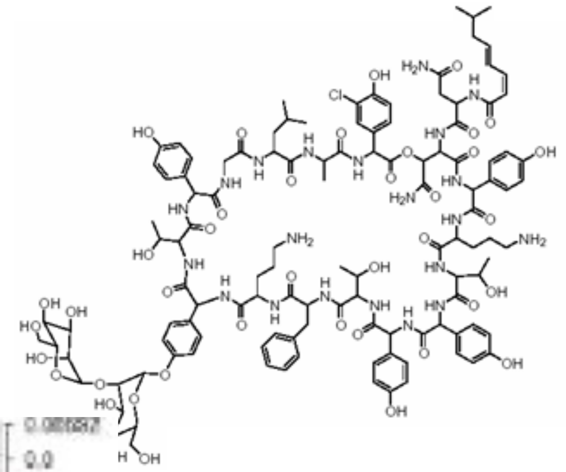


<u>Ex</u> : Decomposition of calcium oxalate (Used in pharmaceutical control)

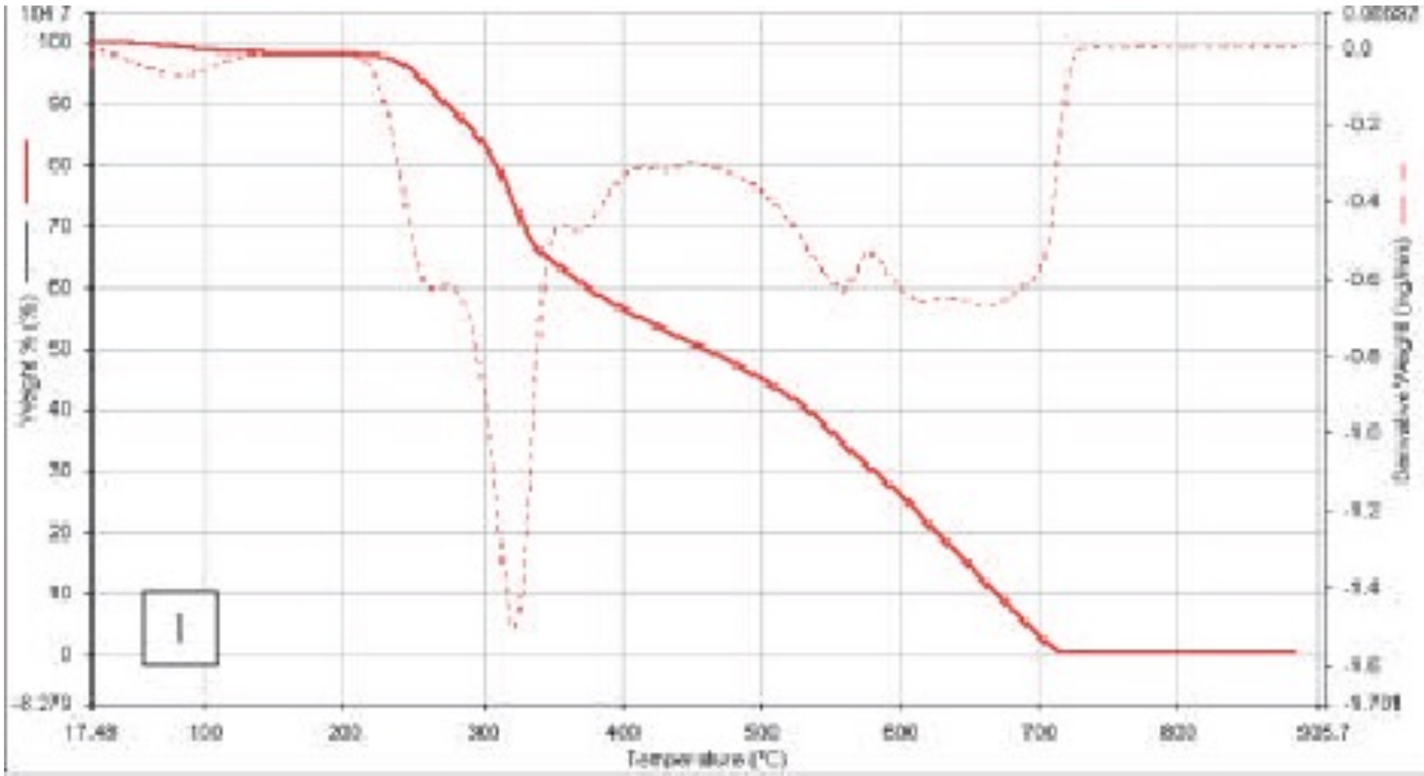


Thermogravimetric analysis

- **Coupling TGA / FTIR**



Ex : Decomposition of Ramoplanin (antibiotic)



Thermogravimetric analysis

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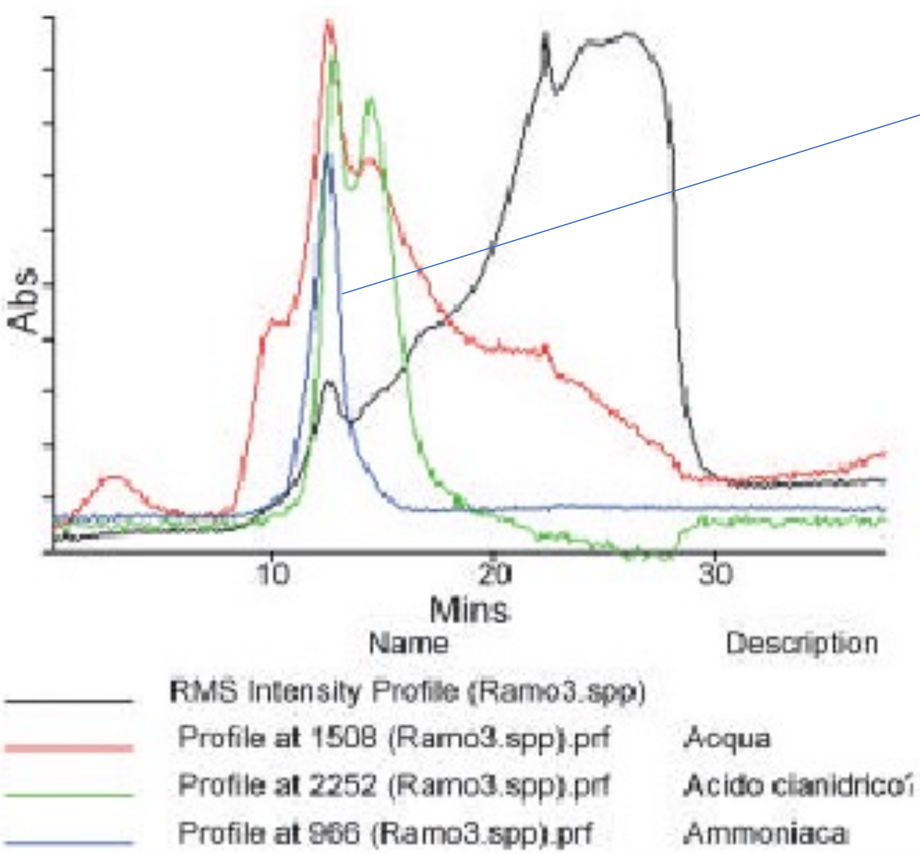

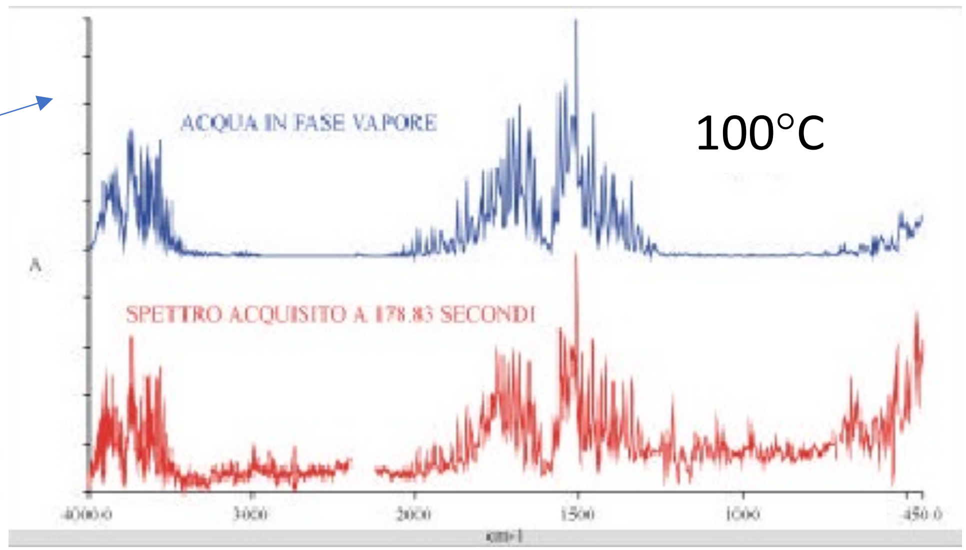

Emission intensity profiles

Thermogravimetric analysis

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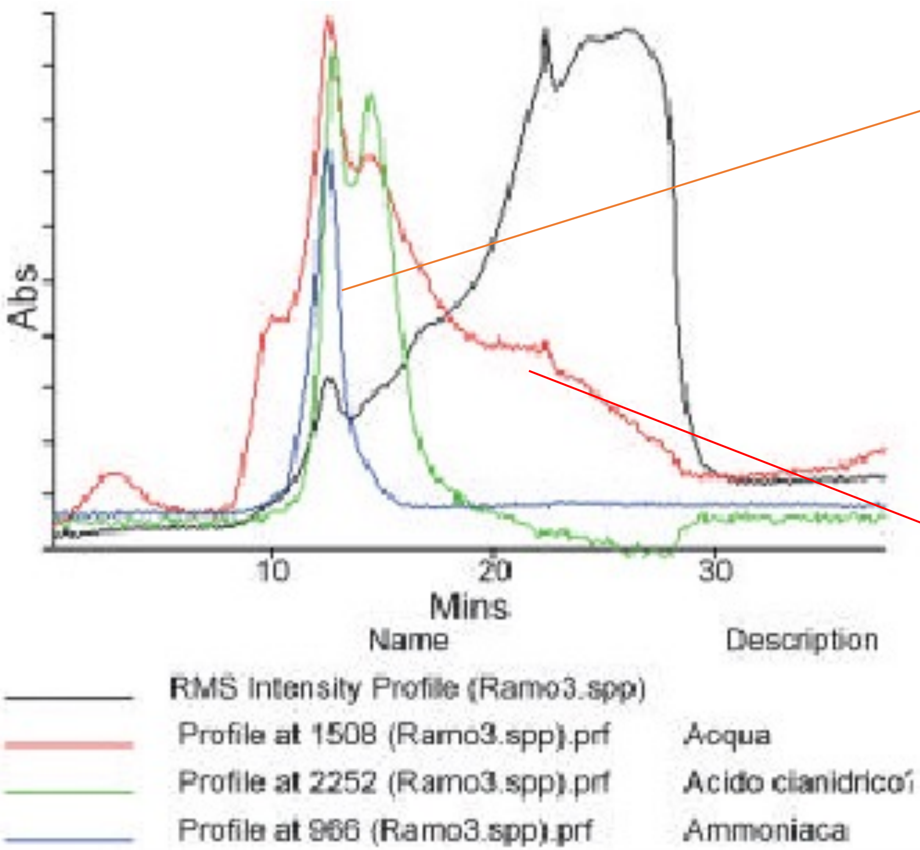

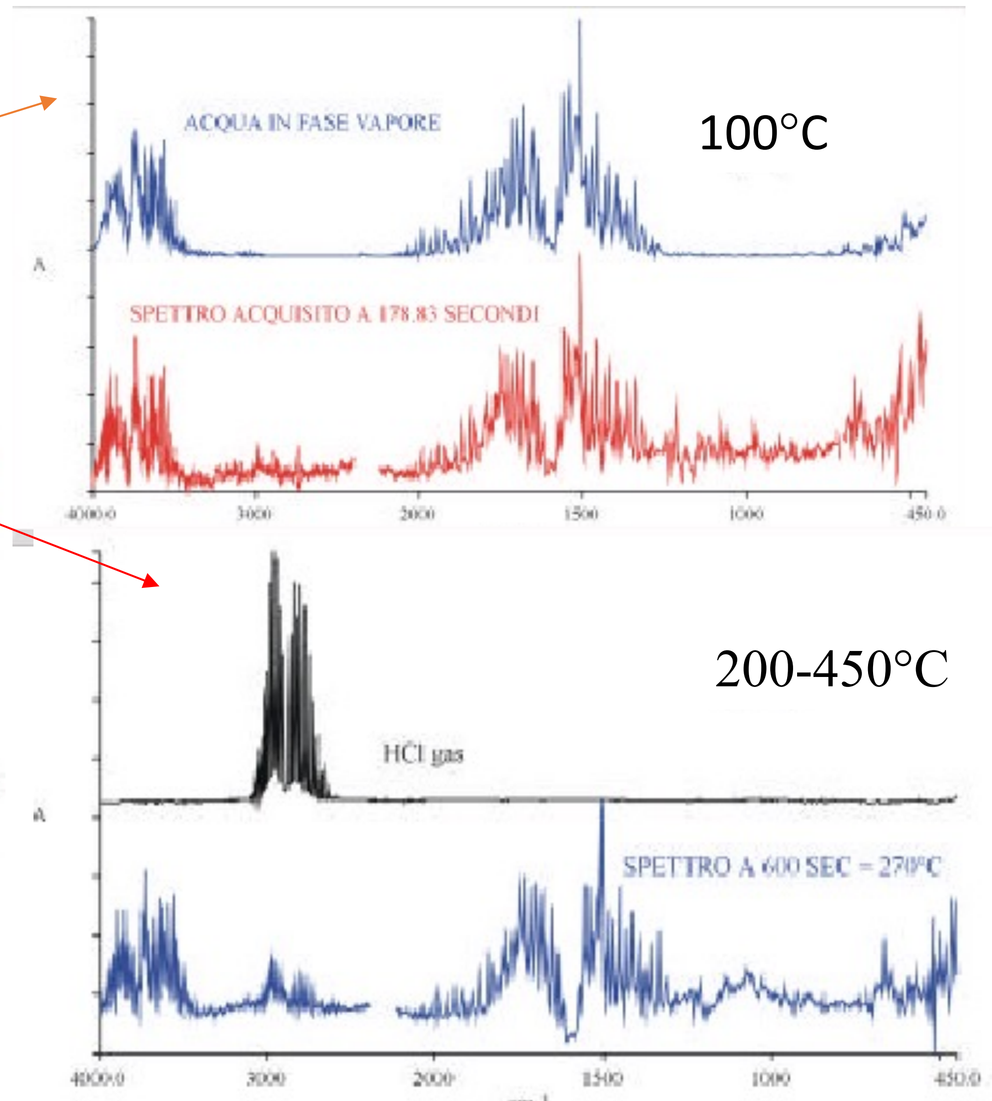

Emission intensity profiles

Thermogravimetric analysis

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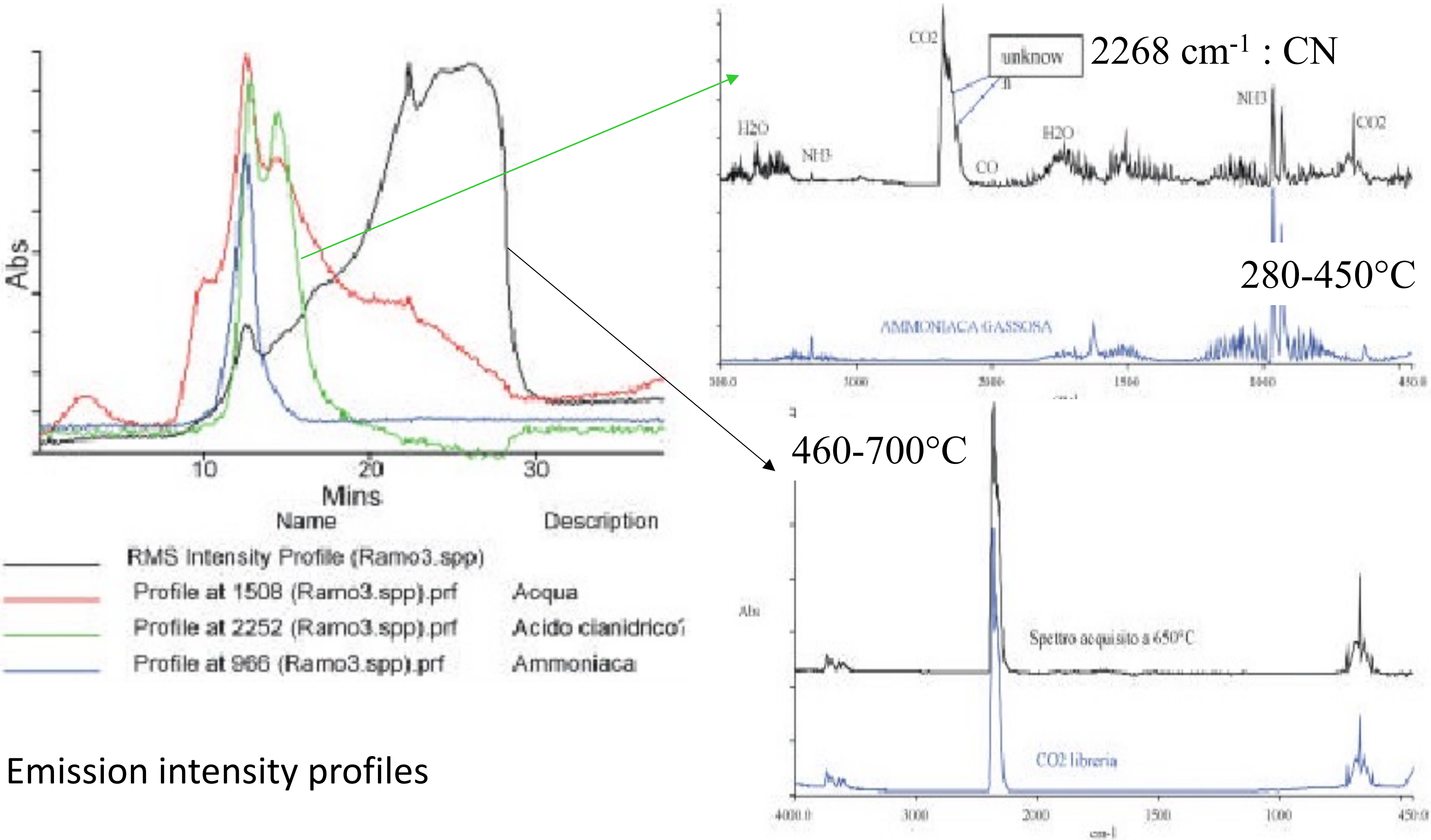

Emission intensity profiles

CONCLUSION

Thermal analysis are referenced at the European Pharmacopea for :

- Identification
- Determination of purity yield
- Water moisture and residual solvents

Development of identification by coupling TGA with other techniques