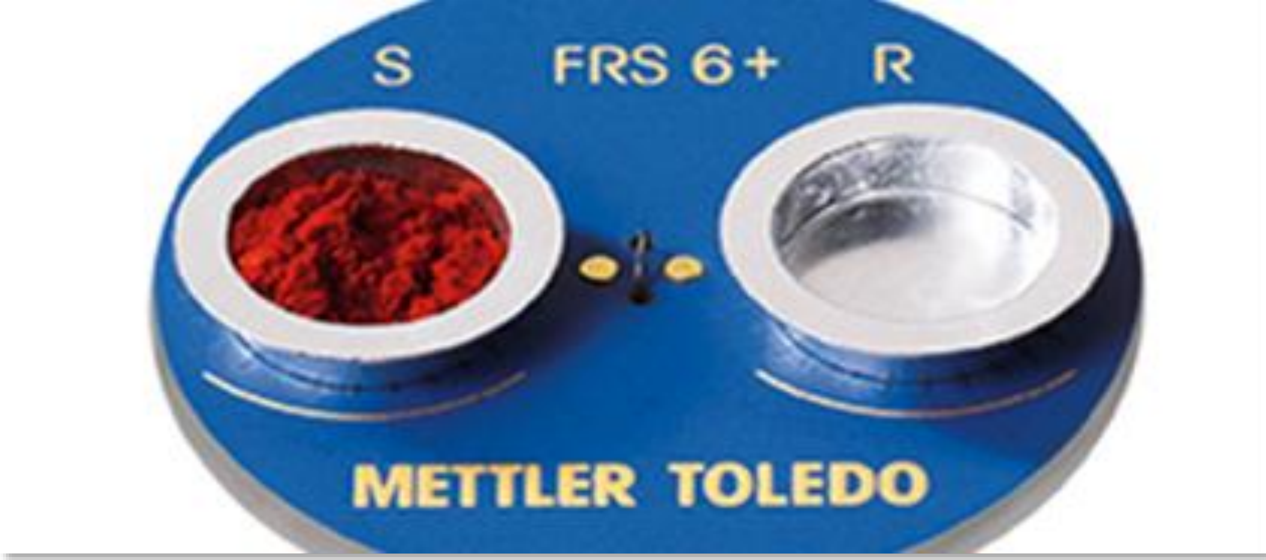
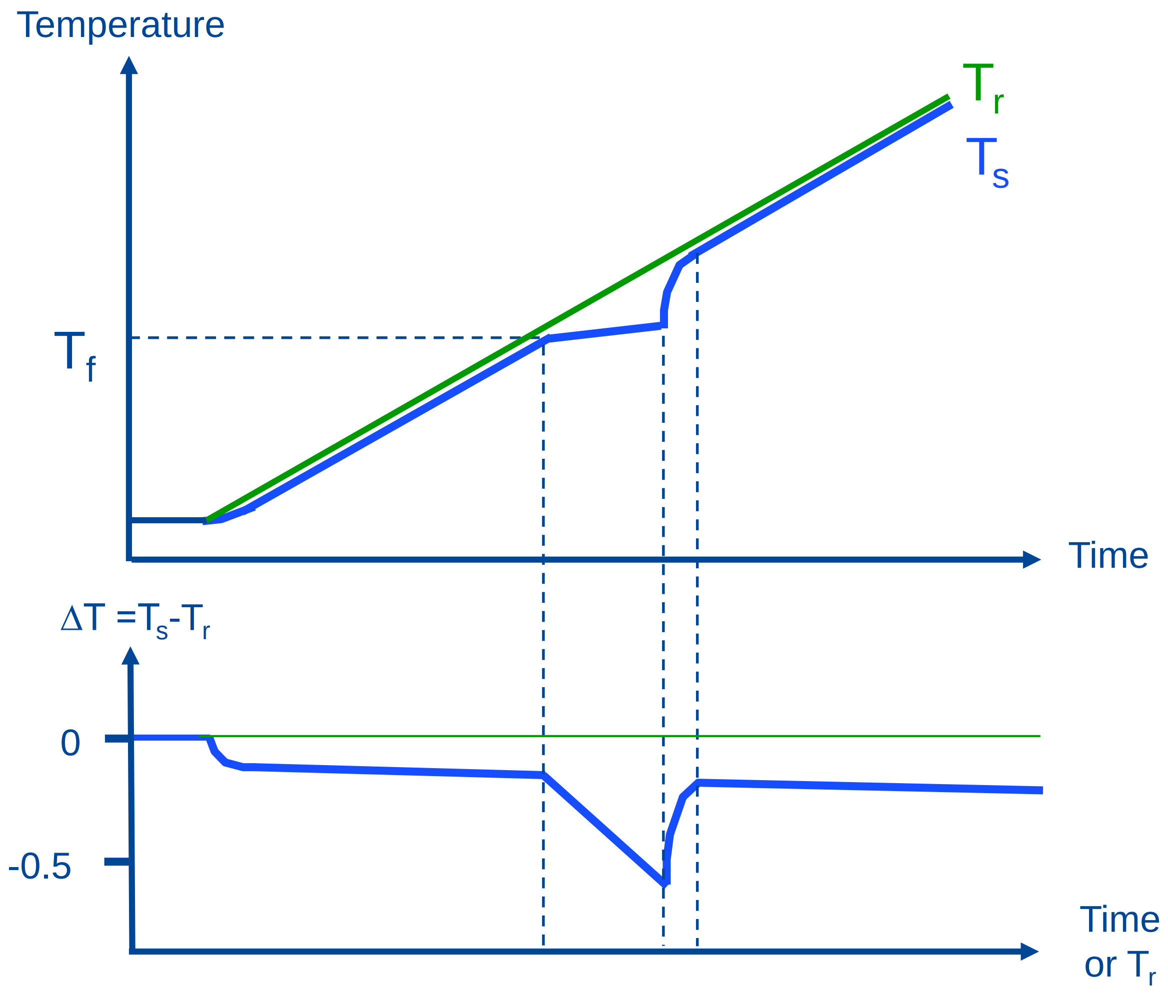


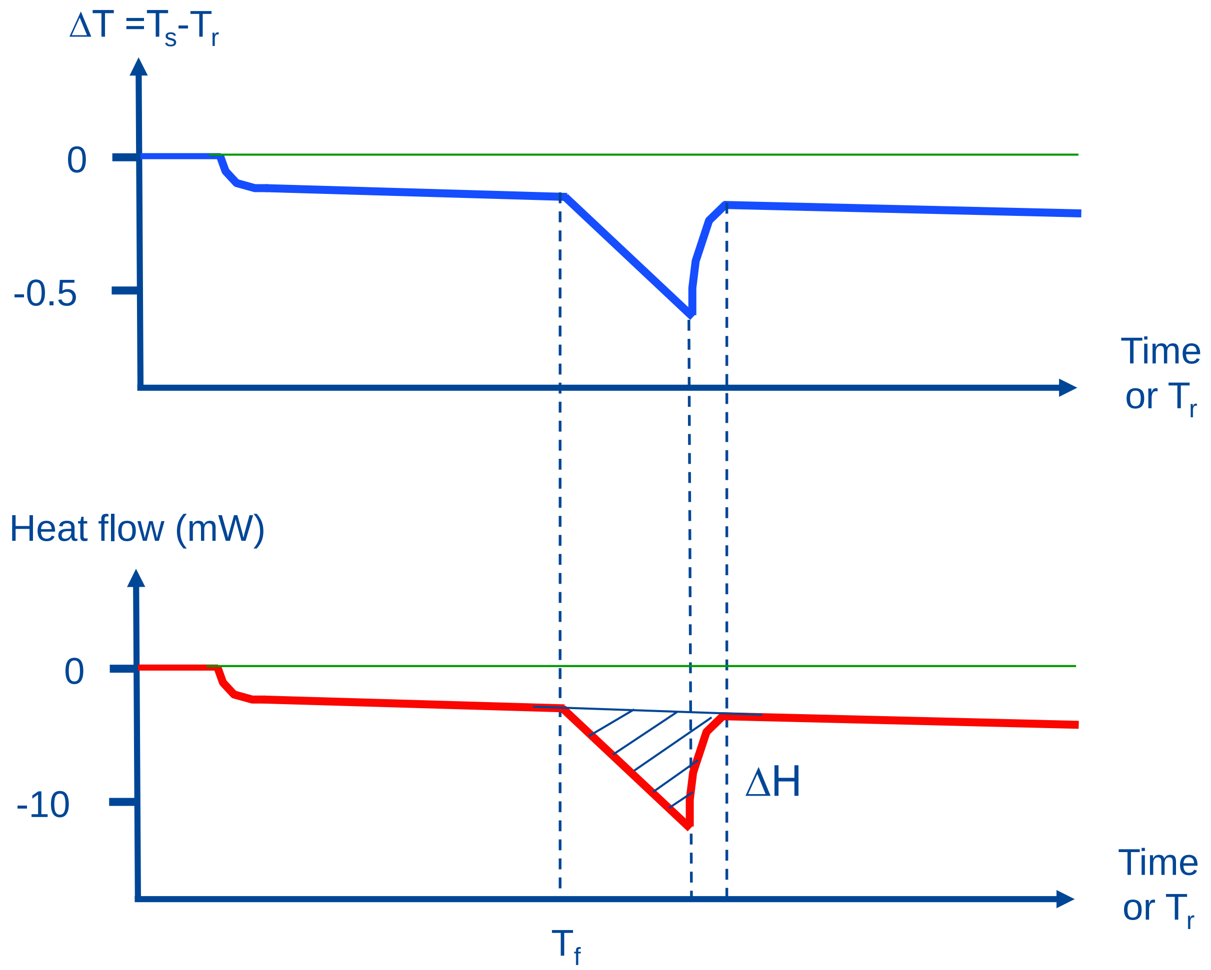
Introducción a la técnica DSC

METTLER TOLEDO

DTA signal



From DTA to DSC signal by calibration



DTA signal,

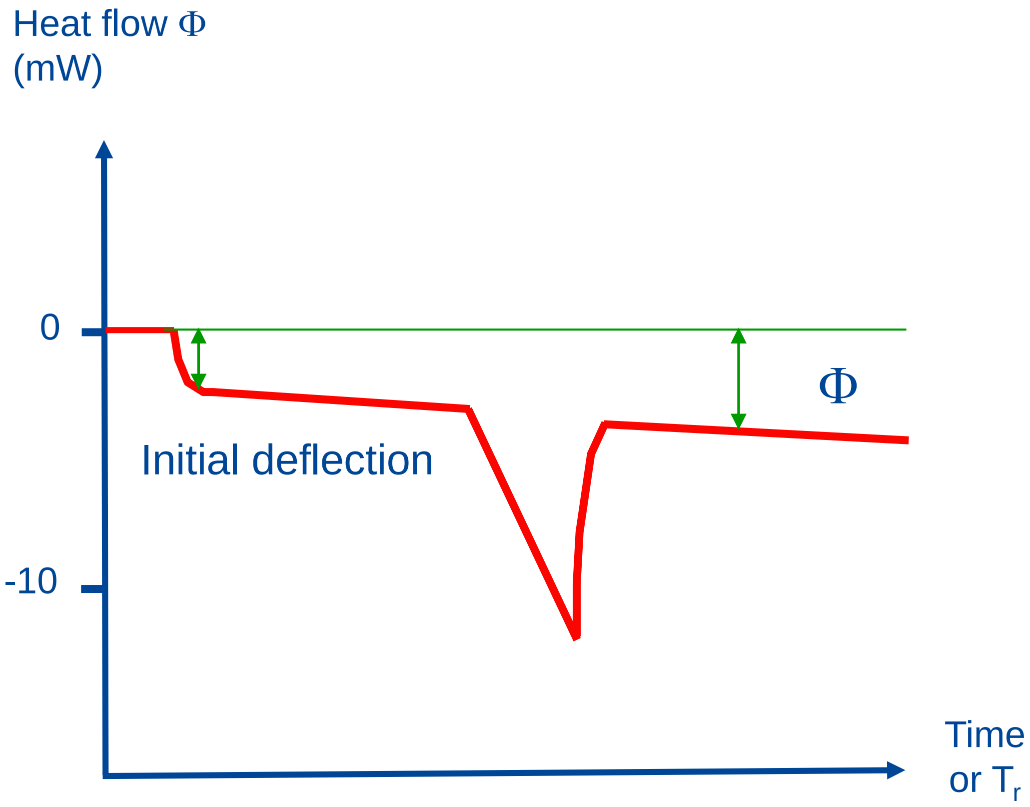
$\Phi=\Delta T/R_{th}$

R_{th}, thermal resistence of the system

DSC signal, Φ

Peak integral -> ΔH

Heat Capacity is not constant with the temperature



$$\Phi = m \cdot c_p \cdot \beta$$

Where,

m is the sample mass
c_p is the specific heat capacity of the sample
β is the heating rate

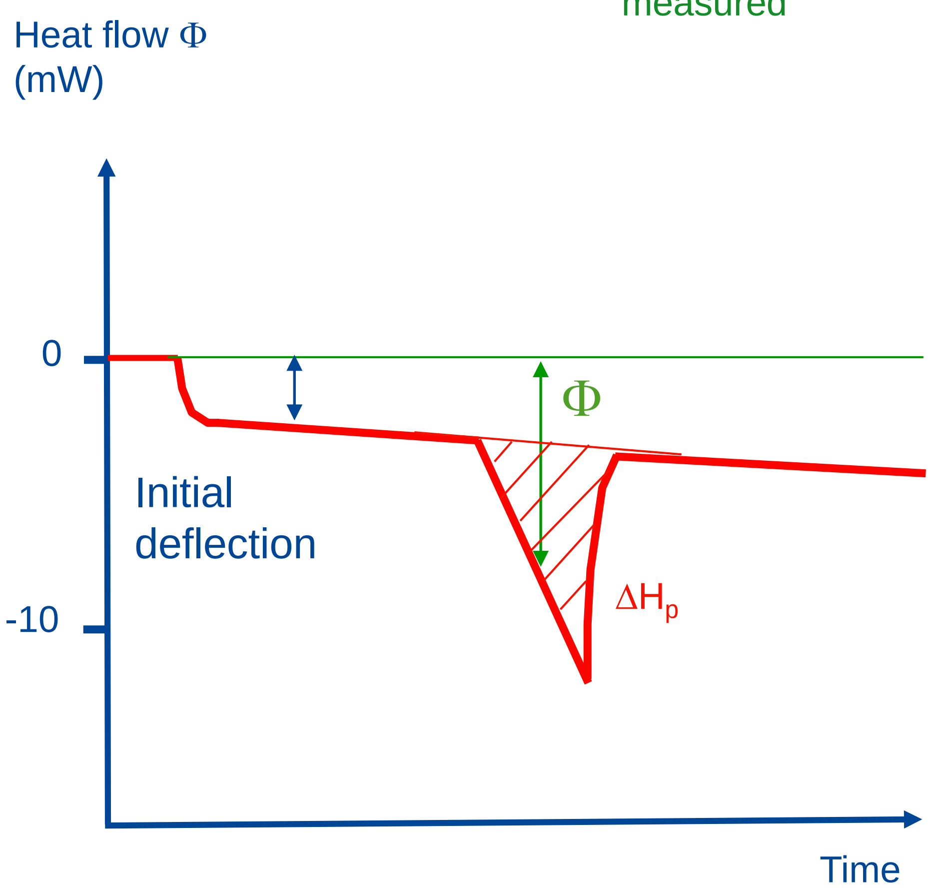
Latent and Sensible Heat

$$\Phi = mc_p\beta + \Delta H_P \frac{d\alpha}{dt}$$

Total heat flow, measured

sensible heat flow, due to increase of temperature; no structural change

latent heat flow due to structural changes



Where:

m is the sample mass

c_p is the specific heat capacity of the sample

β is the heating rate

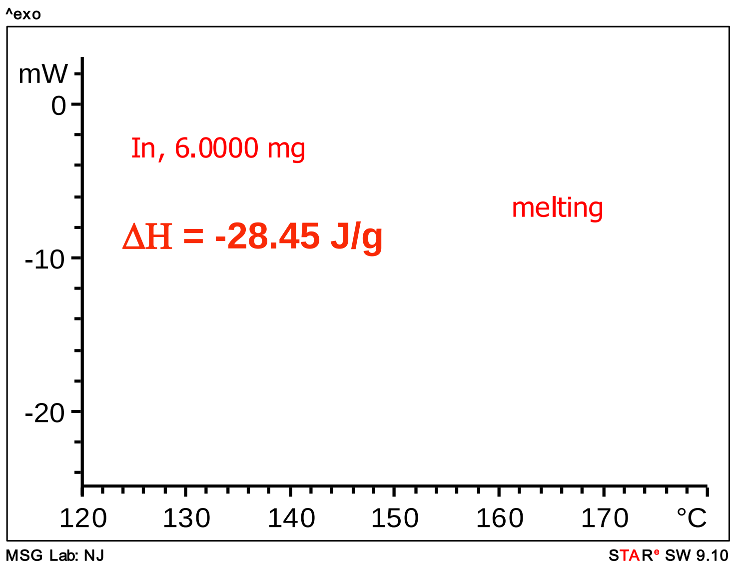
ΔH_p is the enthalpy of a process, e.g. melting, reaction, evaporation

$\frac{d\alpha}{dt}$ is change of conversion per unit time

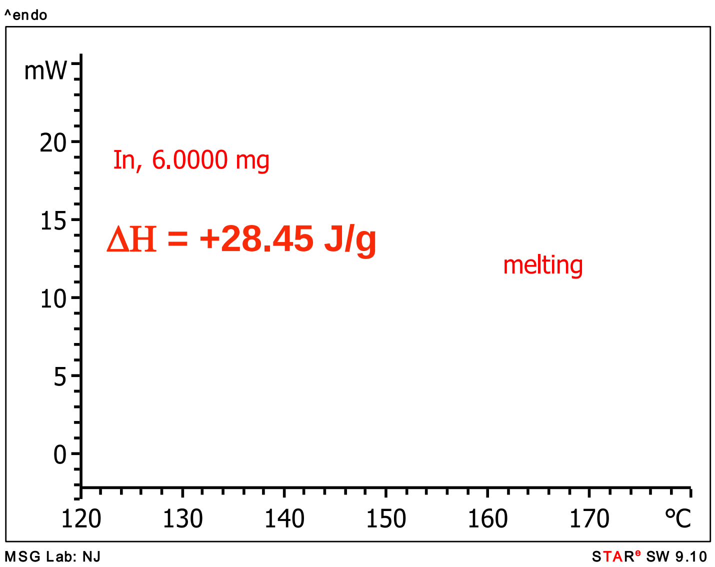
Direction of DSC signal

ICTAC (**I**nternational **C**onfederation for **T**hermal **A**nalysis and **C**alorimetry)

ICTA
endothermic downward,
exothermic upward.



Anti-ICTA
endothermic upward,
exothermic downward.

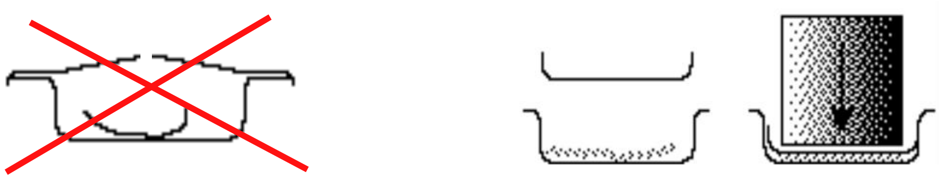


Preparación de la muestra

- Ideal sample geometries: fine powder, liquid and flat disks

- Prepare the sample as flat as possible and load it with flat side facing downwards to get good contact with pan bottom.

- For soft samples with irregular geometry or samples that roll up upon heating e.g. polymer films, use a lid of light Al 20 ul crucible to fix the sample.



Sample preparation

Preparación de la muestra

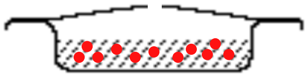
- Hard and coarse samples: grind into fine powder in a mortar if grinding doesn't induce any change (e.g. polymorph) of the sample.

- Fibers:

  - cut into small pieces

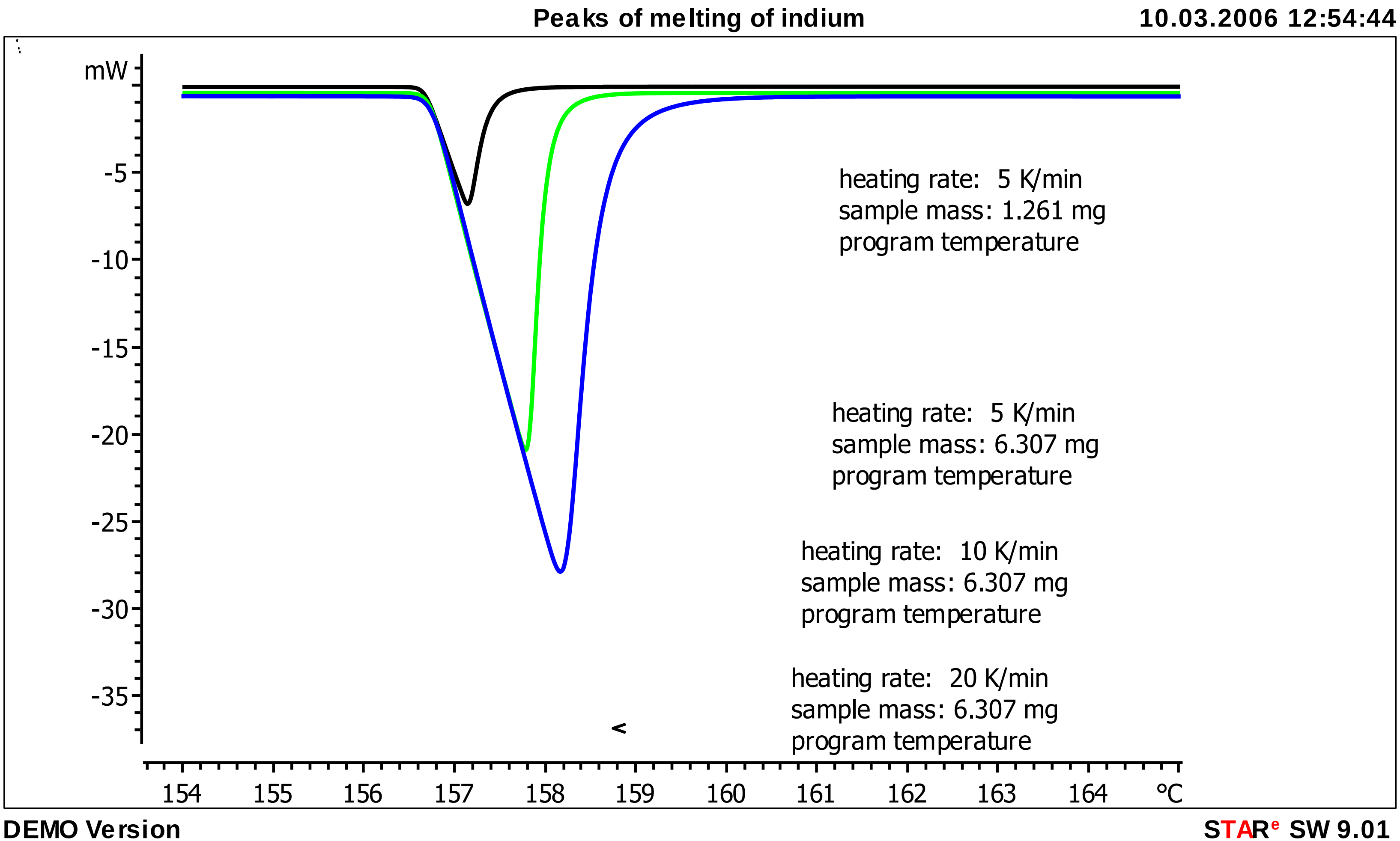
  - or wind the fiber, wrap it into aluminum foil and use a lid of light Al 20 ul crucible to fix the sample.

- Strongly exothermic samples e.g. explosives: dilute the sample in an inert substance e.g. Al2O3.



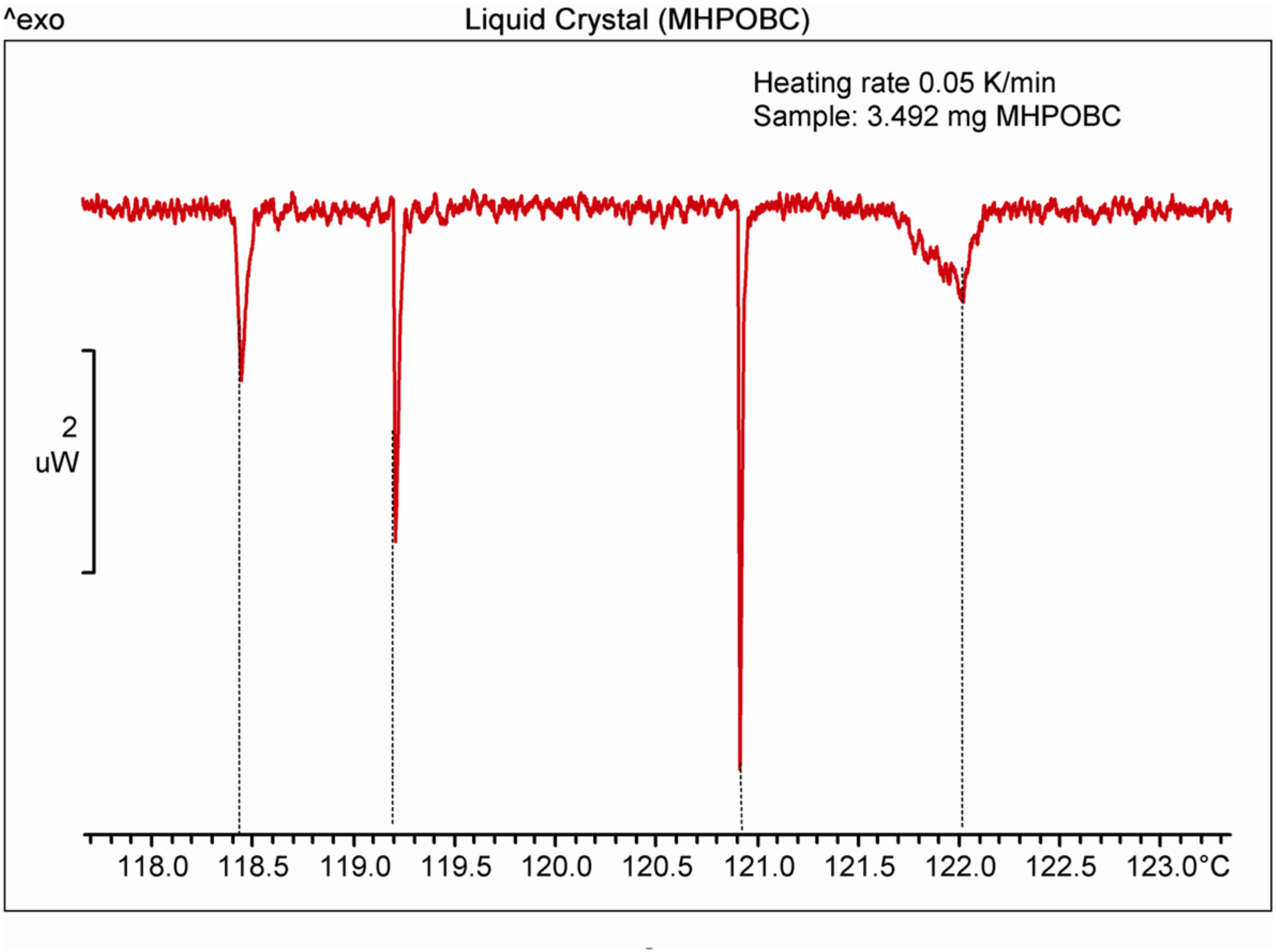
- Liquids: transfer the sample with the aid of a syringe, spatula or needle

Melting onset and peak temperatures



Melting onset is independent of m and β; Peak temperature is dependent.

DSC: Extremely High Sensitivity

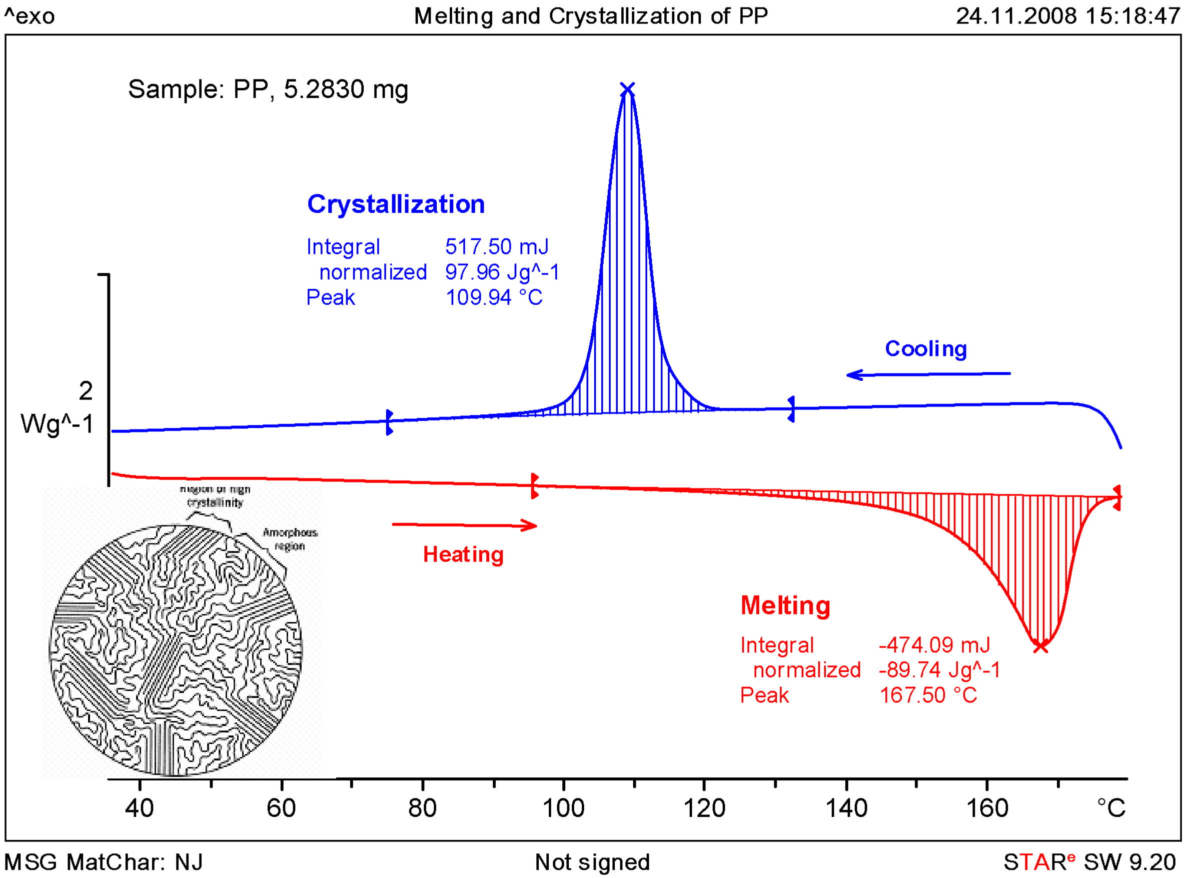


Melting and crystallization

Melting

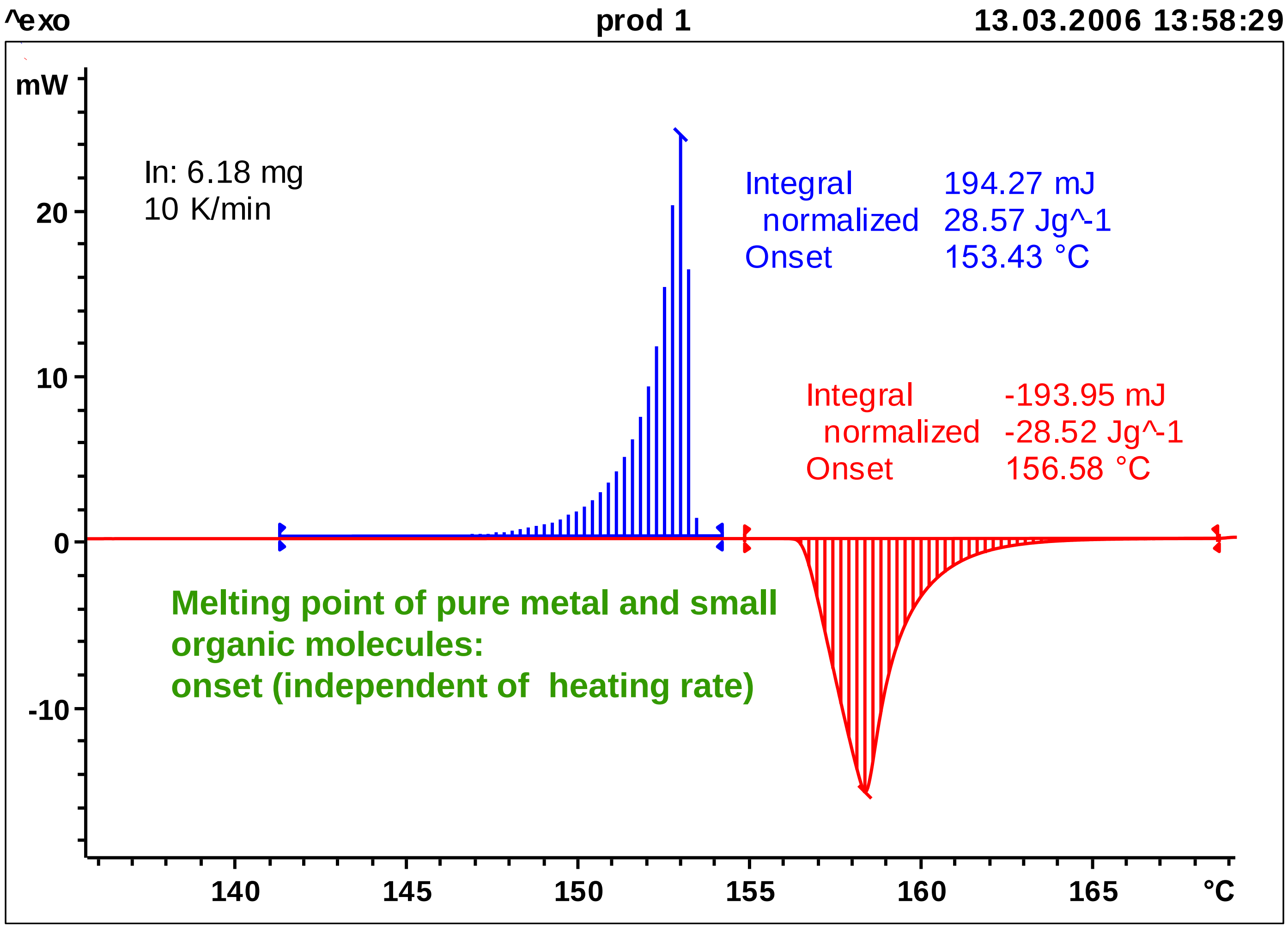
Crystallization

Melting and crystallization of PP

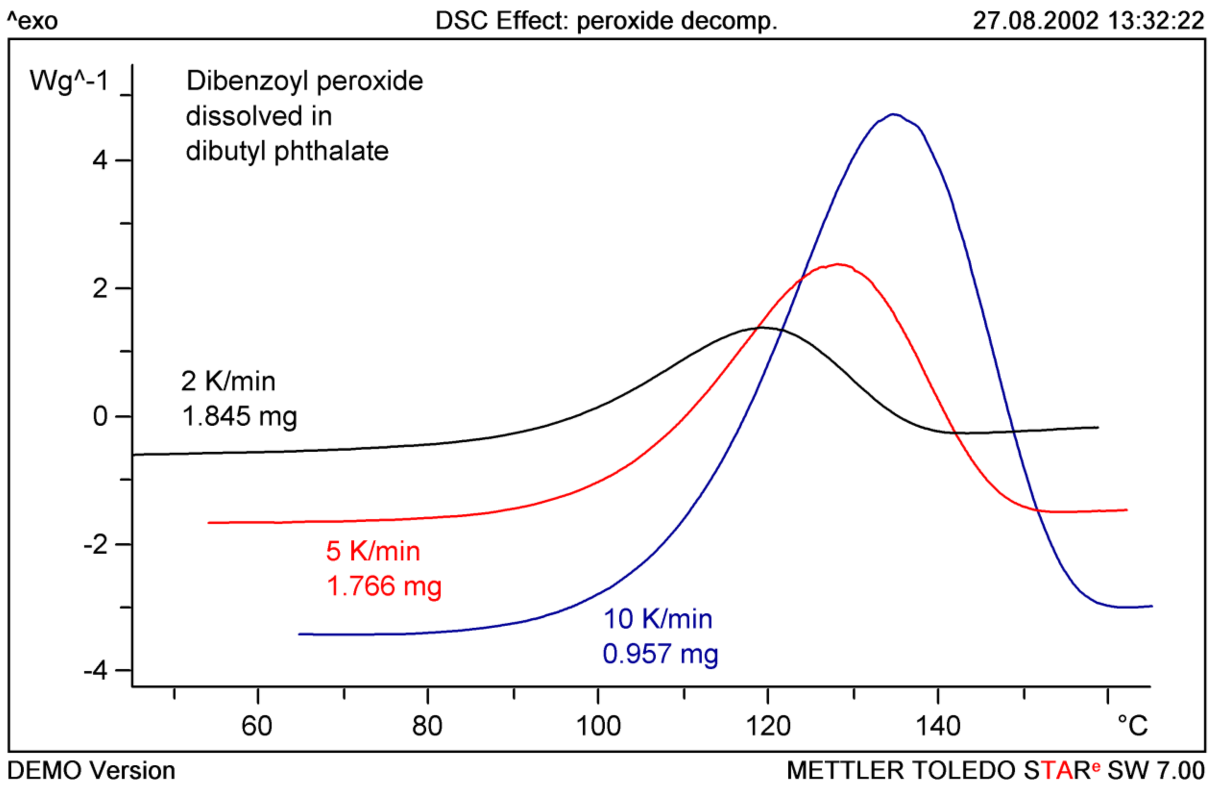


- **Polymers do not have a melting point but a melting range!**
- Peak temperature (depends on β and m) is used to characterize the melting peak.

Melting and crystallization of indium

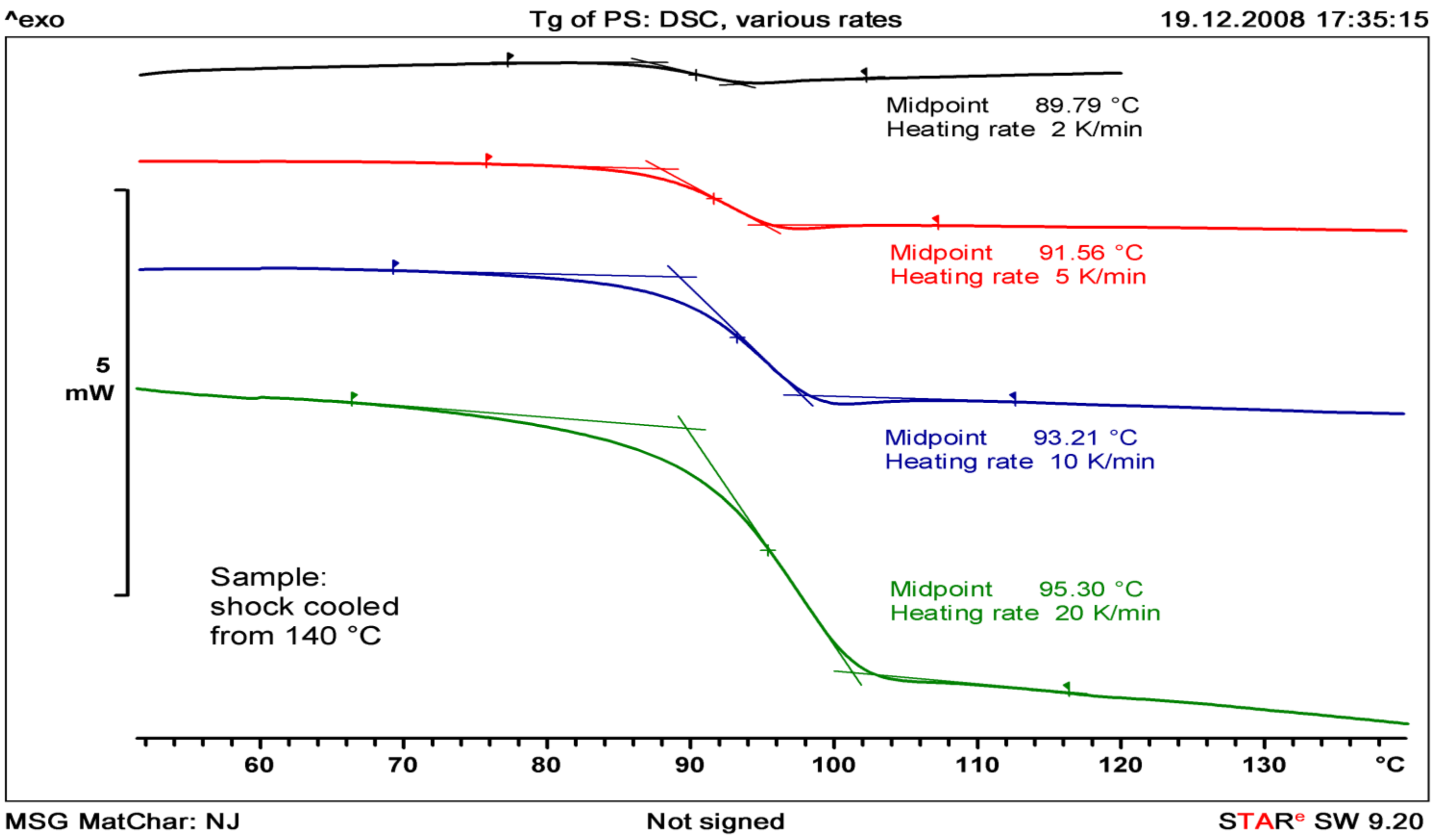


Reacciones químicas



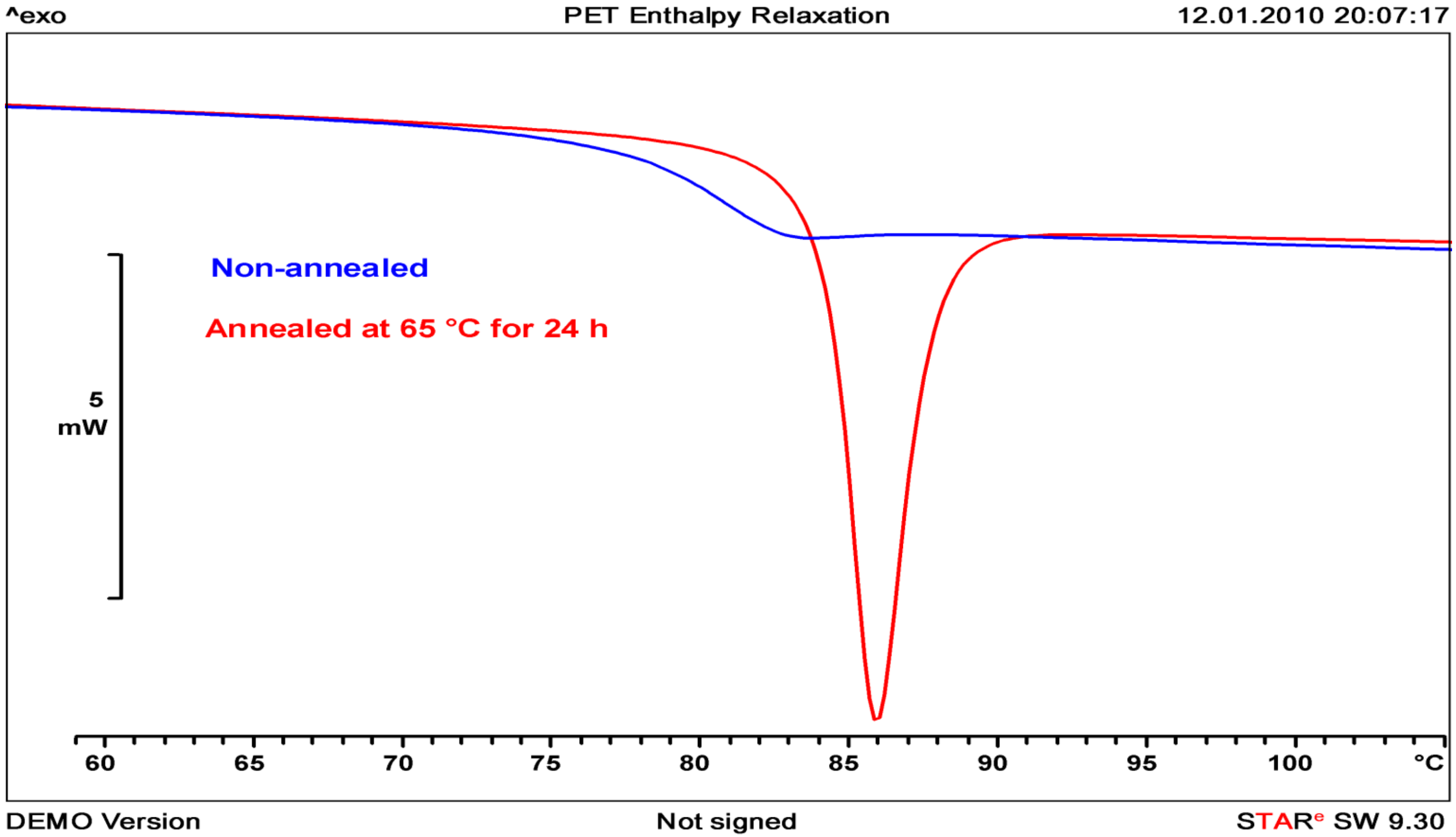
- Energy is absorbed or released during a reaction (enthalpy of reaction)
- Peak temperature and shape depend on heating rate
- Peak area corresponds to enthalpy of reaction and is independent of heating rate

Heating rate influence on Tg



Glass transition becomes more significant with higher heating rate.

Physical aging and enthalpy relaxation



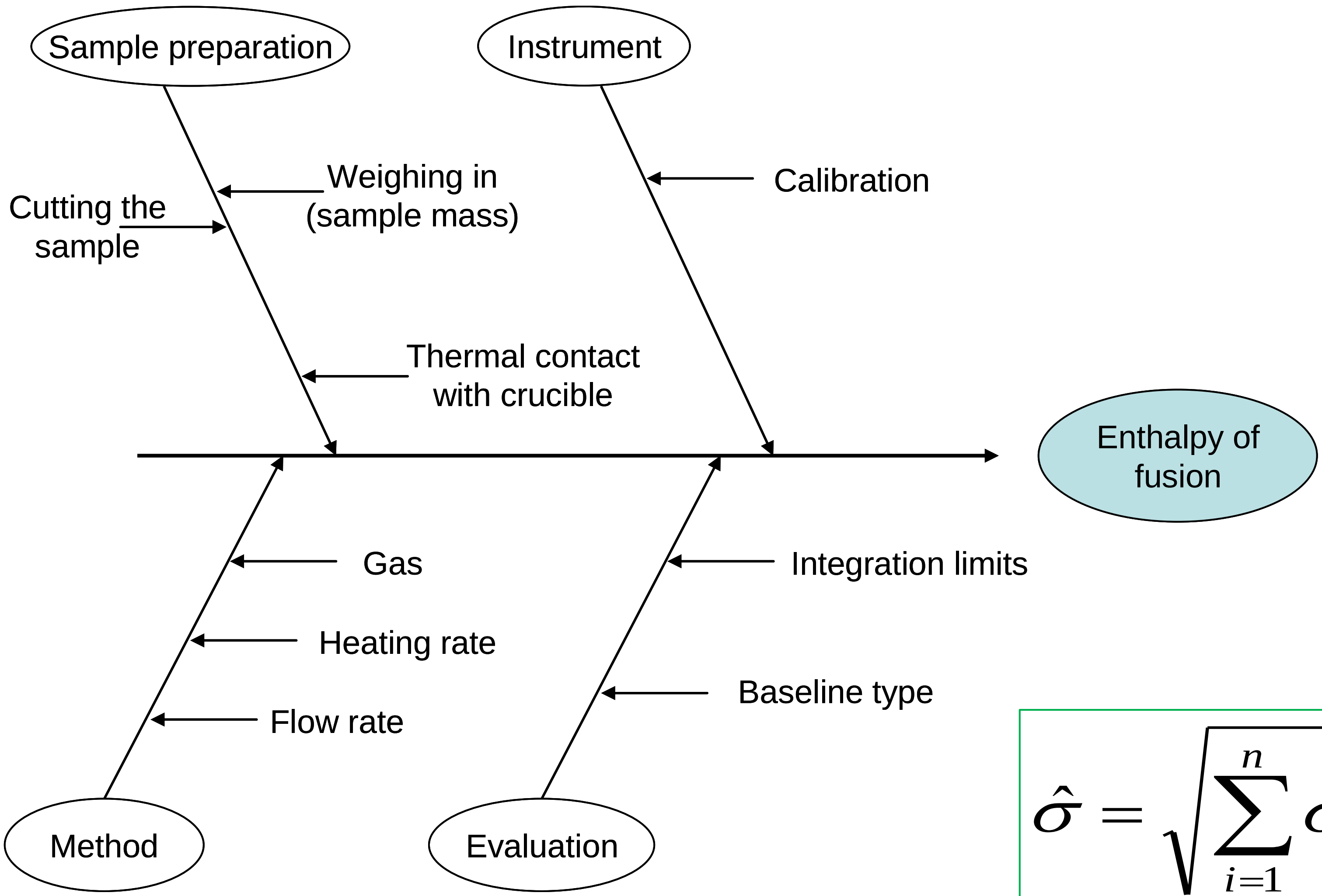
Uncertainty

- In simple terms, the uncertainty of measurement is the range of values within which the true value of the measurement is expected to lie with a stated level of confidence.

- Uncertainty comprises much more than just specifying a standard deviation of an analytical result: sampling process, sample preparation, calibration etc. all contribute to the uncertainty of a measurement result.

- Uncertainty is not an error: uncertainty specifies a range in which the “true” value lies with a certain probability.

Example: uncertainty of the melting enthalpy



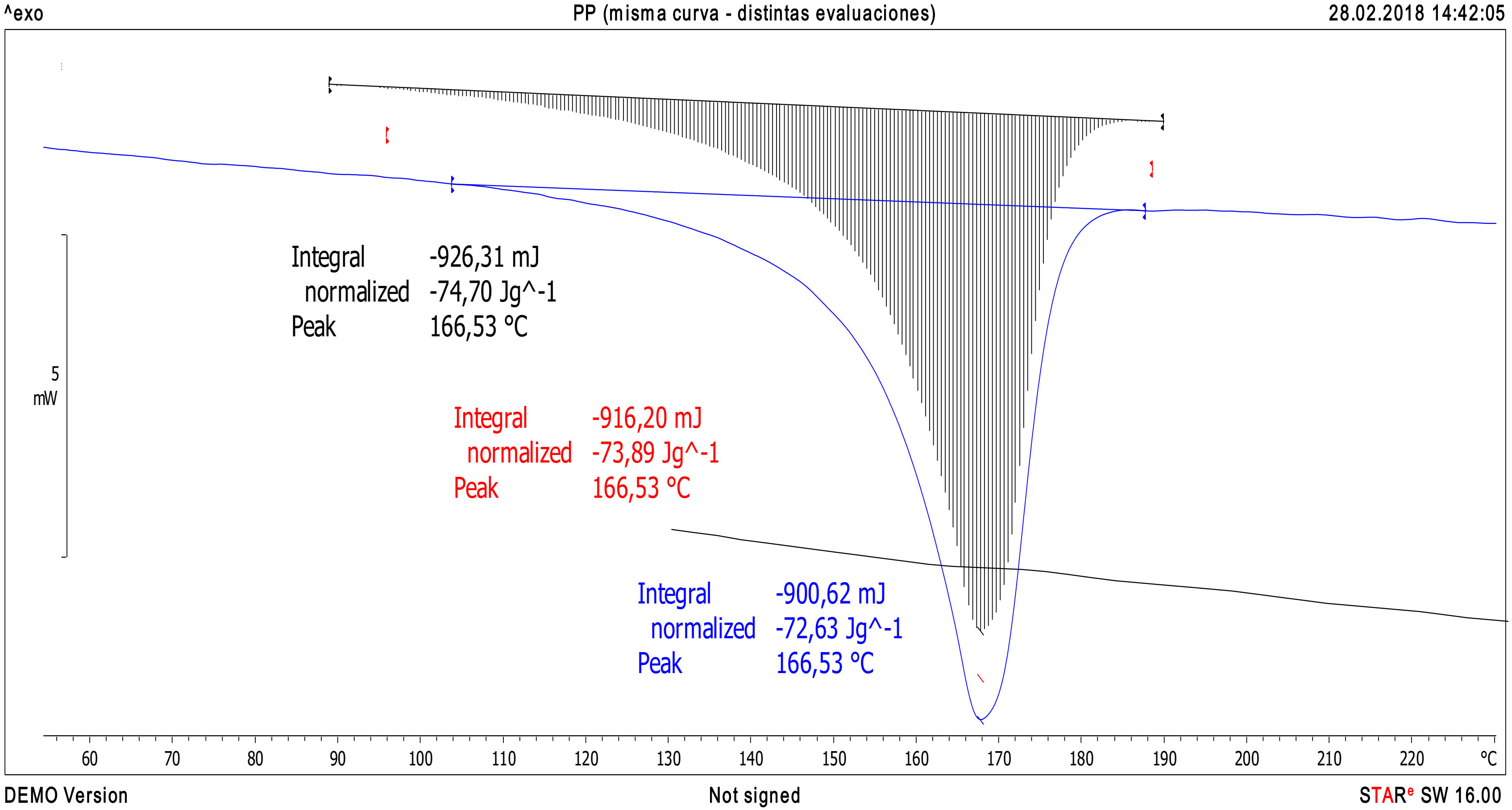
$$\hat{\sigma} = \sqrt{\sum_{i=1}^{n} \hat{\sigma}_i^2}$$

Example: uncertainty of melting enthalpy

Source	**Uncertainty of measurement**
Mass of the test specimen	±20 µg (e.g. reproducibility of the balance); if the mass is about 10 mg, this corresponds to ± 0.2%
Putting the sample into the crucible	negligible
Thermal contact with the crucible	± 0.5% (estimate)
Heating rate	negligible
Gas and gas flow	negligible if the instrument has been adjusted under the same conditions as the measurement
Adjustment	±1.5% (uncertainty of the calibration material)
Integration limits and baseline type	±3% (statistics of repeated evaluations)

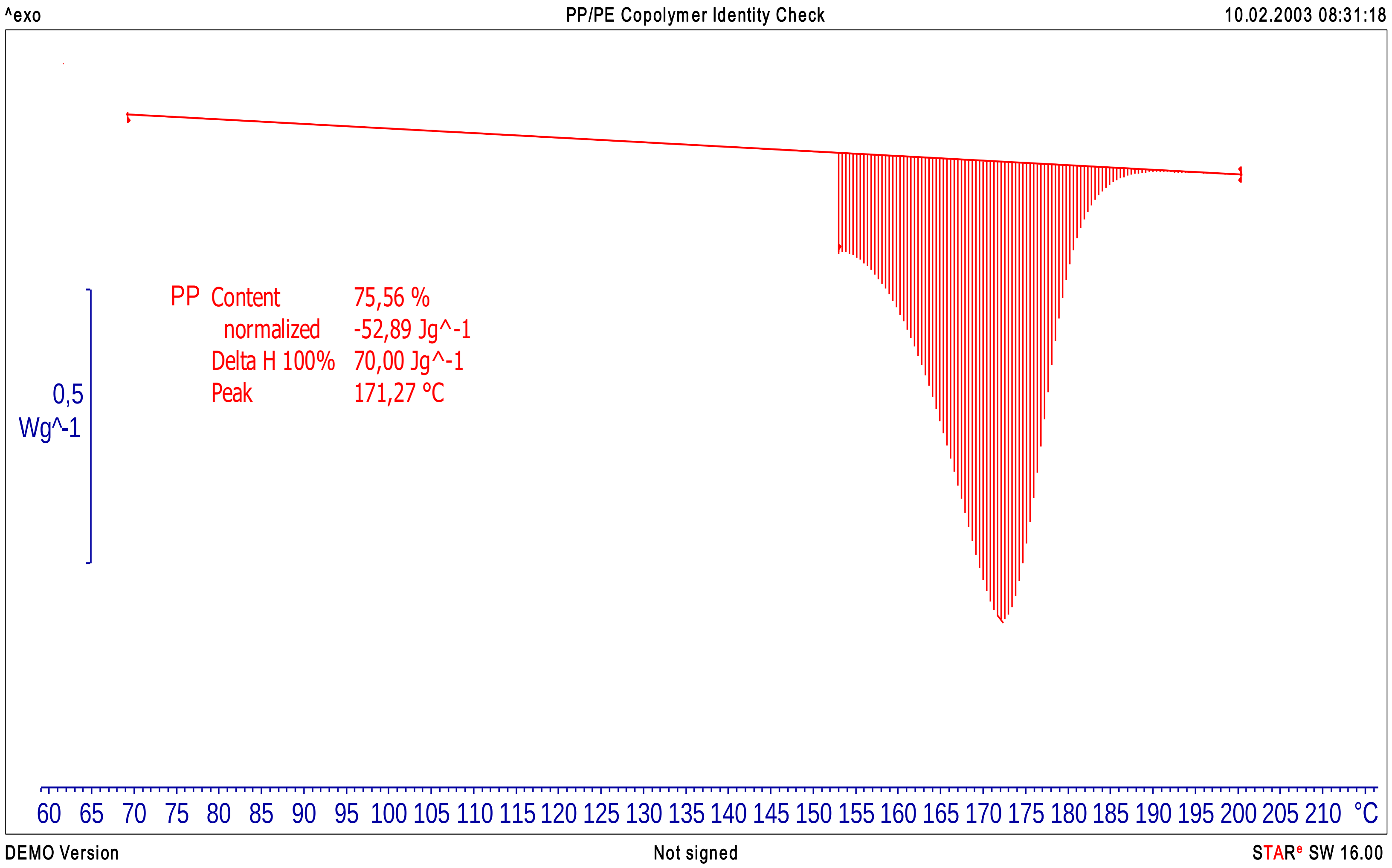
Combined uncertainty = $\sqrt{0.2\%^2 + 0.5\%^2 + 1.5\%^2 + 3\%^2}$ = 3.4%

Example: uncertainty of melting enthalpy

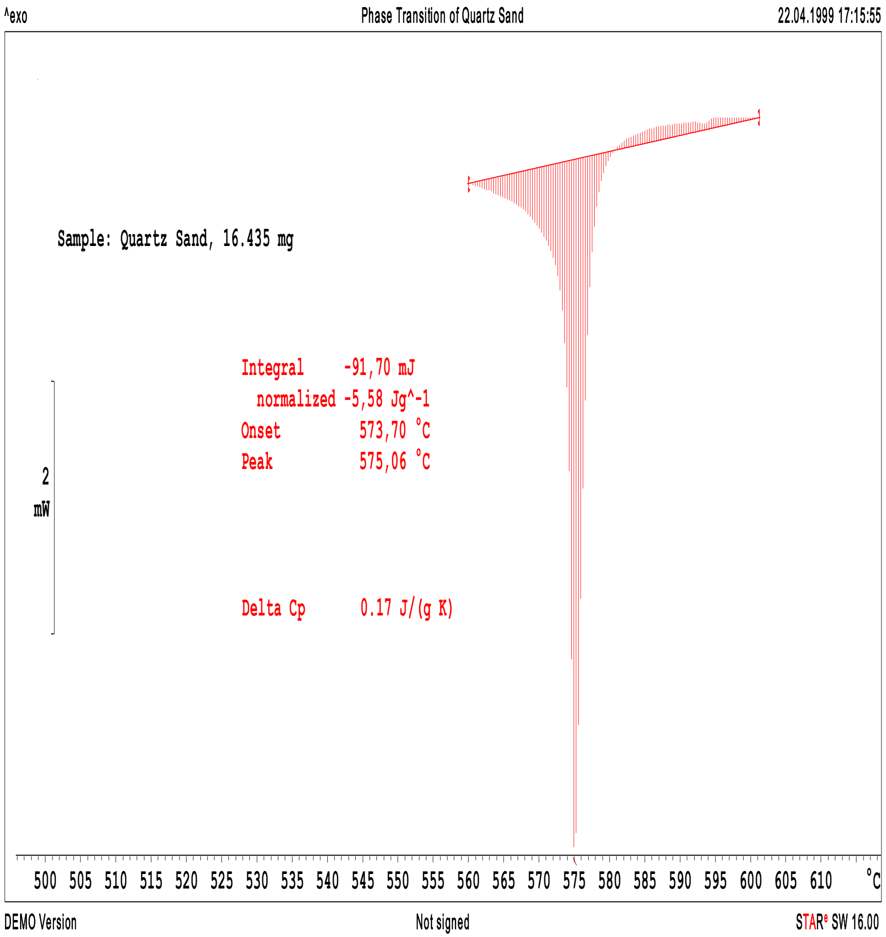


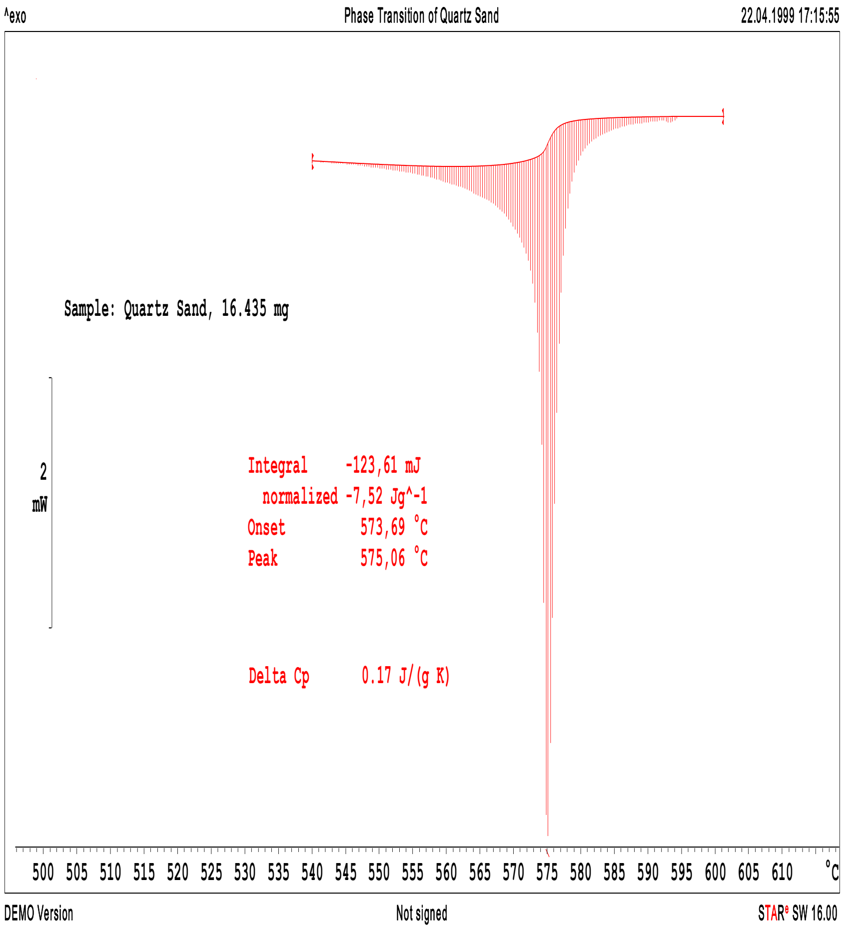
Combined uncertainty = $\sqrt{0.2\%^2 + 0.5\%^2 + 1.5\%^2 + 3\%^2}$ = 3.4%

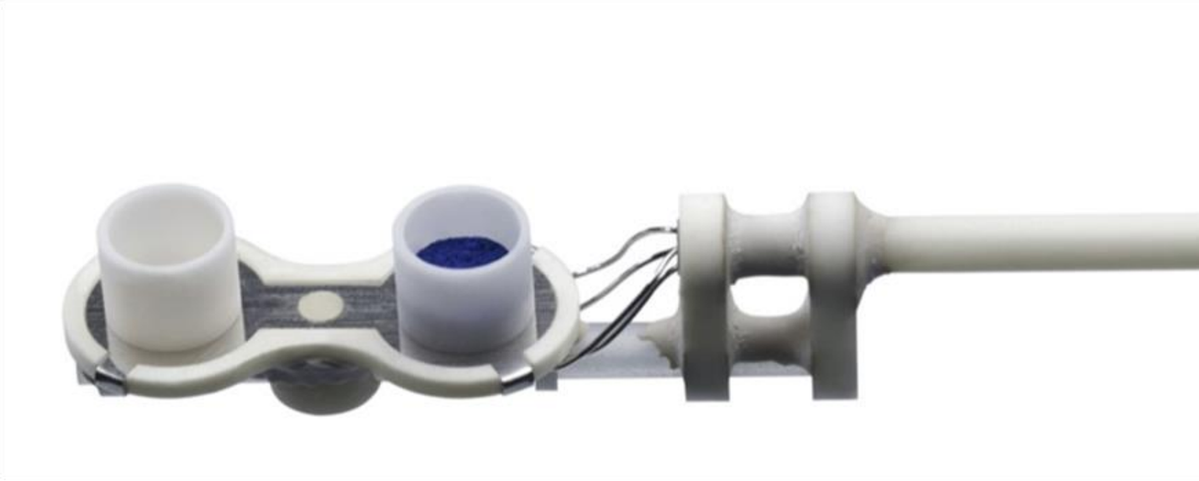
Example: uncertainty of PP content



Linea base


^exo
Phase Transition of Quartz Sand
22.04.1999 17:15:55
Sample: Quartz Sand, 16.435 mg
Integral -91,70 mJ
normalized -5,58 Jg^-1
Onset 573,70 °C
Peak 575,06 °C
Delta Cp 0.17 J/(g K)
2 mW
500 505 510 515 520 525 530 535 540 545 550 555 560 565 570 575 580 585 590 595 600 605 610 °C
DEMO Version
Not signed
STAR® SW 16.00

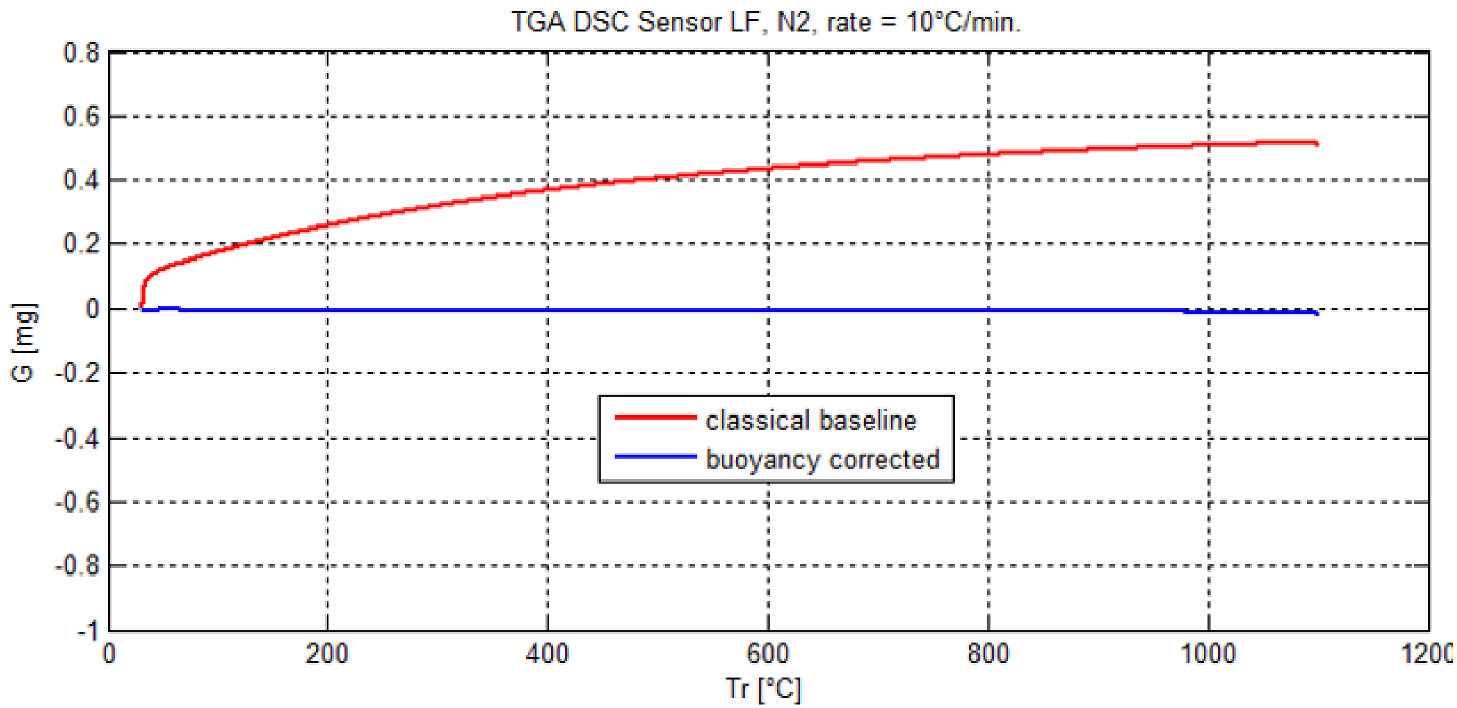

^exo
Phase Transition of Quartz Sand
22.04.1999 17:15:55
Sample: Quartz Sand, 16.435 mg
Integral -123,61 mJ
normalized -7,52 Jg^-1
Onset 573,69 °C
Peak 575,06 °C
Delta Cp 0.17 J/(g K)
2 mW
500 505 510 515 520 525 530 535 540 545 550 555 560 565 570 575 580 585 590 595 600 605 610 °C
DEMO Version
Not signed
STAR® SW 16.00

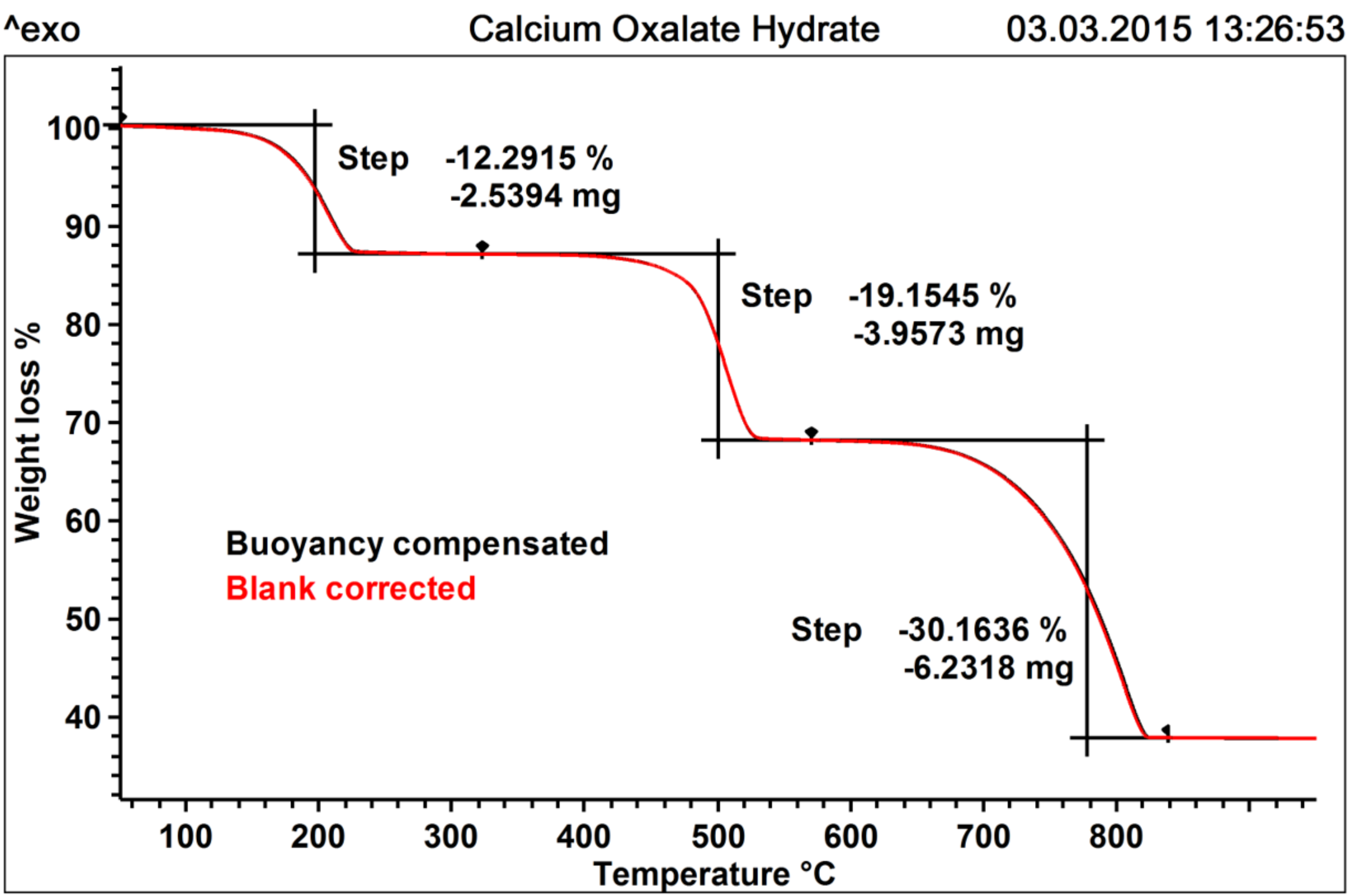


Introducción a la técnica TGA

METTLER TOLEDO

- Blank comparison
- Empty sample holder



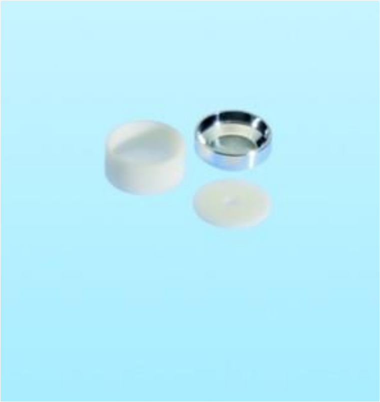

^exo
Calcium Oxalate Hydrate
03.03.2015 13:26:53
Weight loss %
100
90
80
70
60
50
40
Step -12.2915 %
-2.5394 mg
Step -19.1545 %
-3.9573 mg
Step -30.1636 %
-6.2318 mg
Buoyancy compensated
Blank corrected
100
200
300
400
500
600
700
800
Temperature °C

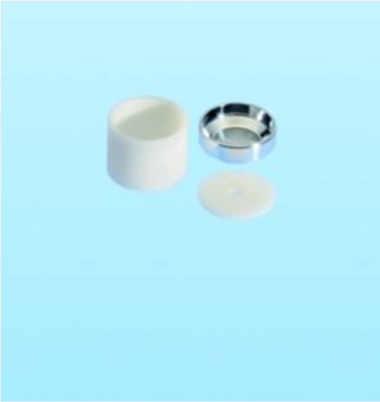
TGA: Crucibles

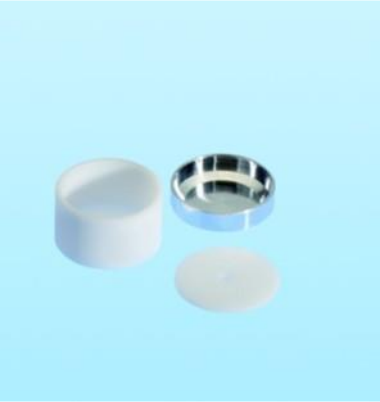
From simple to demanding applications.
You can choose from more than 30 types of crucibles.

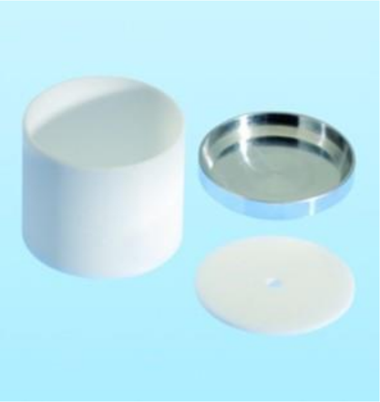
Alumina crucibles

- Alumina crucibles with lids: 30 µl, 70 µl, 150 µl, 300 µl, 600 µl and 900 µl
- Special aluminum lids to prevent contamination and evaporation before the measurement

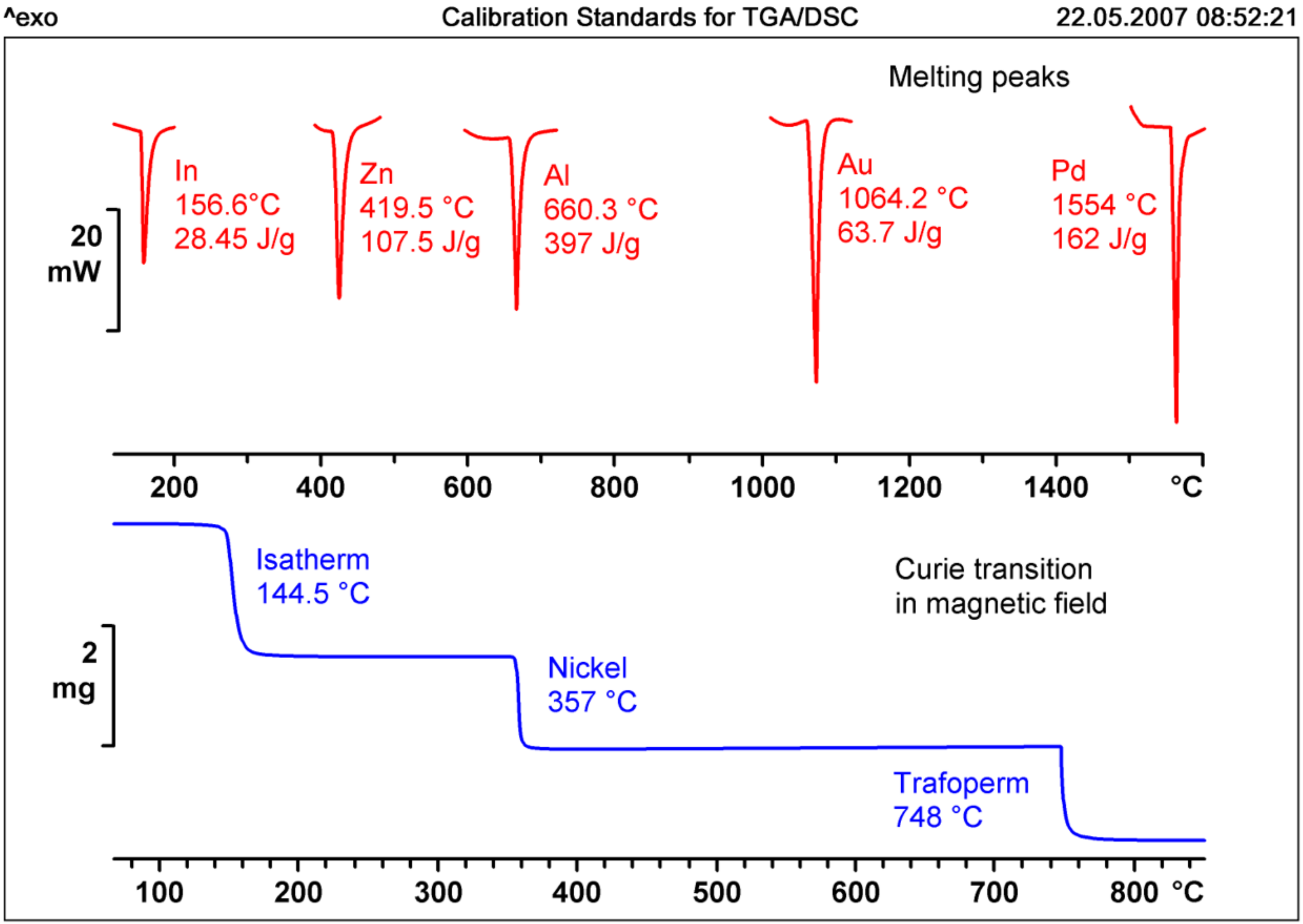




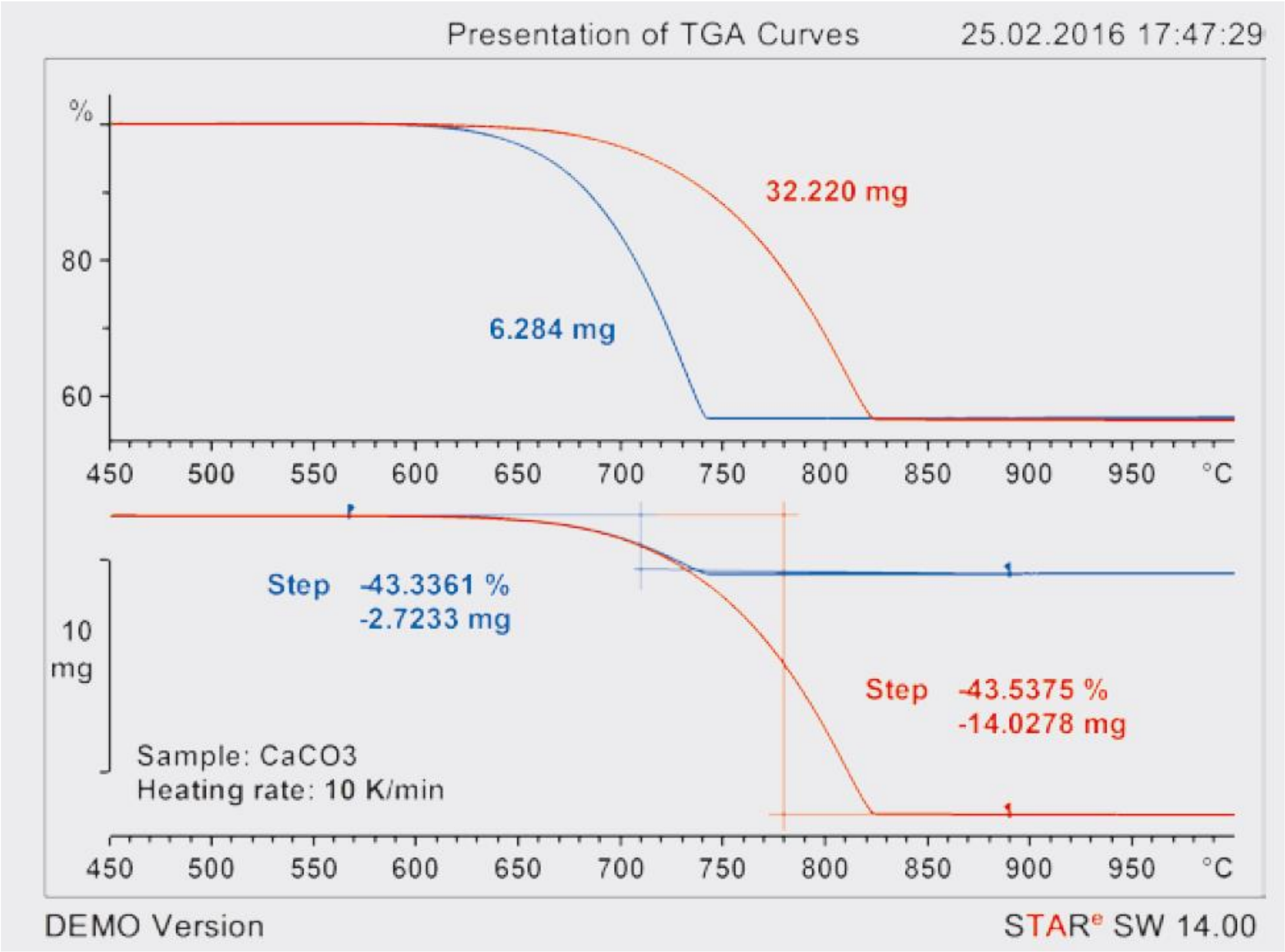




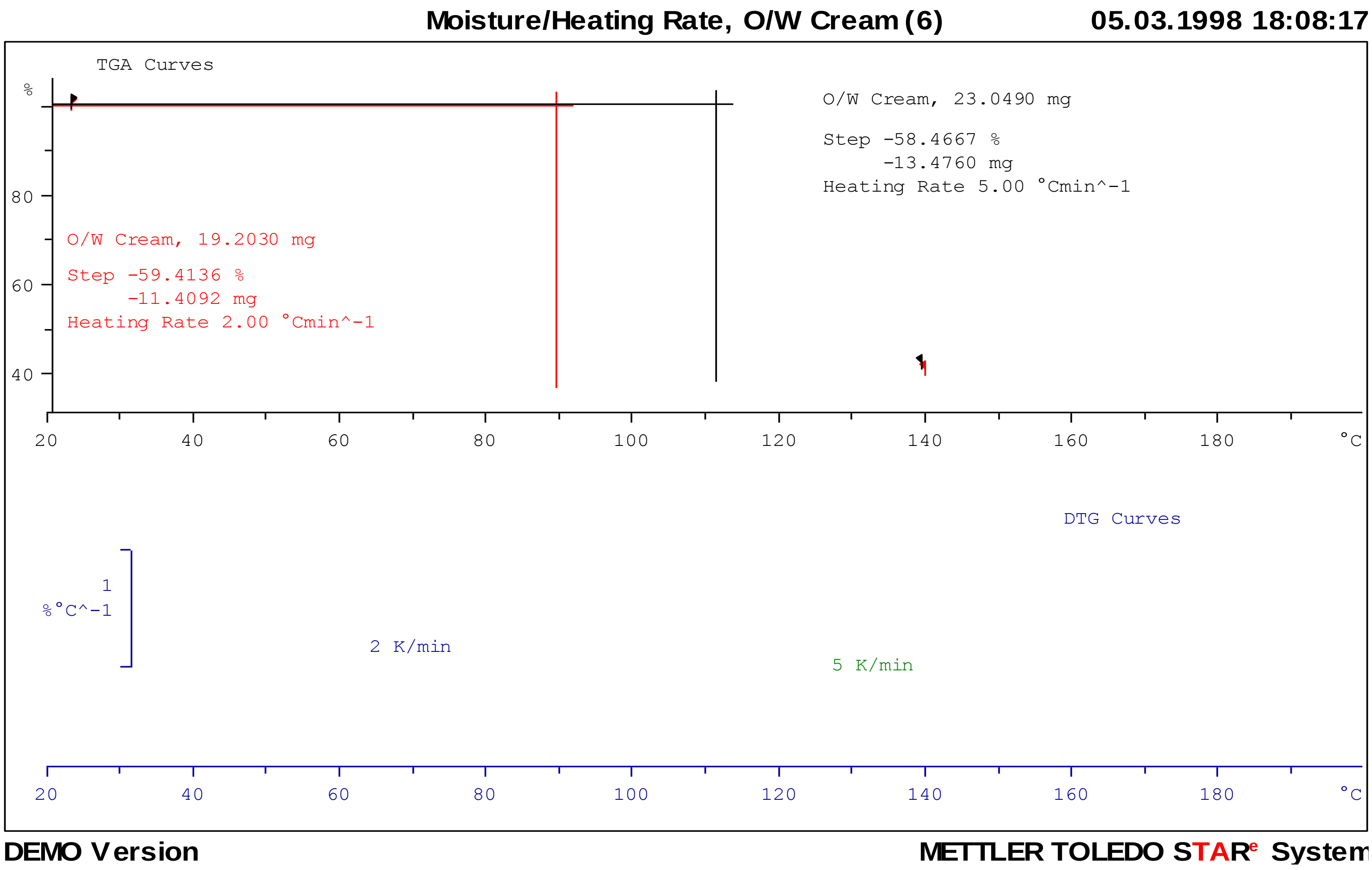
TGA/DSC 3+: Applications (VII)

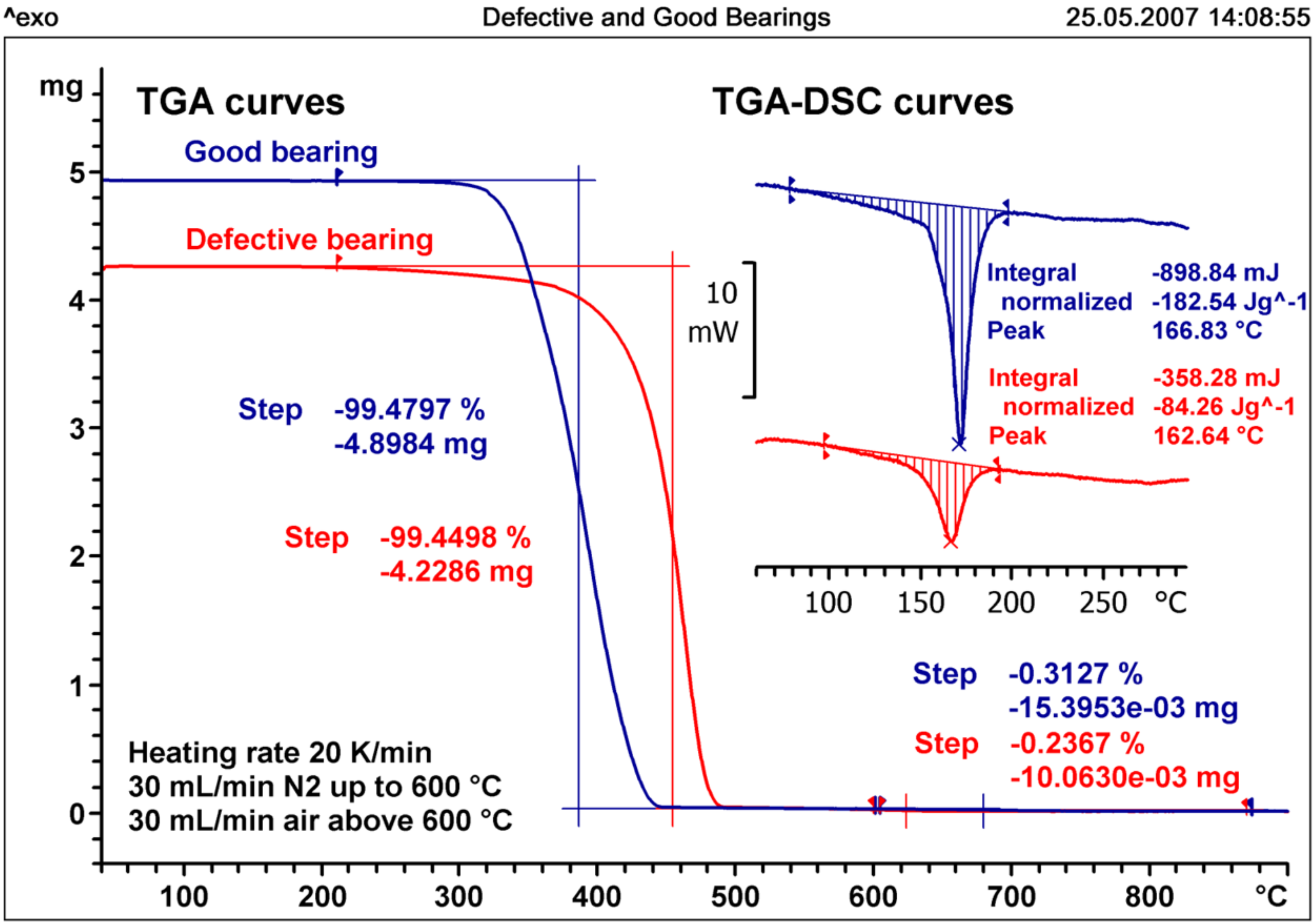


Efecto del tamaño de muestra

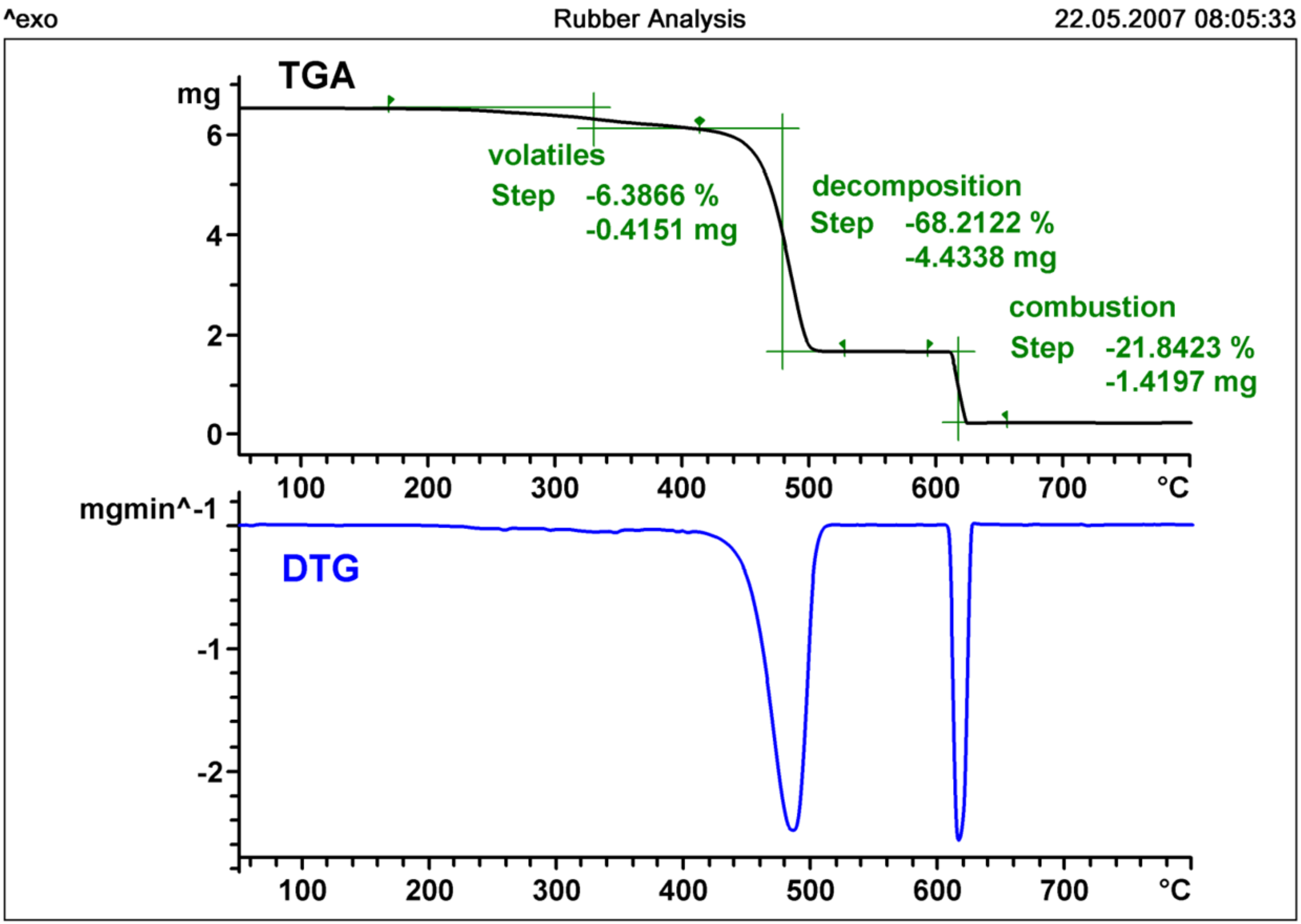


Efecto de la velocidad

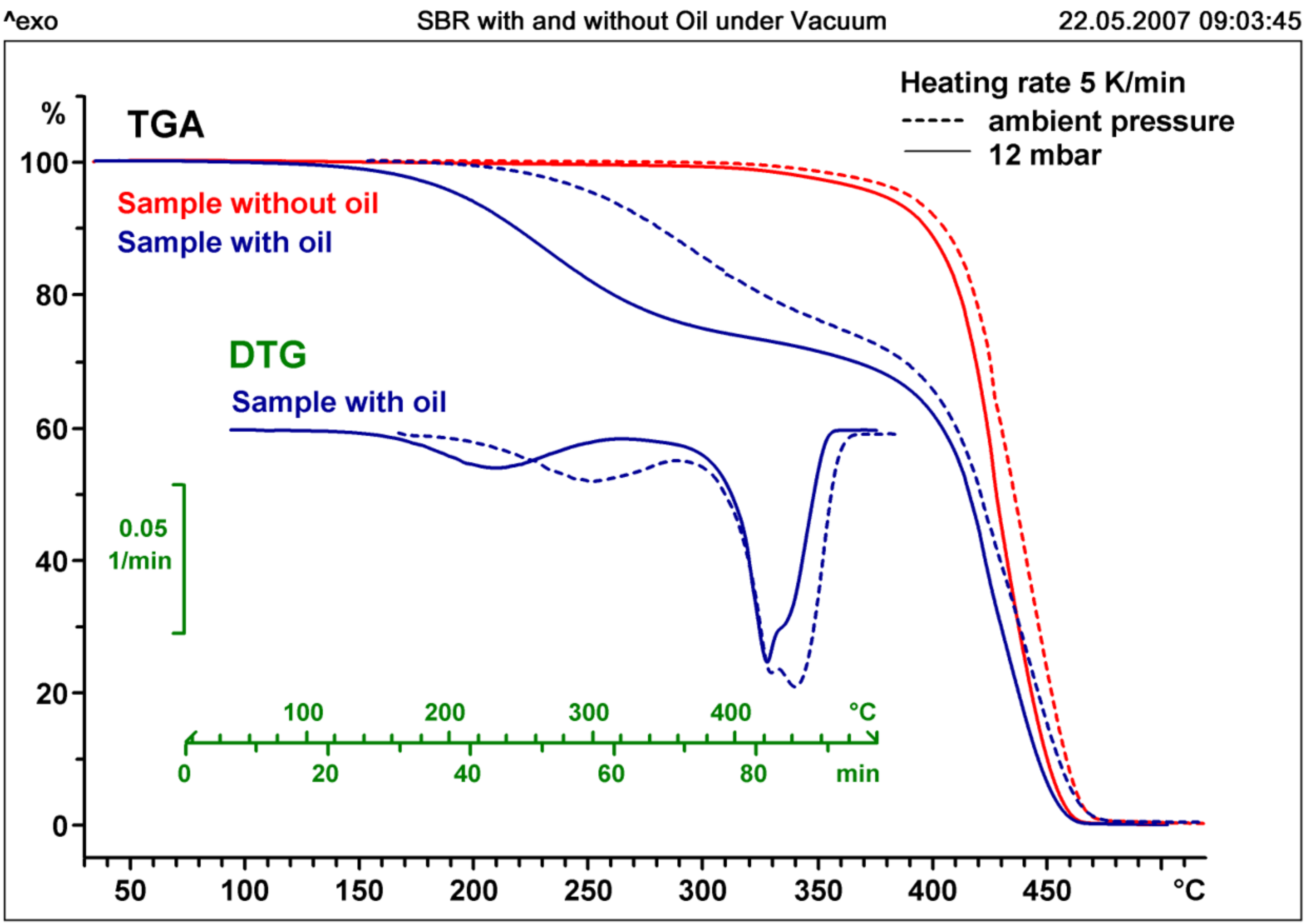



^exo
Defective and Good Bearings
25.05.2007 14:08:55
mg
TGA curves
TGA-DSC curves
Good bearing
Defective bearing
10
mW
Integral -898.84 mJ
normalized -182.54 Jg^-1
Peak 166.83 °C
Integral -358.28 mJ
normalized -84.26 Jg^-1
Peak 162.64 °C
Step -99.4797 %
-4.8984 mg
Step -99.4498 %
-4.2286 mg
100 150 200 250 °C
Step -0.3127 %
-15.3953e-03 mg
Step -0.2367 %
-10.0630e-03 mg
Heating rate 20 K/min
30 mL/min N2 up to 600 °C
30 mL/min air above 600 °C
0 1 2 3 4 5
100 200 300 400 500 600 700 800 °C

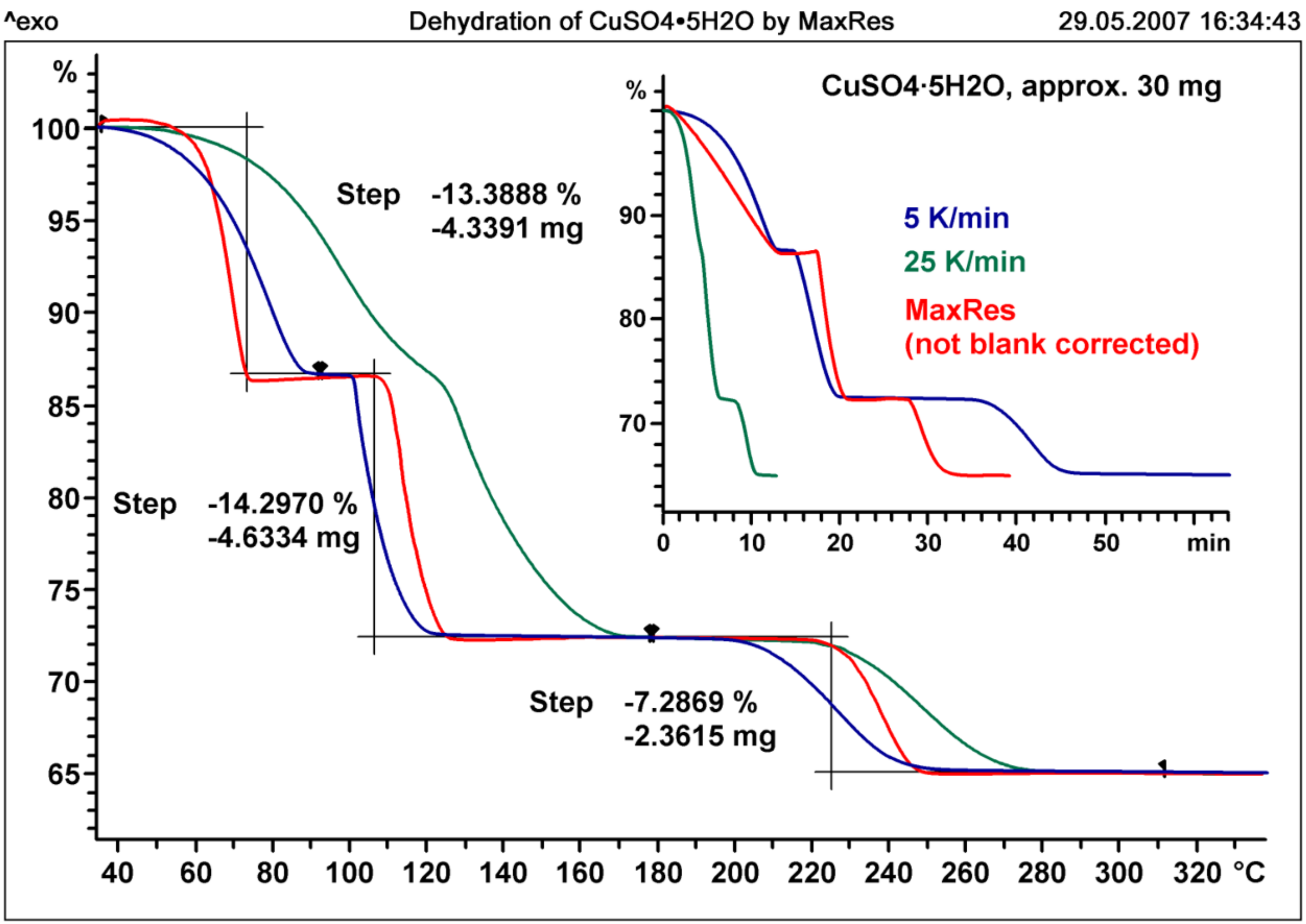
TGA 2: Applications (II)

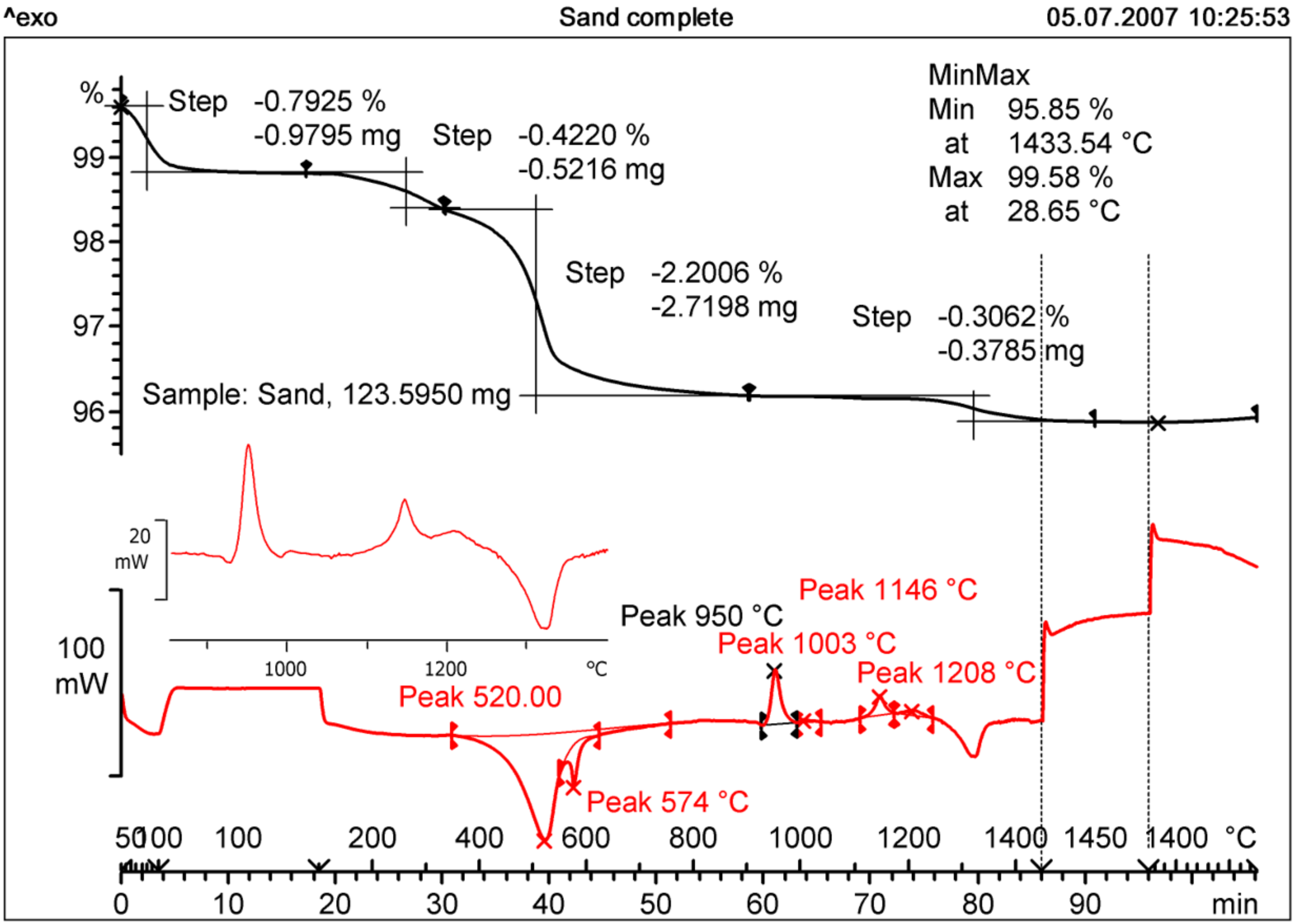


TGA 2: Applications (V)



Reducir la velocidad mejora la resolución




^exo
Sand complete
05.07.2007 10:25:53
MinMax
Min 95.85 %
at 1433.54 °C
Max 99.58 %
at 28.65 °C
Step -0.7925 %
-0.9795 mg
Step -0.4220 %
-0.5216 mg
Step -2.2006 %
-2.7198 mg
Step -0.3062 %
-0.3785 mg
Sample: Sand, 123.5950 mg
%
99
98
97
96
20 mW
1000
1200
°C
100 mW
Peak 950 °C
Peak 1146 °C
Peak 1003 °C
Peak 1208 °C
Peak 520.00
Peak 574 °C
50100 100 200 400 600 800 1000 1200 1400 1450 1400 °C
0 10 20 30 40 50 60 70 80 90 min

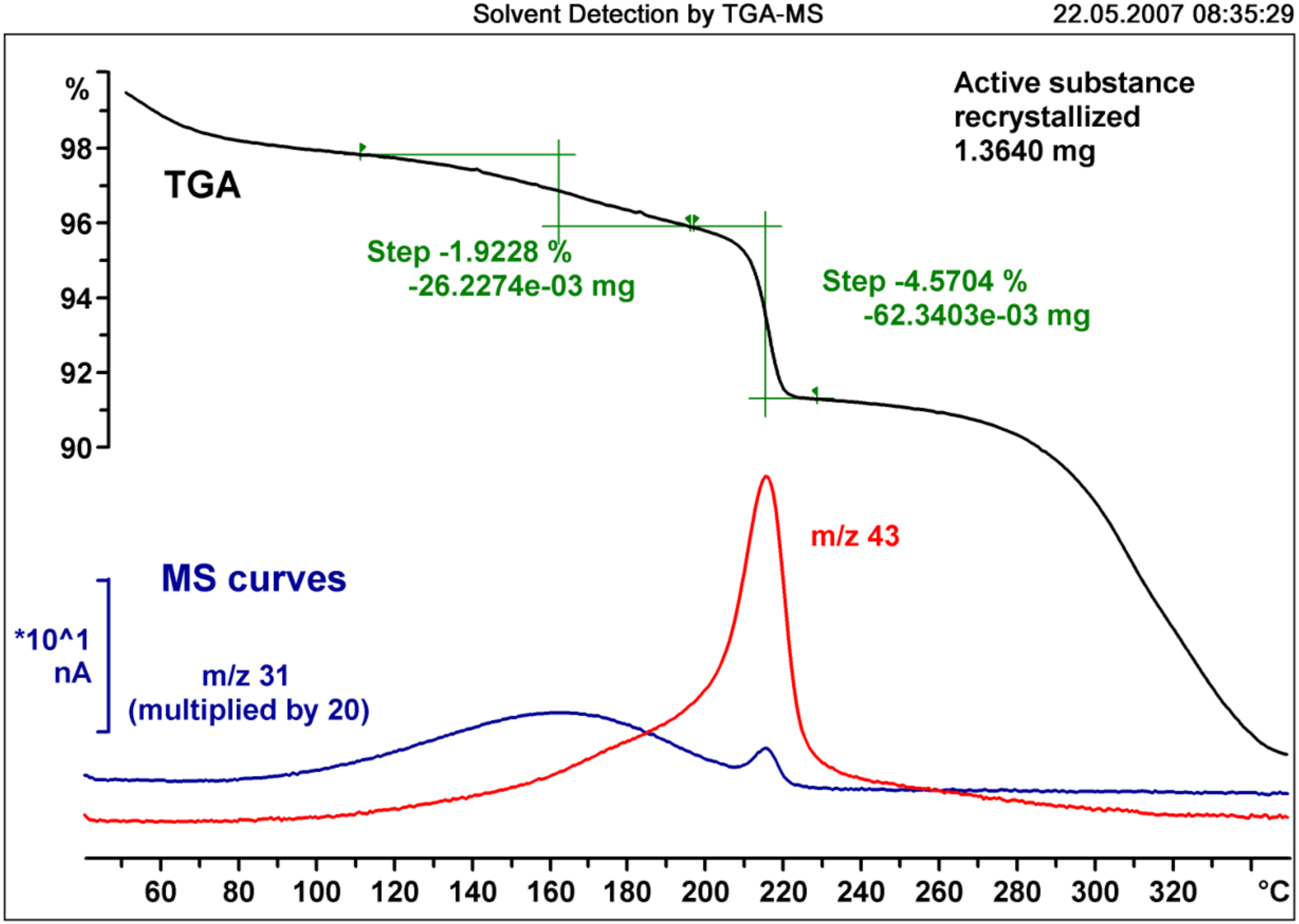
The evolved gas is transferred from the TGA to the gas cell through a heated line.

Standard

MS

FTIR

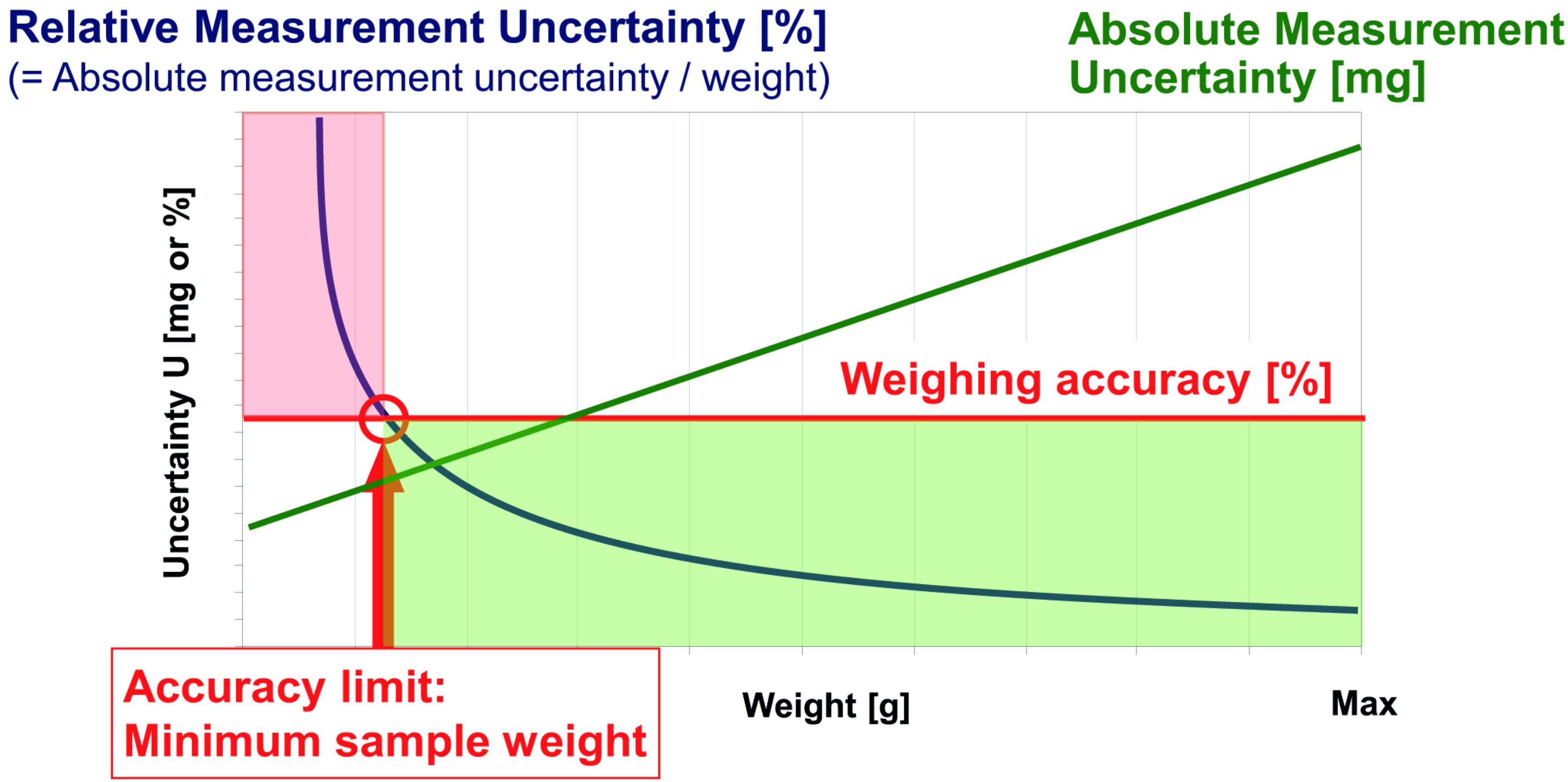
Sorption


Solvent Detection by TGA-MS
22.05.2007 08:35:29
Active substance
recrystallized
1.3640 mg
TGA
%
98
96
94
92
90
Step -1.9228 %
-26.2274e-03 mg
Step -4.5704 %
-62.3403e-03 mg
m/z 43
MS curves
*10^1
nA
m/z 31
(multiplied by 20)
60
80
100
120
140
160
180
200
220
240
260
280
300
320
°C

- In simple terms, the uncertainty of measurement is the range of values within which the true value of the measurement is expected to lie with a stated level of confidence.

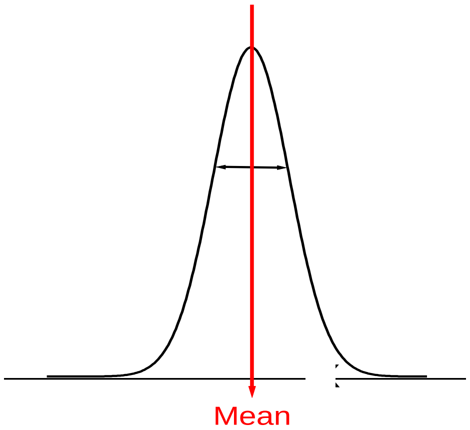
- Uncertainty comprises much more than just specifying a standard deviation of an analytical result: sampling process, sample preparation, calibration etc. all contribute to the uncertainty of a measurement result.

- Uncertainty is not an error: uncertainty specifies a range in which the “true” value lies with a certain probability.


Relative Measurement Uncertainty [%]
(= Absolute measurement uncertainty / weight)
Absolute Measurement Uncertainty [mg]
Uncertainty U [mg or %]
Weighing accuracy [%]
Accuracy limit:
Minimum sample weight
Weight [g]
Max

Weighing uncertainty for a balance is given by the repeatability

$$m_{\mathrm{min}} \approx \frac{k \cdot s_{\mathrm{RP}}}{A_{\mathrm{req}}}$$

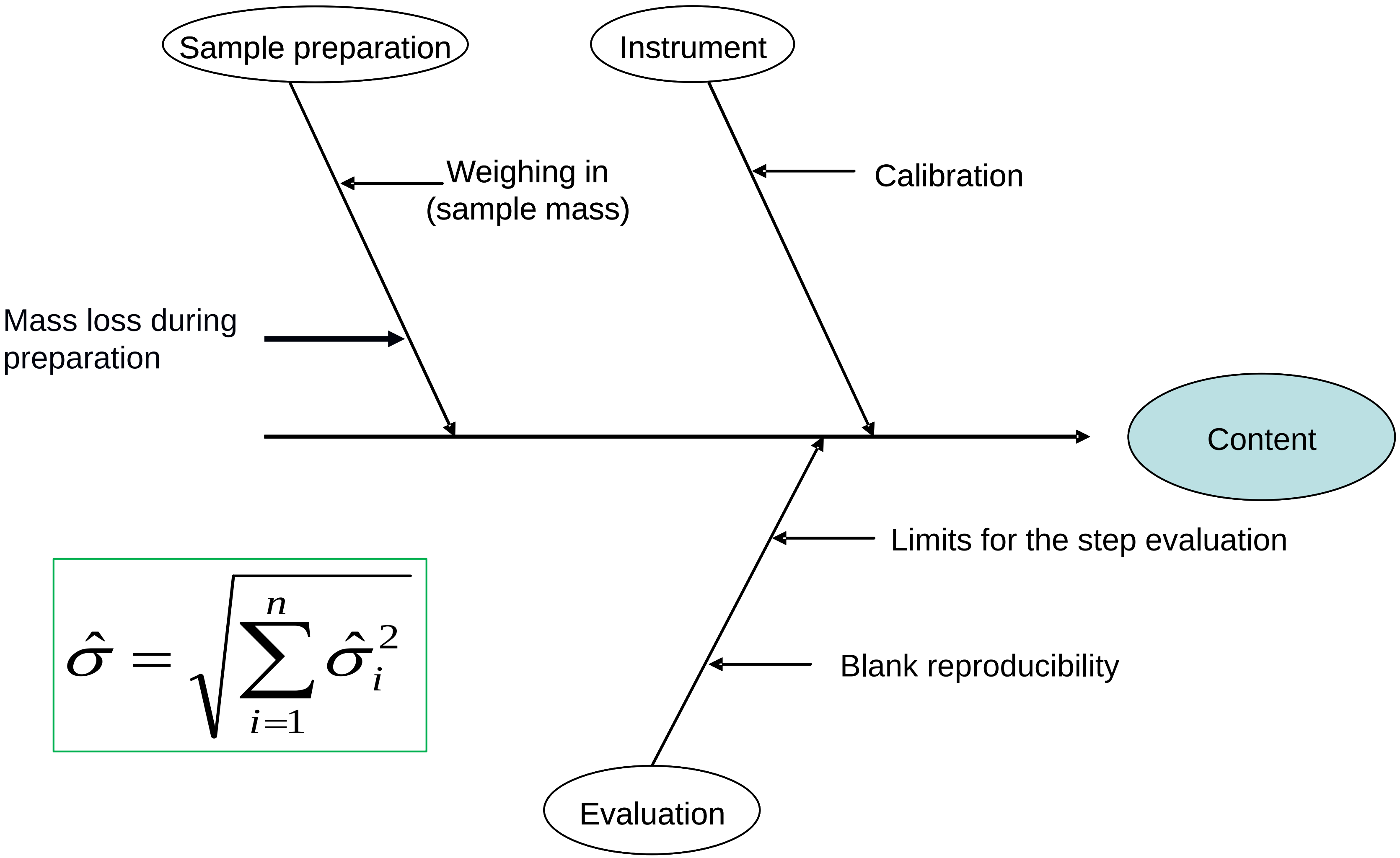


k = coverage factor, usually 2
s_{RP} = standard deviation (repeatability)
A_{req} = relative uncertainty required

- Example: Repeatability 1 ug, A_{req} 1%, k =2

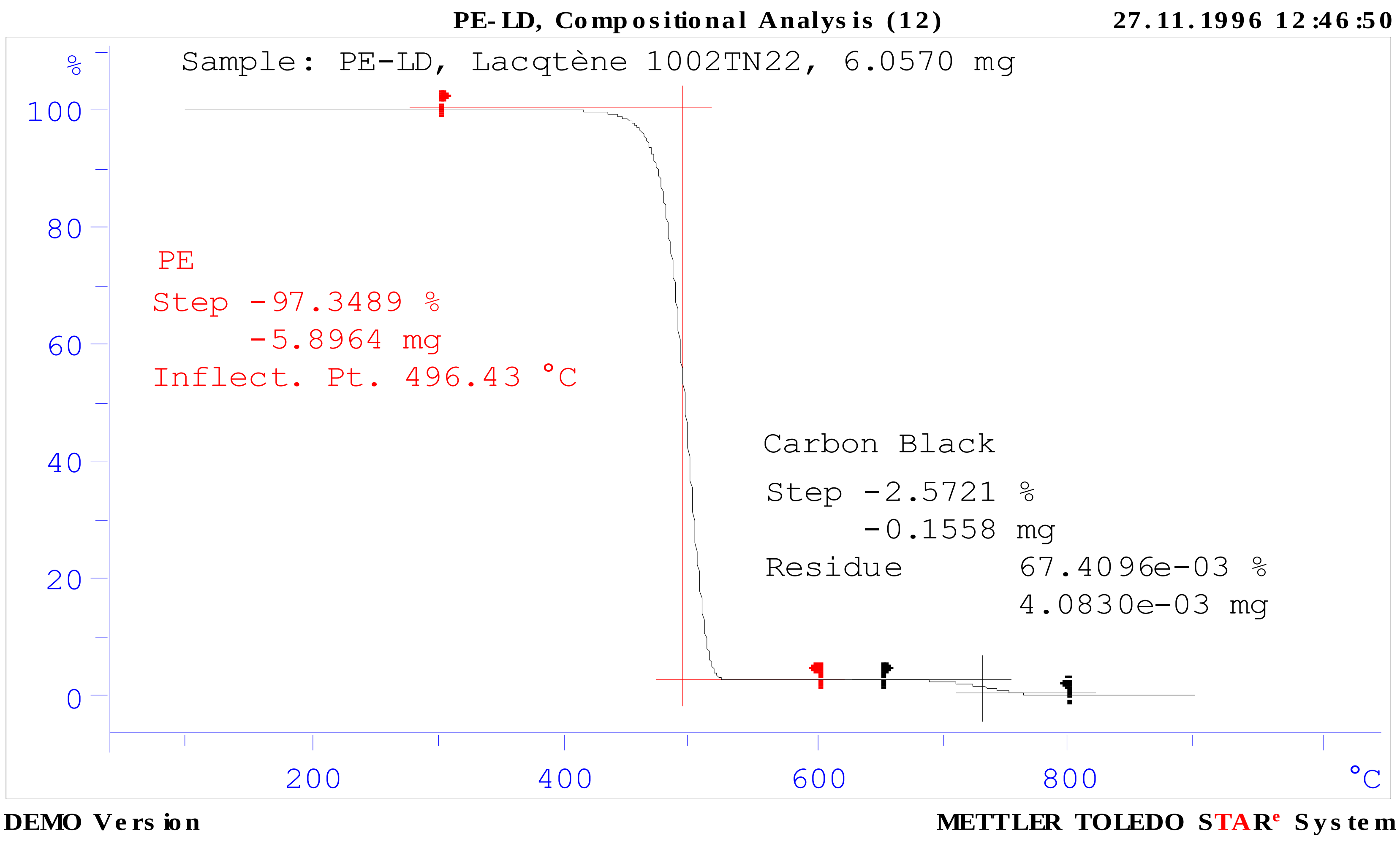
$$m_{min} = 200\ \mathrm{ug}$$

Example: uncertainty of a step evaluation



$$\hat{\sigma} = \sqrt{\sum_{i=1}^{n} \hat{\sigma}_i^2}$$

Incerteza en medidas TGA



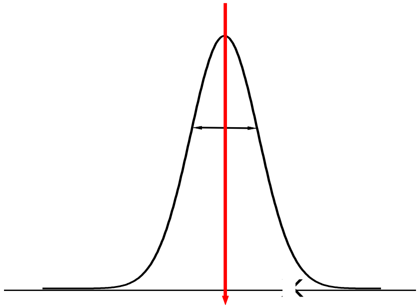
$$m_{\mathrm{min}} \approx \frac{k \cdot s_{\mathrm{RP}}}{A_{\mathrm{req}} \cdot EP}$$

k = coverage factor (usually 2)
A_{req} = required accuracy in %
EP = Expected percentage of the "effect" (residue, step)
s = Standard deviation of the "effect" (step or residue)

Rules of thumb:

s for steps: 0.3 ug (ruido de fondo)
s for residues: 15 ug (reproducibilidad de la línea base)

$$m_{\min} \approx \frac{k \times s}{0.01 \cdot A_{\text{req}} \cdot 0.01 \cdot EP}$$



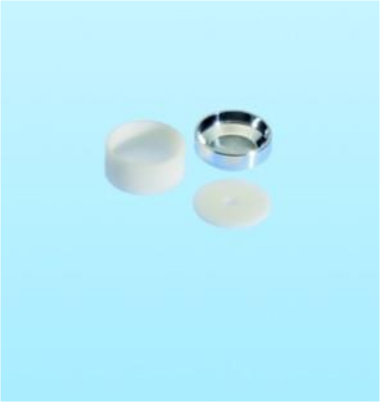
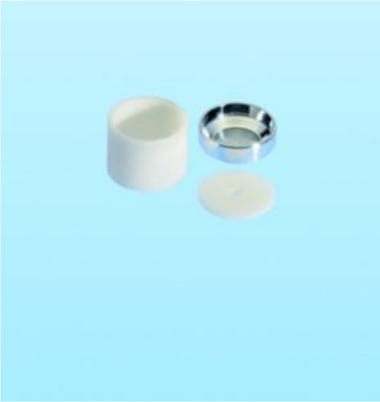
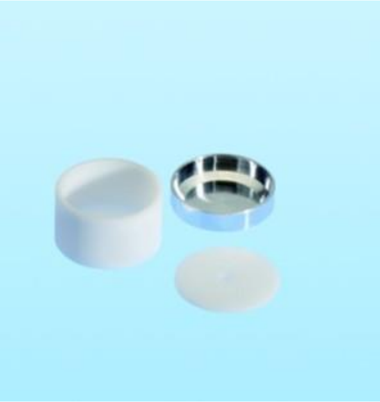
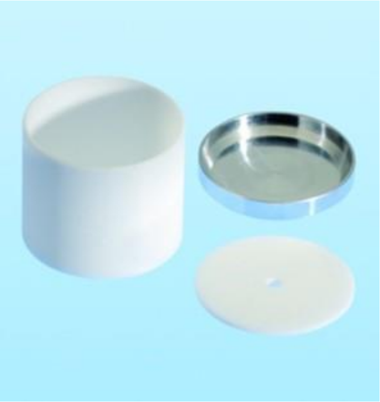
- Factor de cobertura: 2 (95% de probabilidad)
- Exactitud deseada: 1%
- Porcentaje de carbono: 1%
- Incertidumbre del TGA: 10µg (desviación máxima en 1 hora)

$$P_{\min} \approx \frac{2 \times 10}{0{,}01 \times 0{,}01} = 200.000 \mu g = 200 mg$$

From simple to demanding applications.
You can choose from more than 30 types of crucibles.

Alumina crucibles

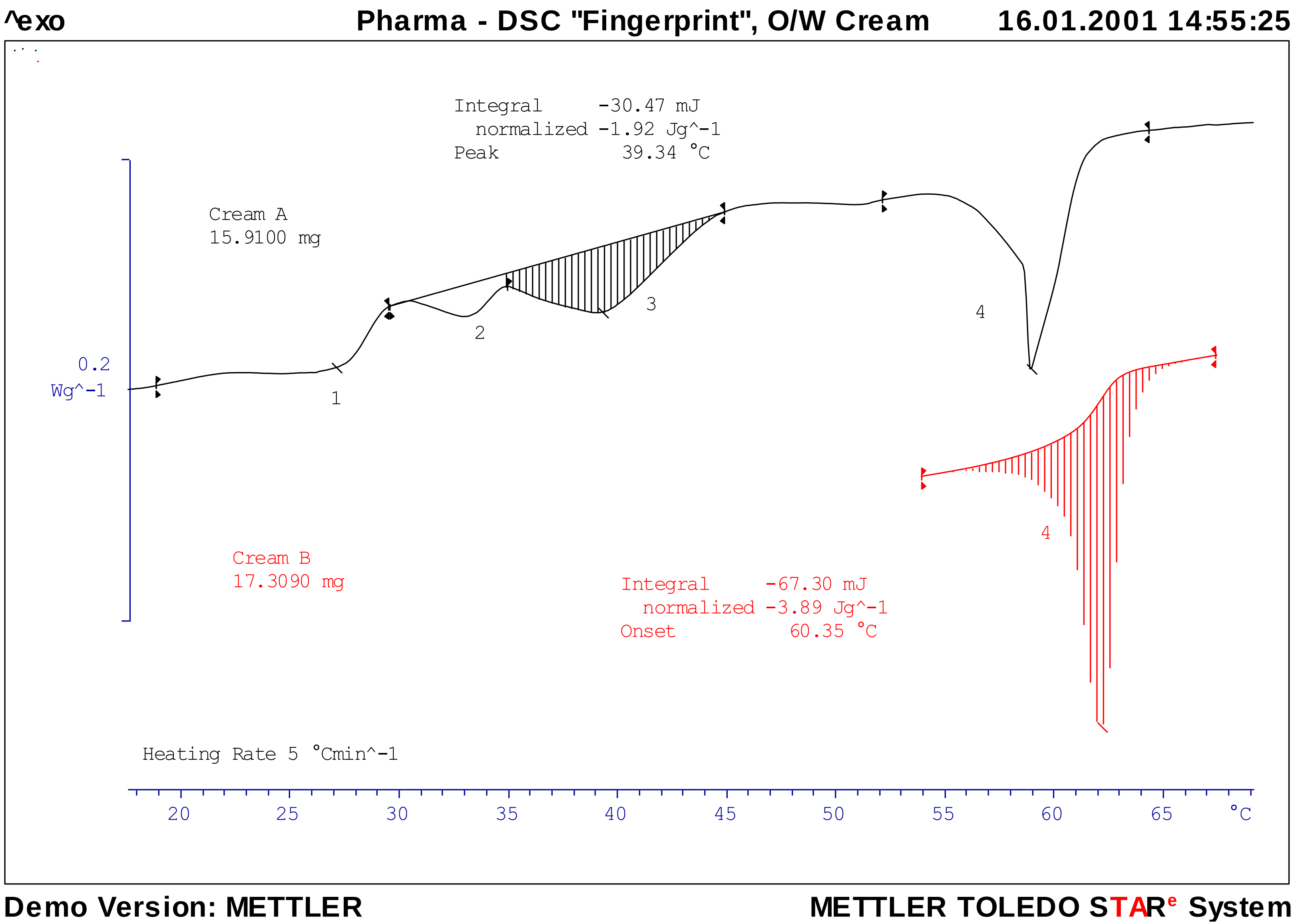
- Alumina crucibles with lids: 30 µl, 70 µl, 150 µl, 600 µl and 900 µl
- Special aluminum lids to prevent contamination and evaporation before the measurement

Química Farmacéutica

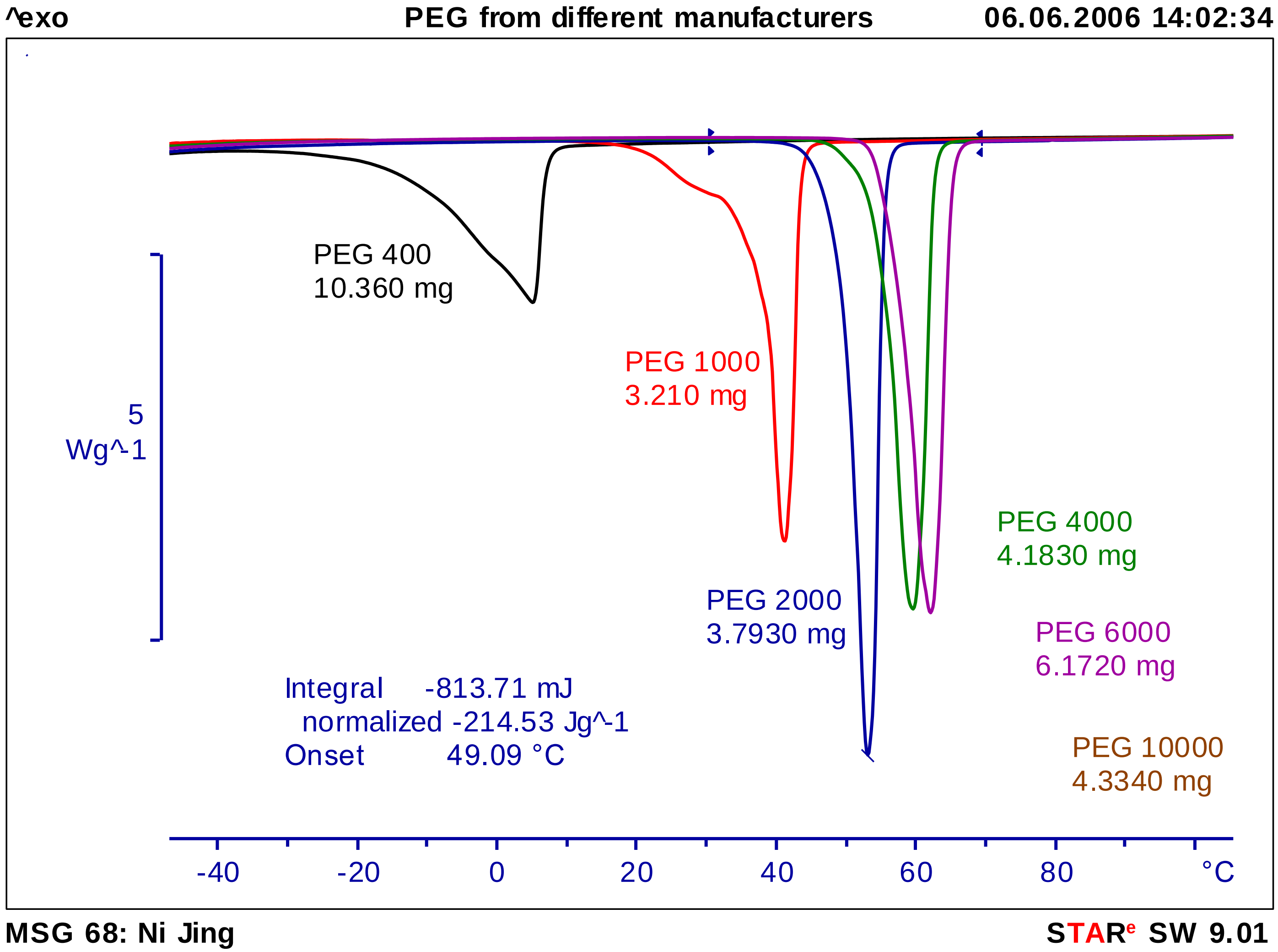
Aplicaciones DSC y TGA

METTLER TOLEDO



^exo
Pharma - DSC "Fingerprint", O/W Cream
16.01.2001 14:55:25
Integral -30.47 mJ
normalized -1.92 Jg^-1
Peak 39.34 °C
Cream A
15.9100 mg
0.2
Wg^-1
1
2
3
4
Cream B
17.3090 mg
4
Integral -67.30 mJ
normalized -3.89 Jg^-1
Onset 60.35 °C
Heating Rate 5 °Cmin^-1
20
25
30
35
40
45
50
55
60
65
°C
Demo Version: METTLER
METTLER TOLEDO STARe System

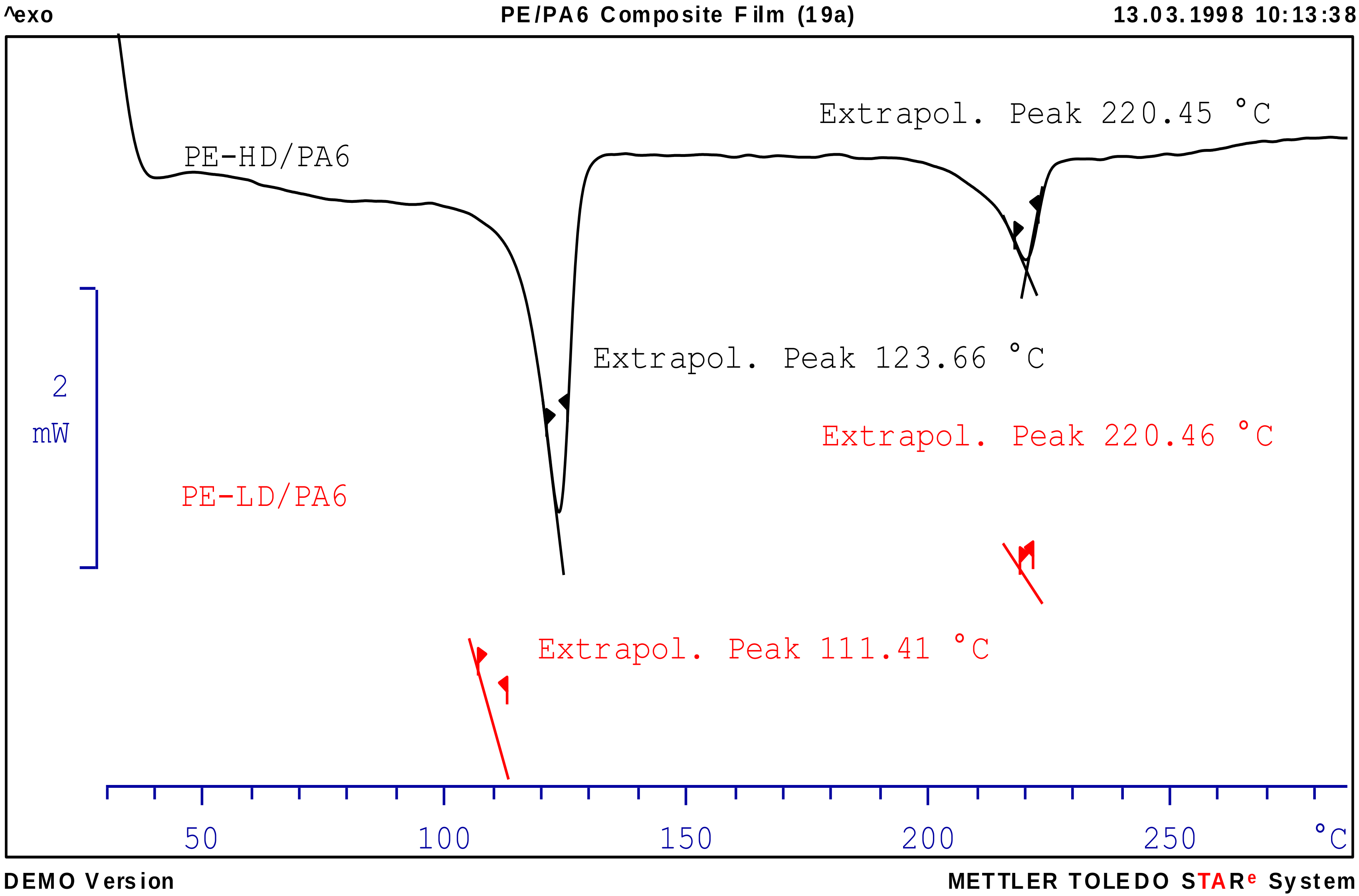
Melting behavior of different PEGs



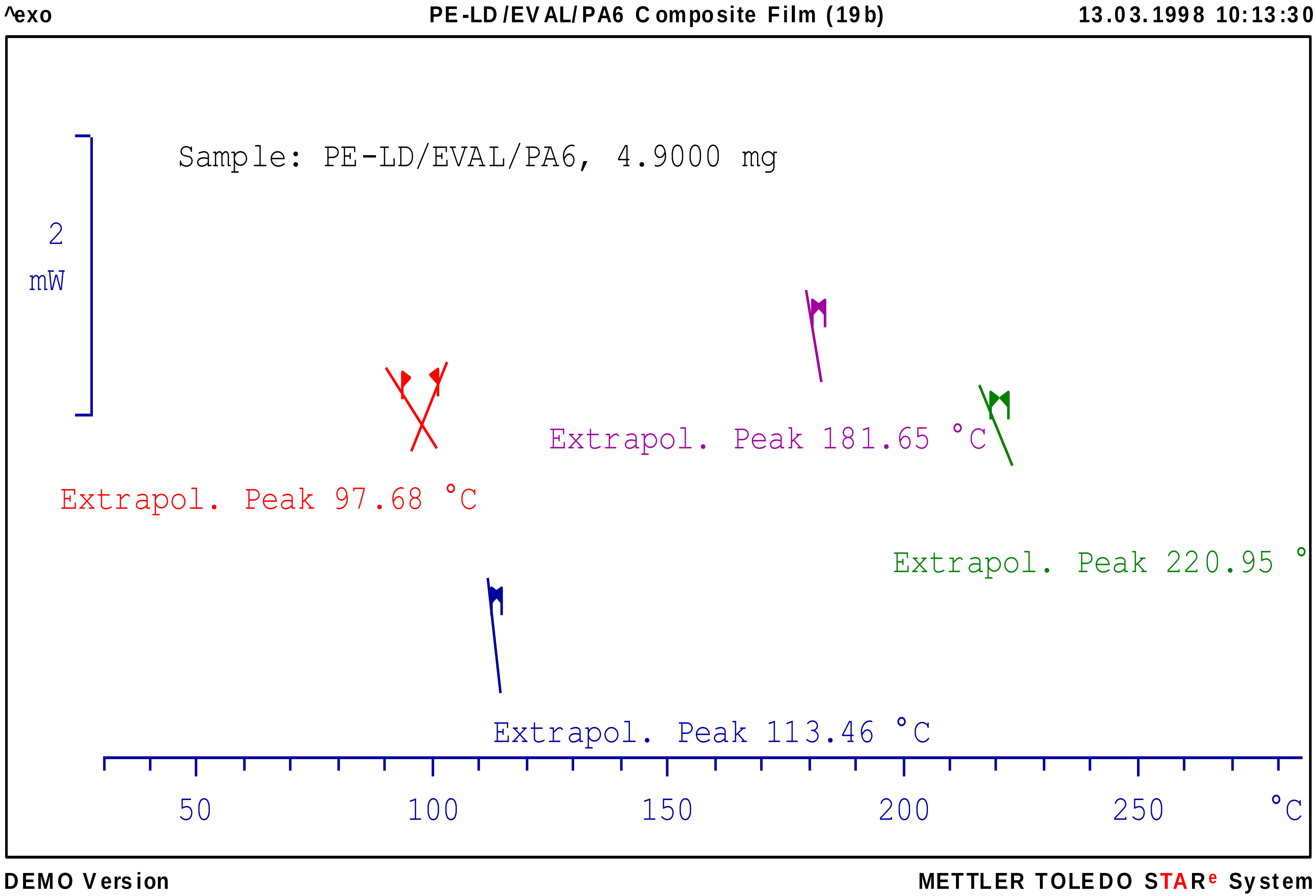
Packaging films are best analyzed by DSC. Here are some examples and tips on how to characterize such films.

- Packaging materials:
  - external packaging
  - in direct contact with the pharmaceutical preparation, stringent requirements
- Synthetic polymers (e.g. PE) are increasingly being used.
- Thermal analysis is used for the quality control and identification purposes.

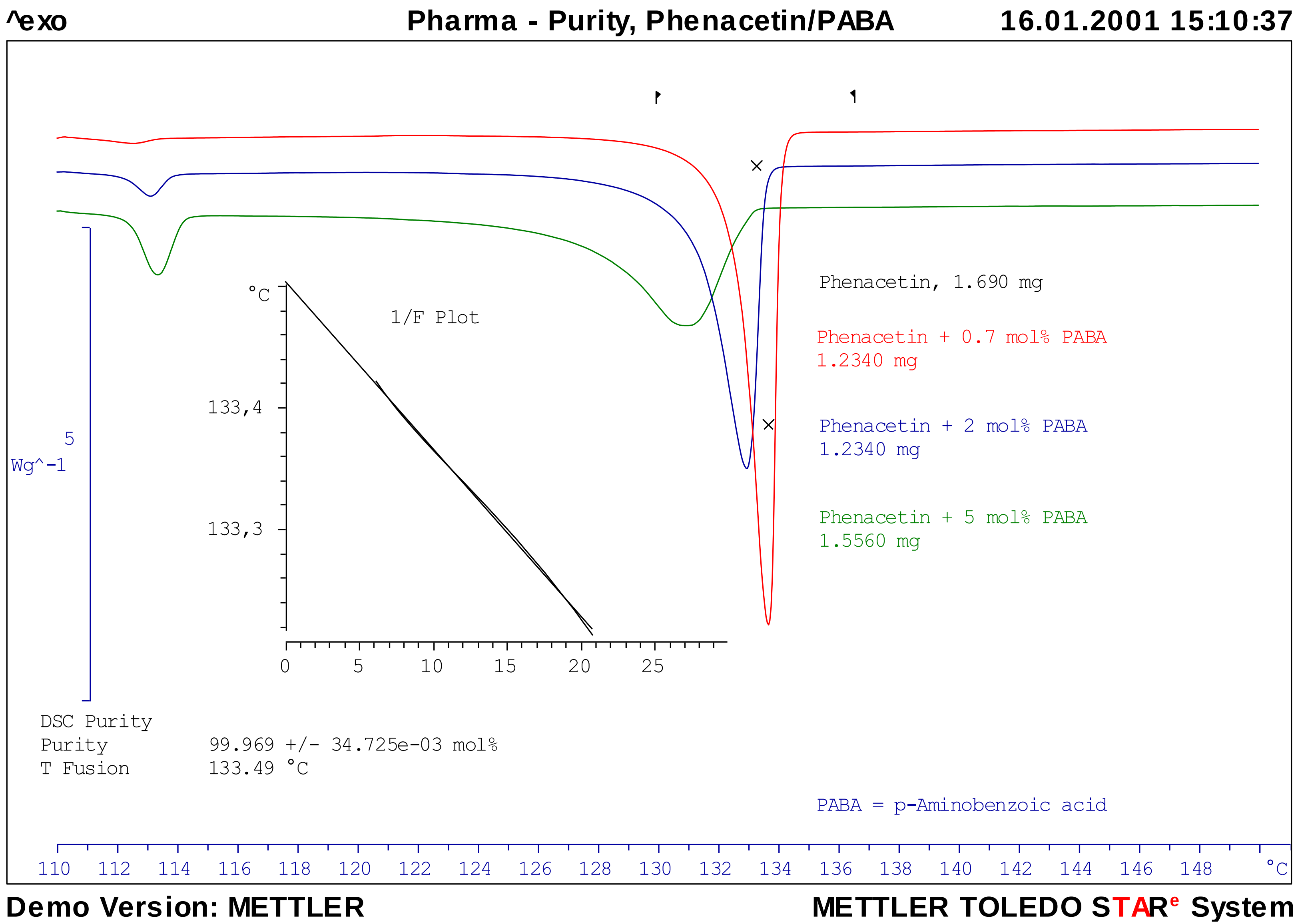
Termoplásticos utilizados en envases



Composición de films en envases

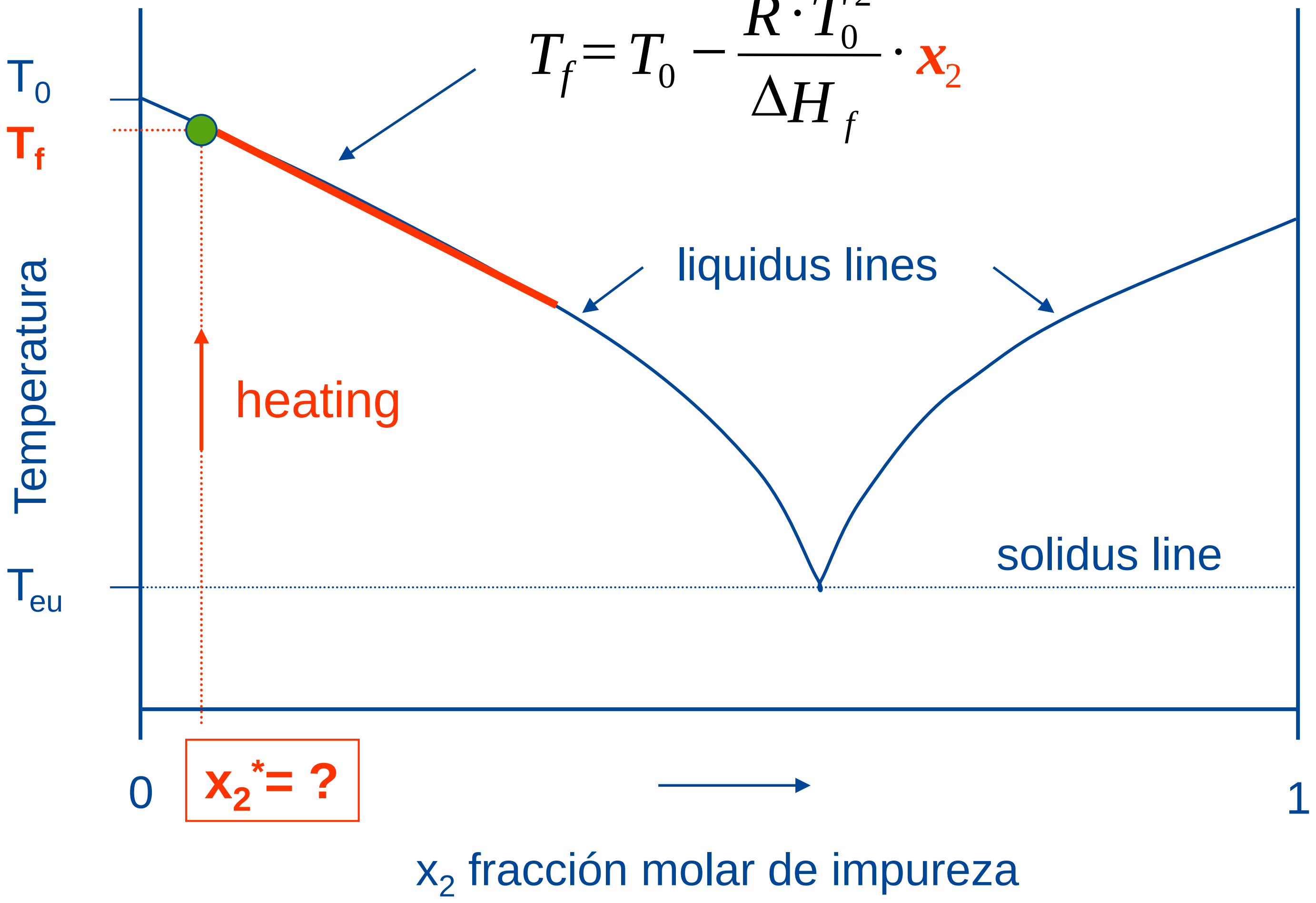


Pureza

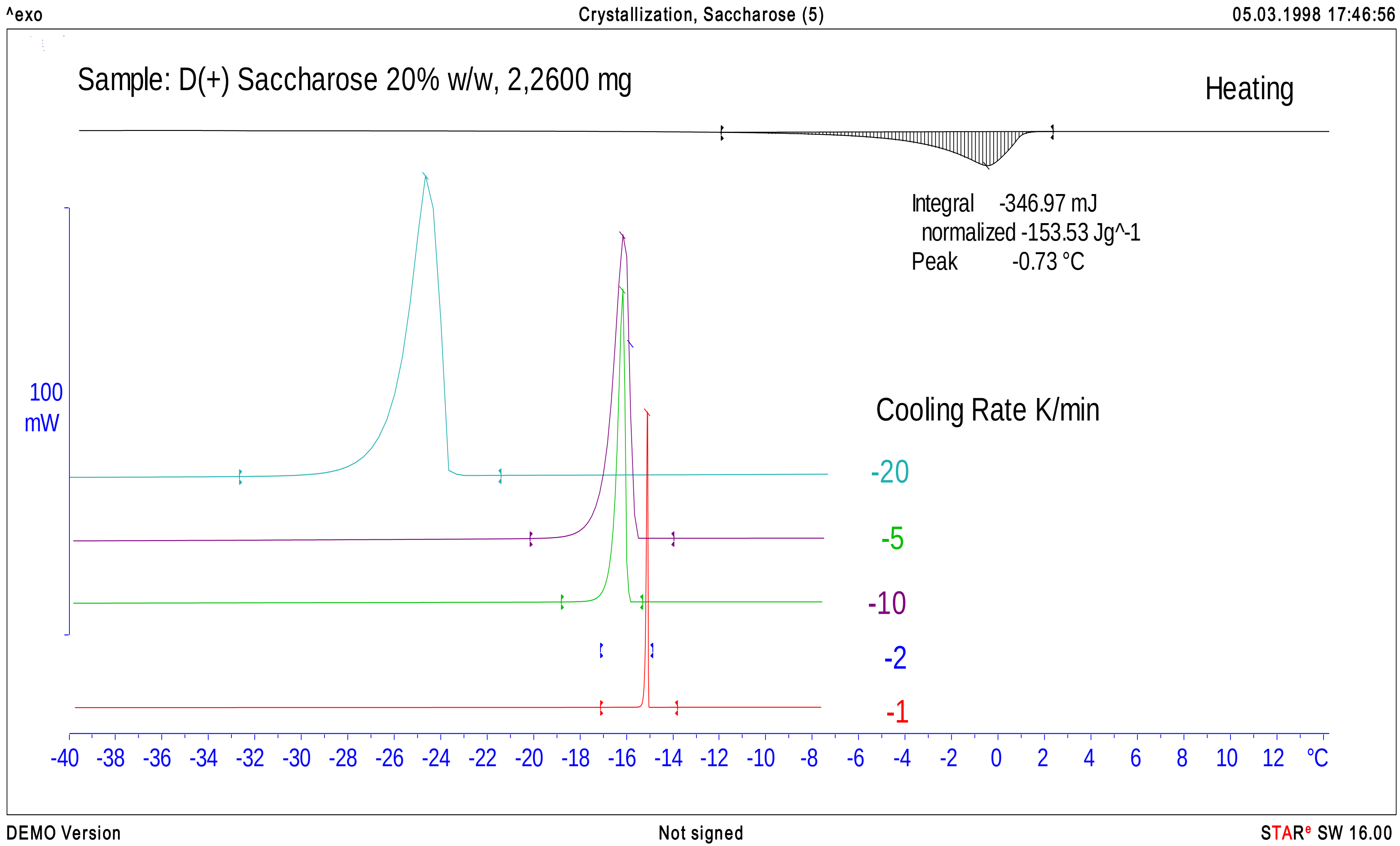

^exo
Pharma - Purity, Phenacetin/PABA
16.01.2001 15:10:37
°C
1/F Plot
133,4
133,3
0
5
10
15
20
25
5
Wg^-1
Phenacetin, 1.690 mg
Phenacetin + 0.7 mol% PABA
1.2340 mg
Phenacetin + 2 mol% PABA
1.2340 mg
Phenacetin + 5 mol% PABA
1.5560 mg
DSC Purity
Purity 99.969 +/- 34.725e-03 mol%
T Fusion 133.49 °C
PABA = p-Aminobenzoic acid
110 112 114 116 118 120 122 124 126 128 130 132 134 136 138 140 142 144 146 148 °C
Demo Version: METTLER
METTLER TOLEDO STARe System

Pureza

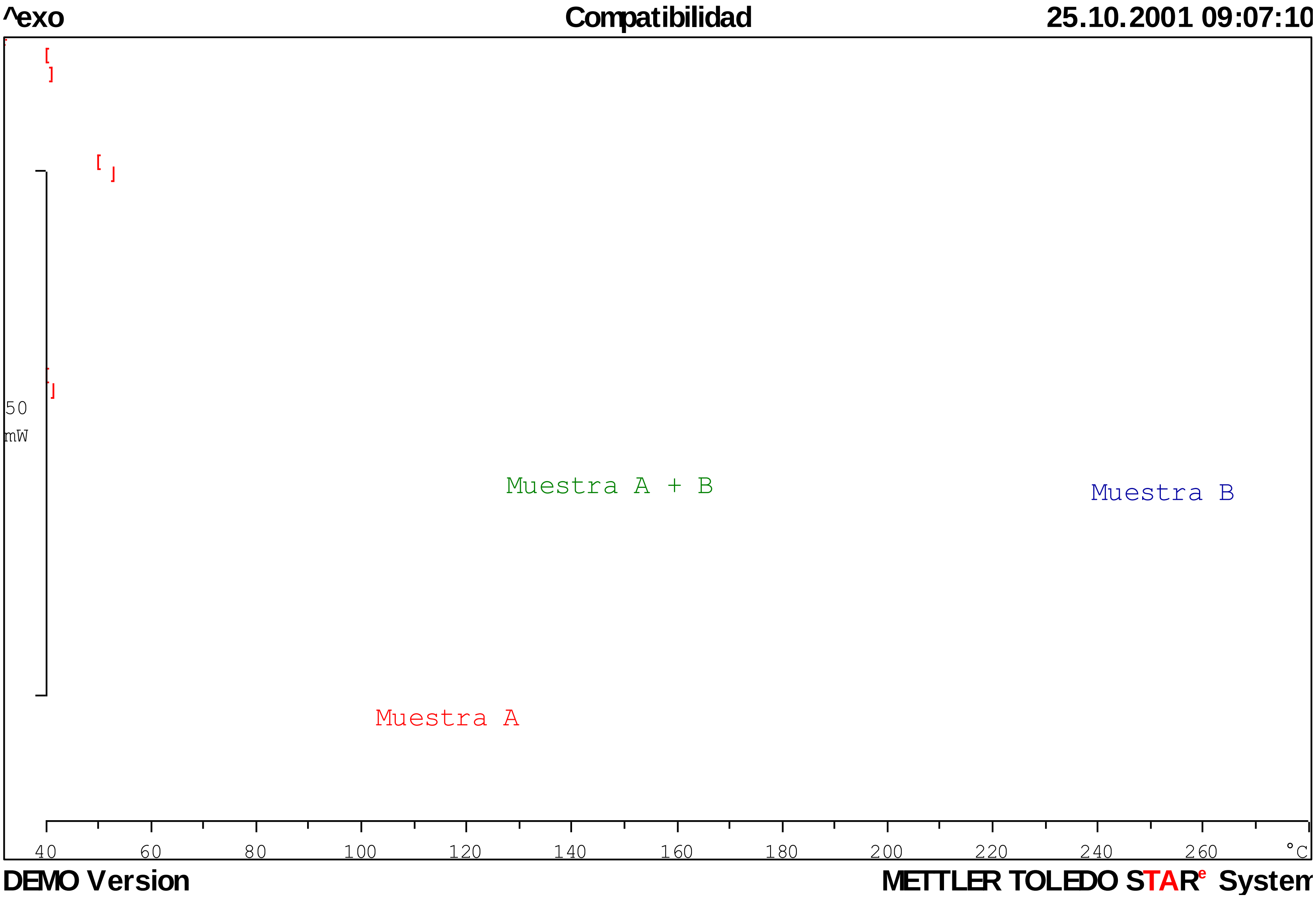
$$T_f = T_0 - \frac{R \cdot T_0^2}{\Delta H_f} \cdot x_2$$



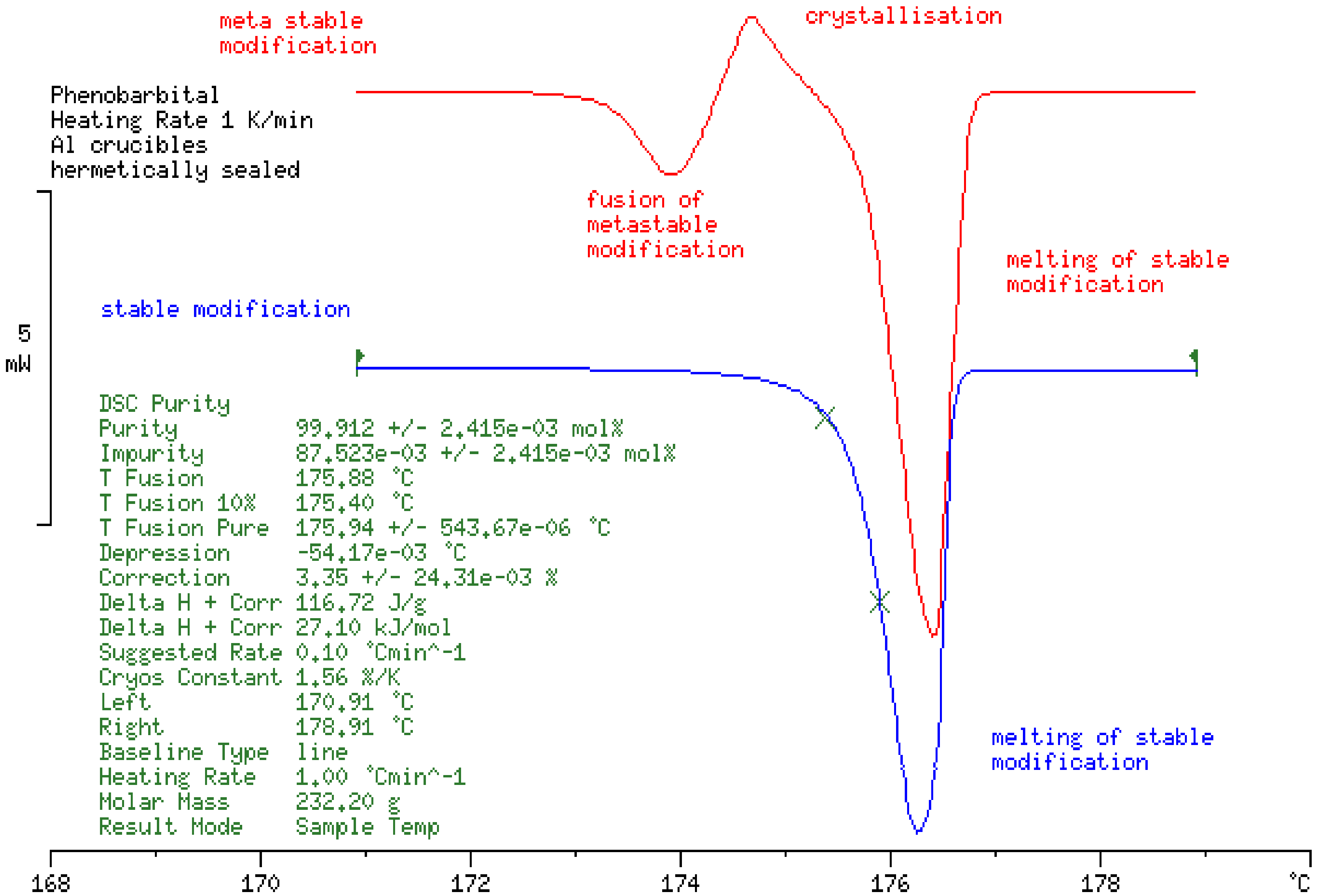
Caracterización

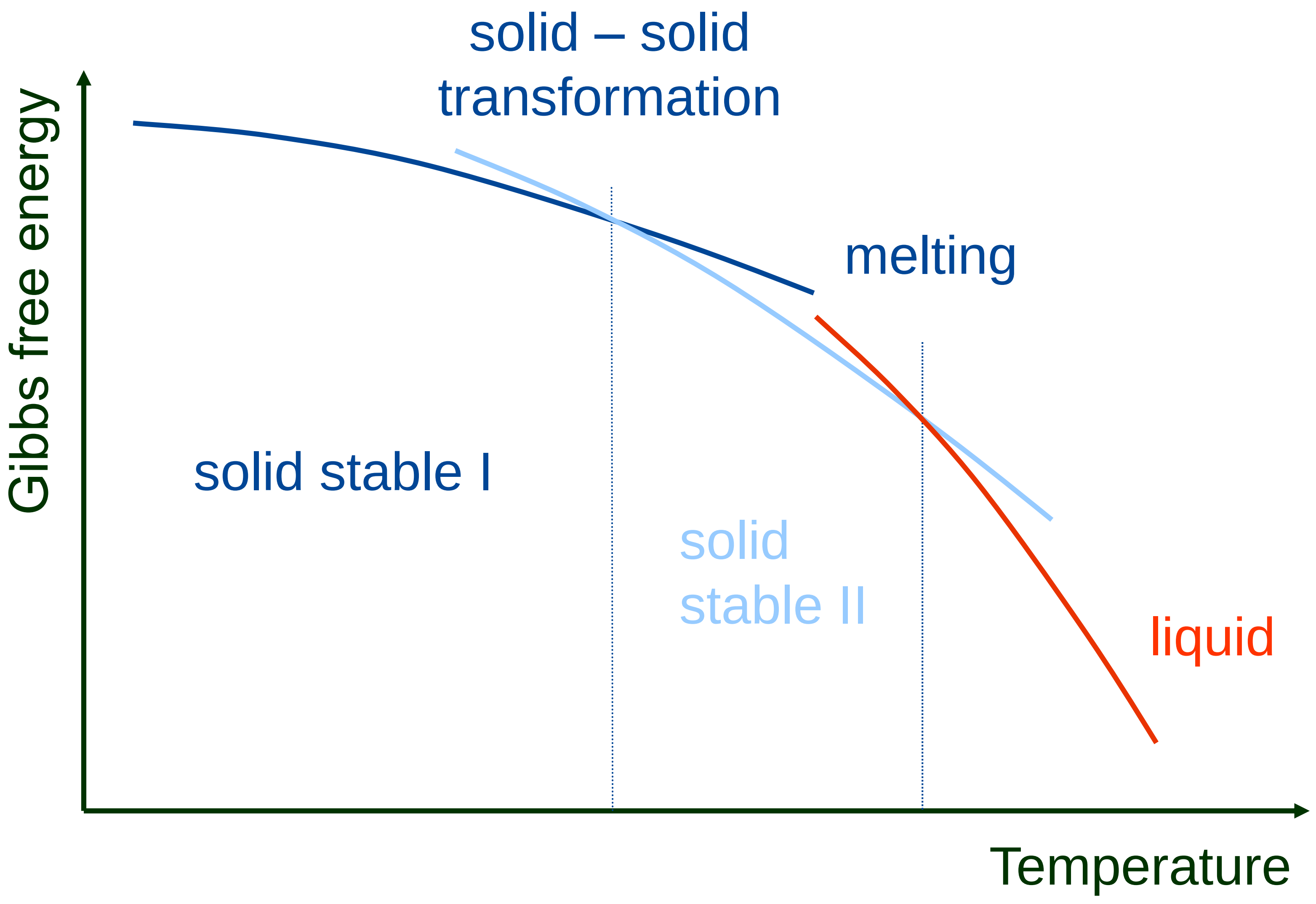


Estudio de compatibilidad

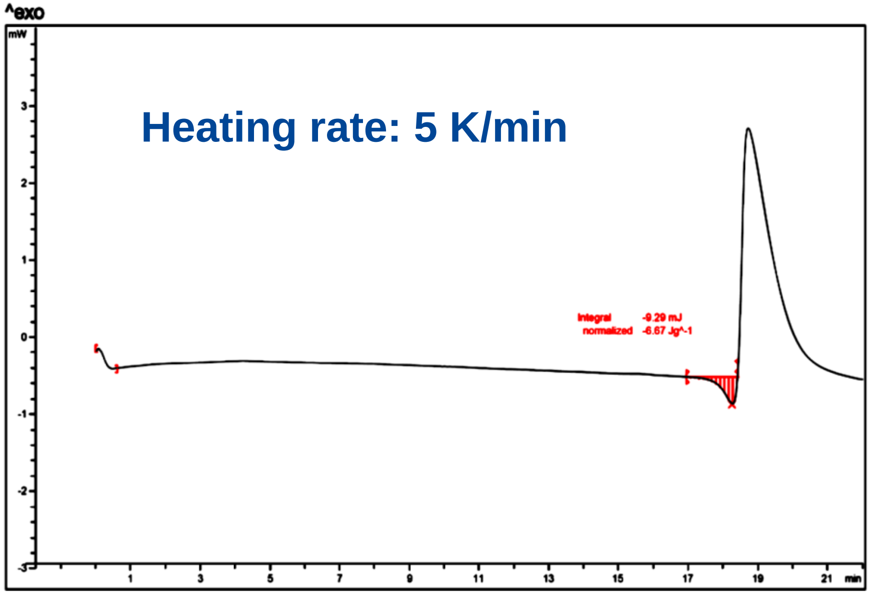


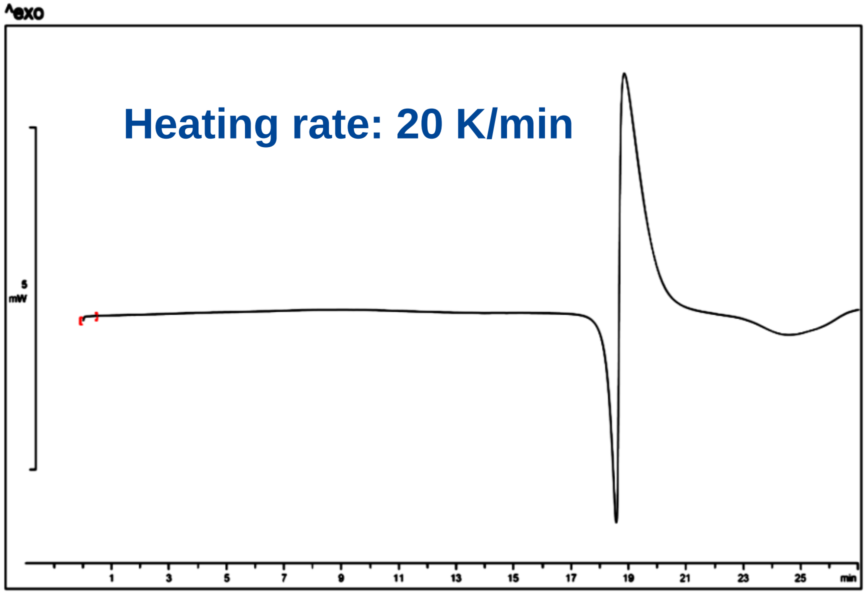
Polimorfismo: Fenobarbital



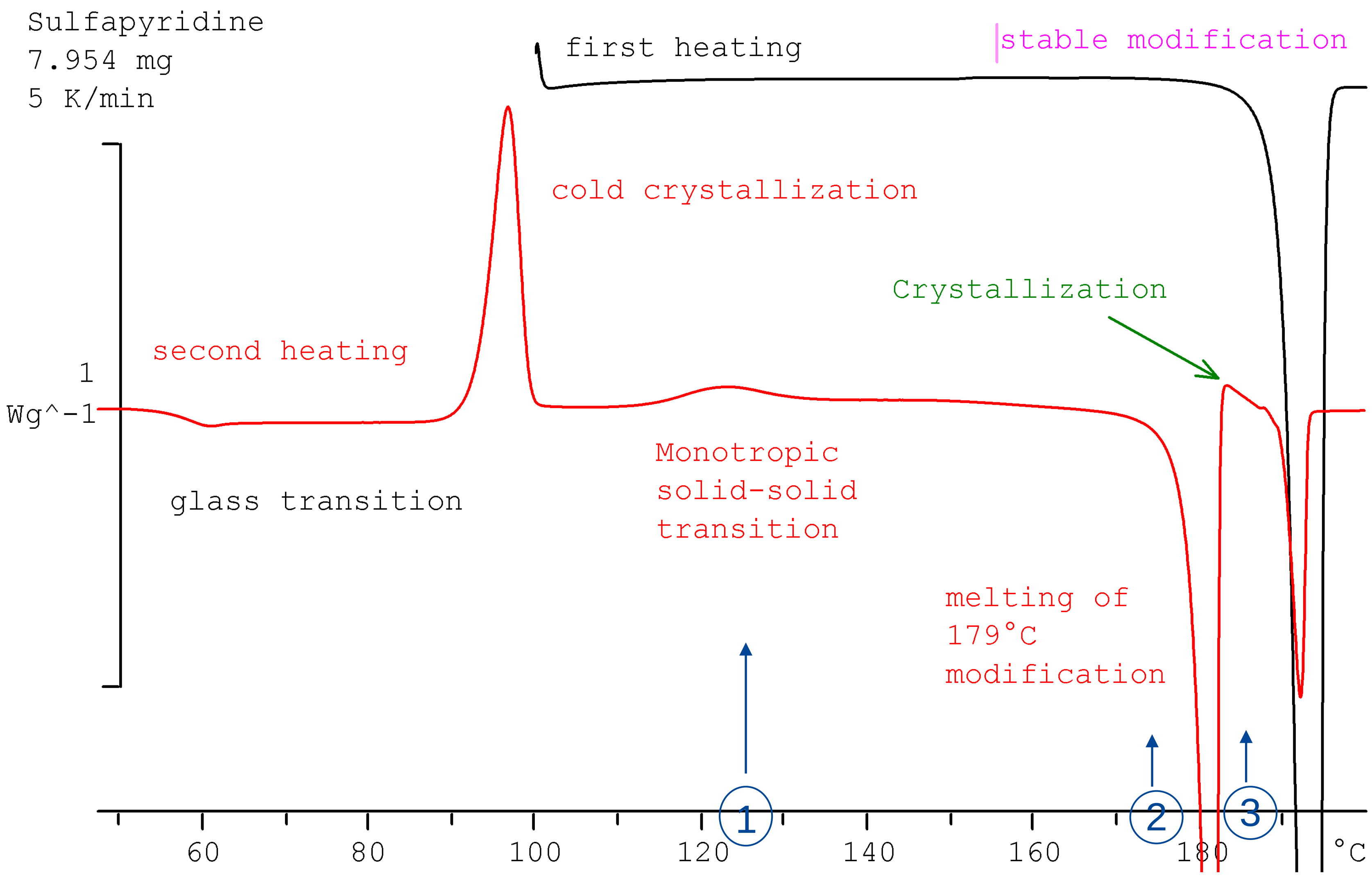

solid – solid
transformation
Gibbs free energy
melting
solid stable I
solid
stable II
liquid
Temperature

Fusión y descomposición

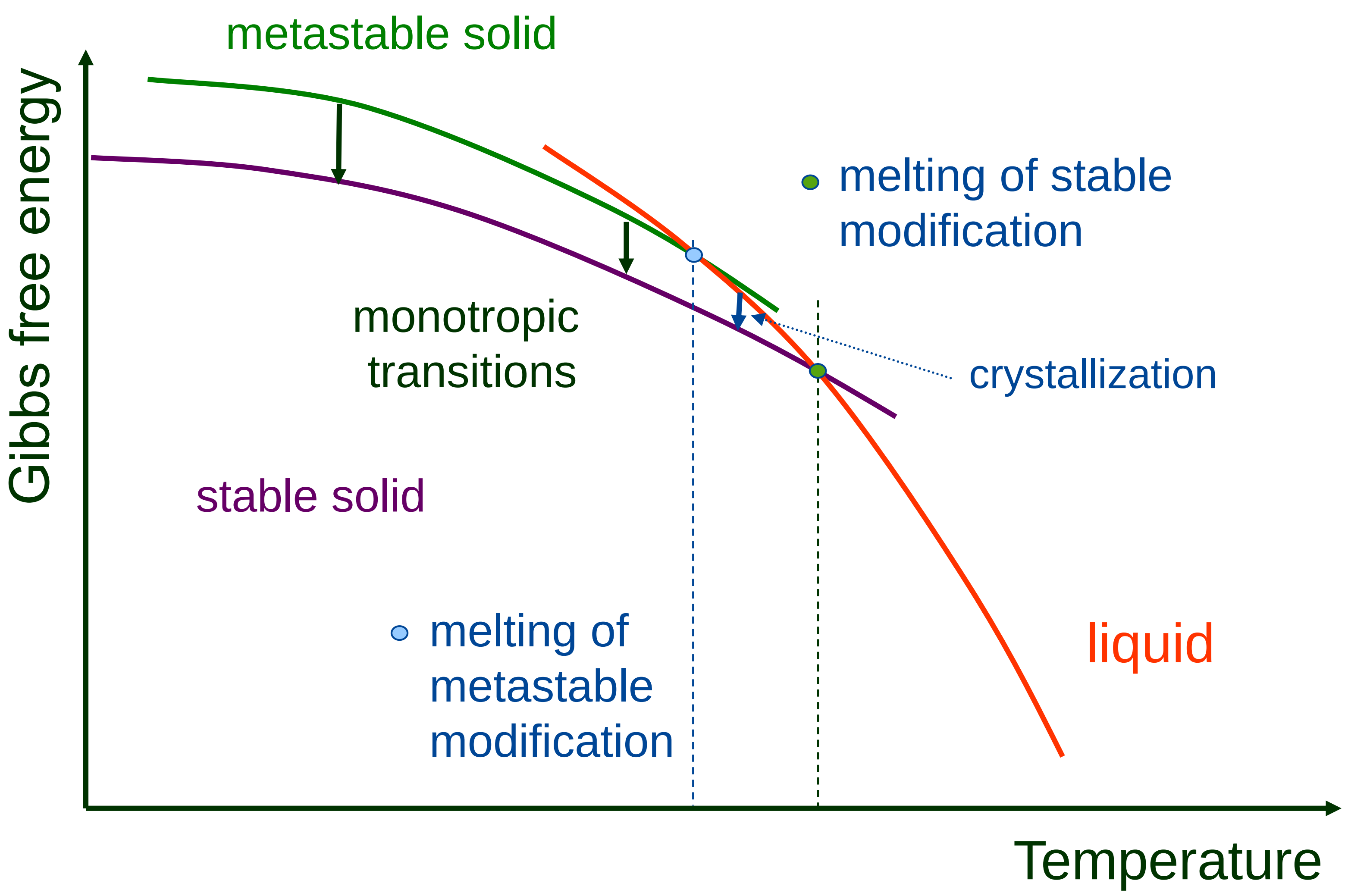




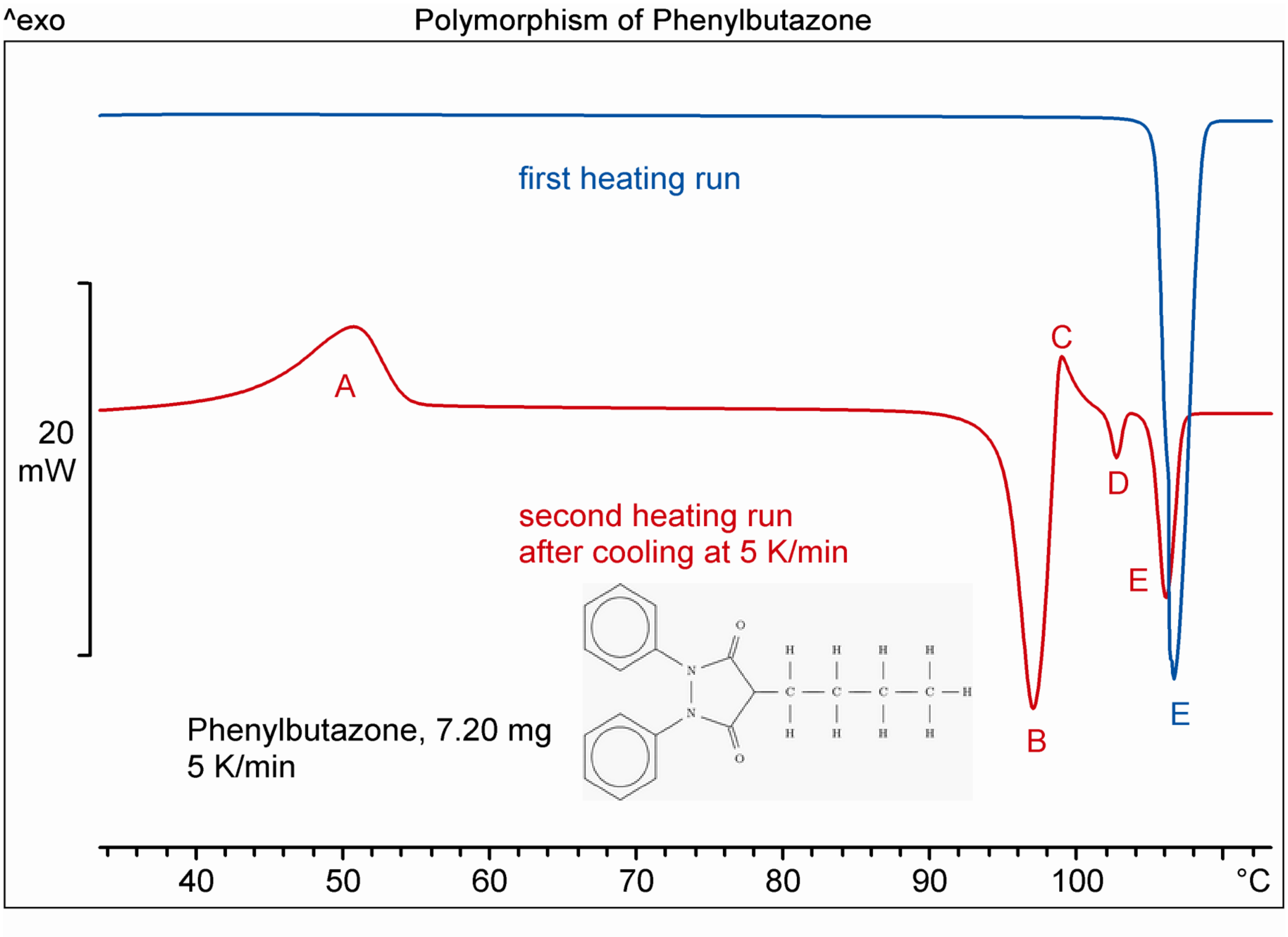
- Gráficas cedidas por CRISFORMA (ICIQ) -


Sulfapyridine
7.954 mg
5 K/min
first heating
stable modification
cold crystallization
Crystallization
second heating
1
Wg^-1
glass transition
Monotropic
solid-solid
transition
melting of
179°C
modification
1
2
3
60
80
100
120
140
160
180
°C

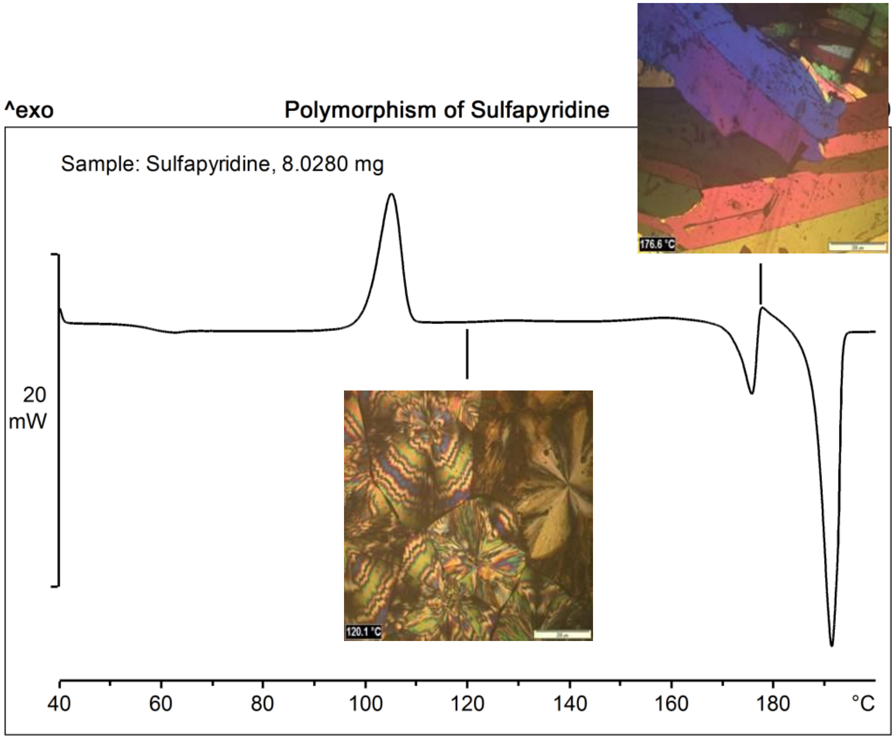
Monotropic transition and melting



DSC 1: Amazing Resolution



Thermomicroscopy (or hot-stage microscopy) is when the sample is observed while under a microscope, as it is heated or cooled.



A typical HS investigation of a polymorphic transition:

120 °C spherulites after cold crystallization at 100 °C

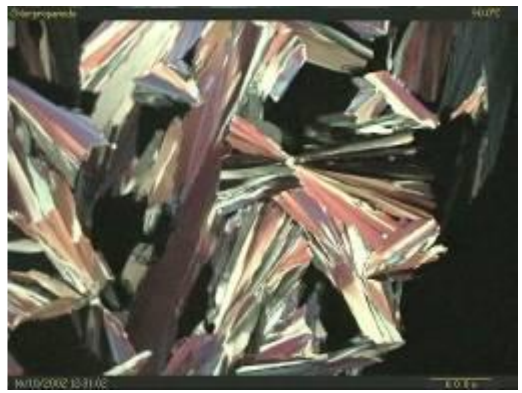
176 °C rhomboid after melting and recrystallization

Crystallization of chlorpropamide

Crystallization temperature ↑

- lower nucleation rate, less crystals
- higher crystal growth rate, bigger crystals

Cooled from 135 °C at 10 K/min and held isothermally at **80 °C**.

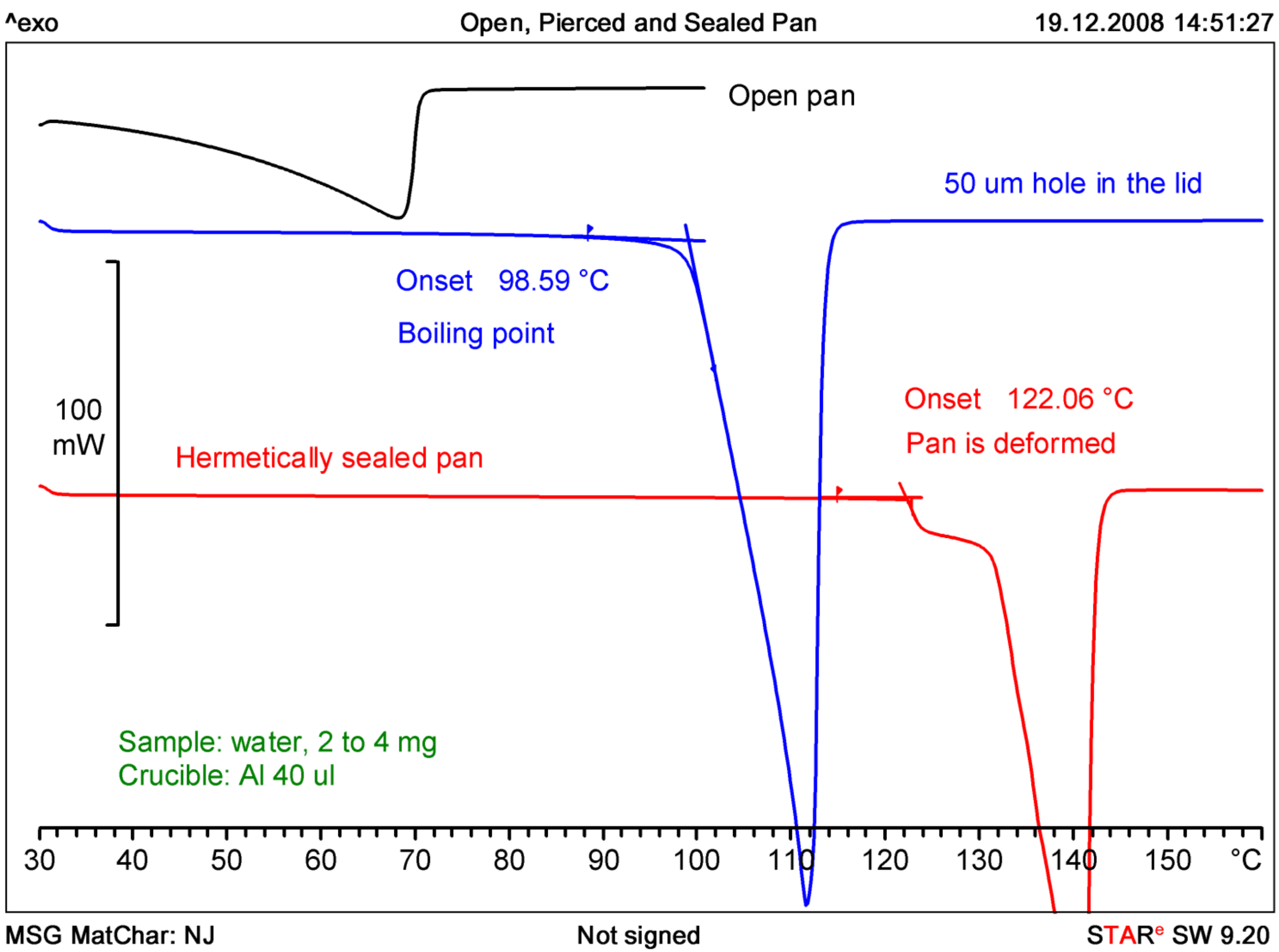


Cooled from 135 °C at 10 K/min and held isothermally at **90 °C**.

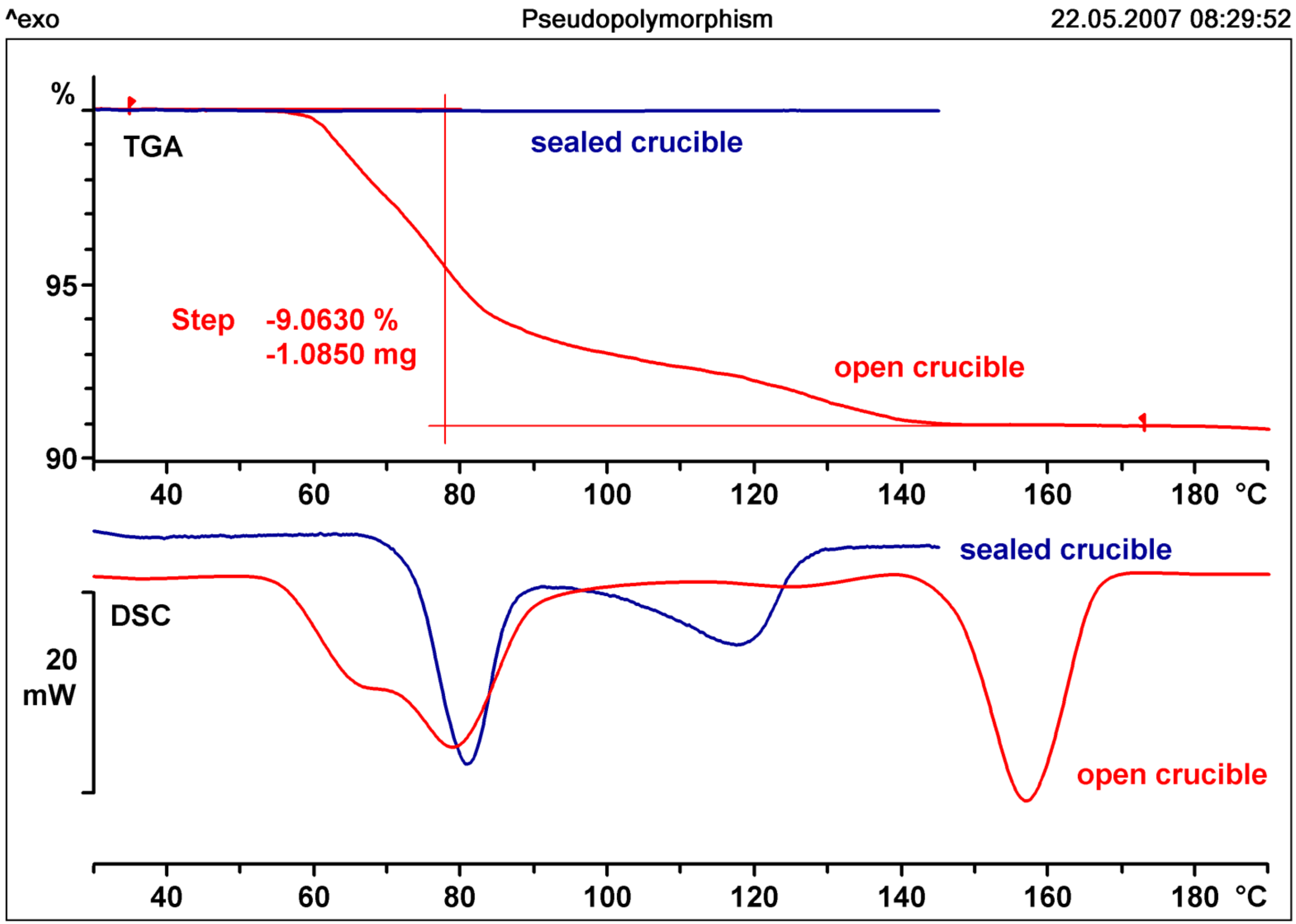
Cooled from 135 °C at 10 K/min and held isothermally at **100 °C**.

Hot-stage microscope enables visual observation of polymorphic transitions.

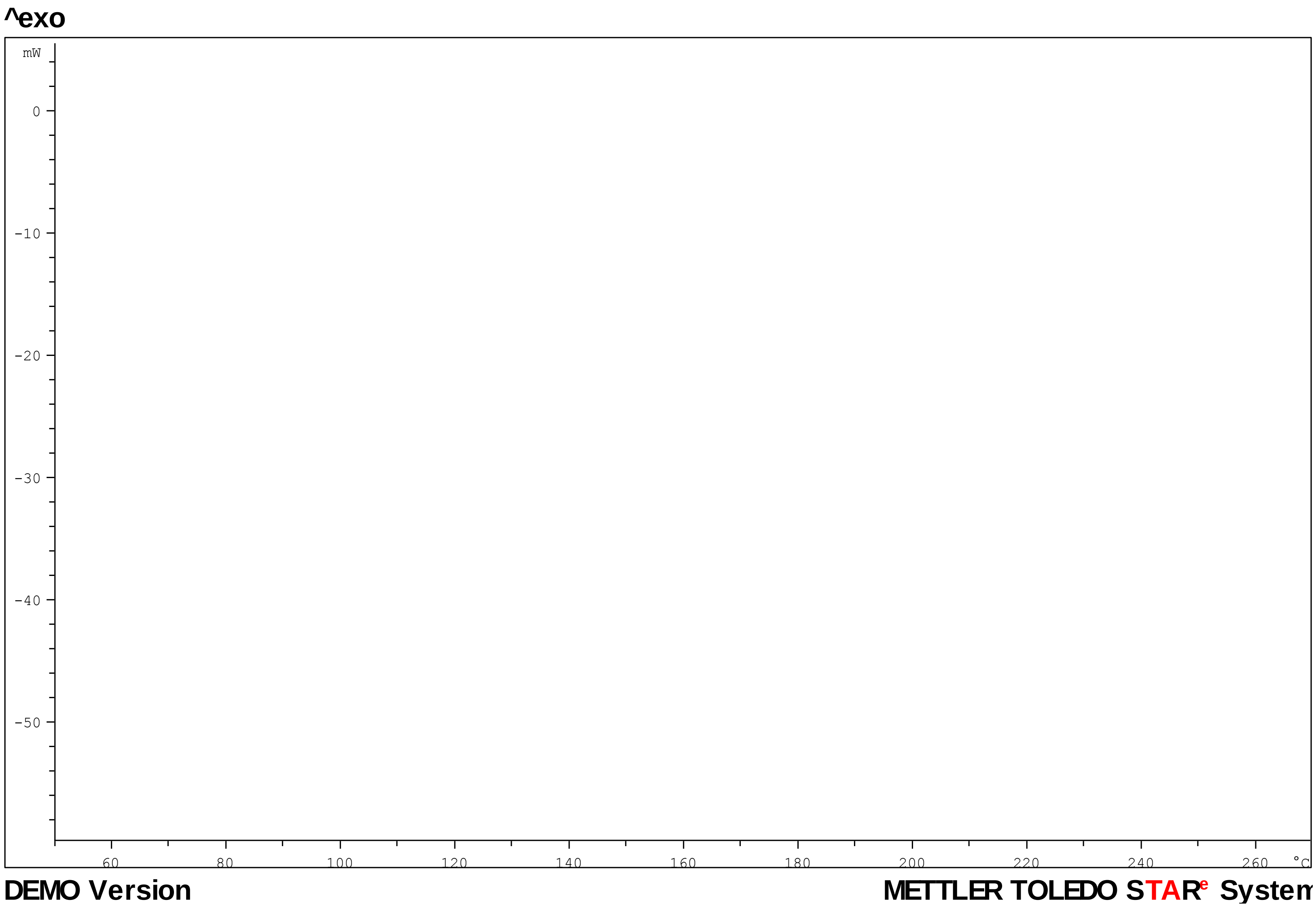
Influence of gas atmosphere on water vaporization



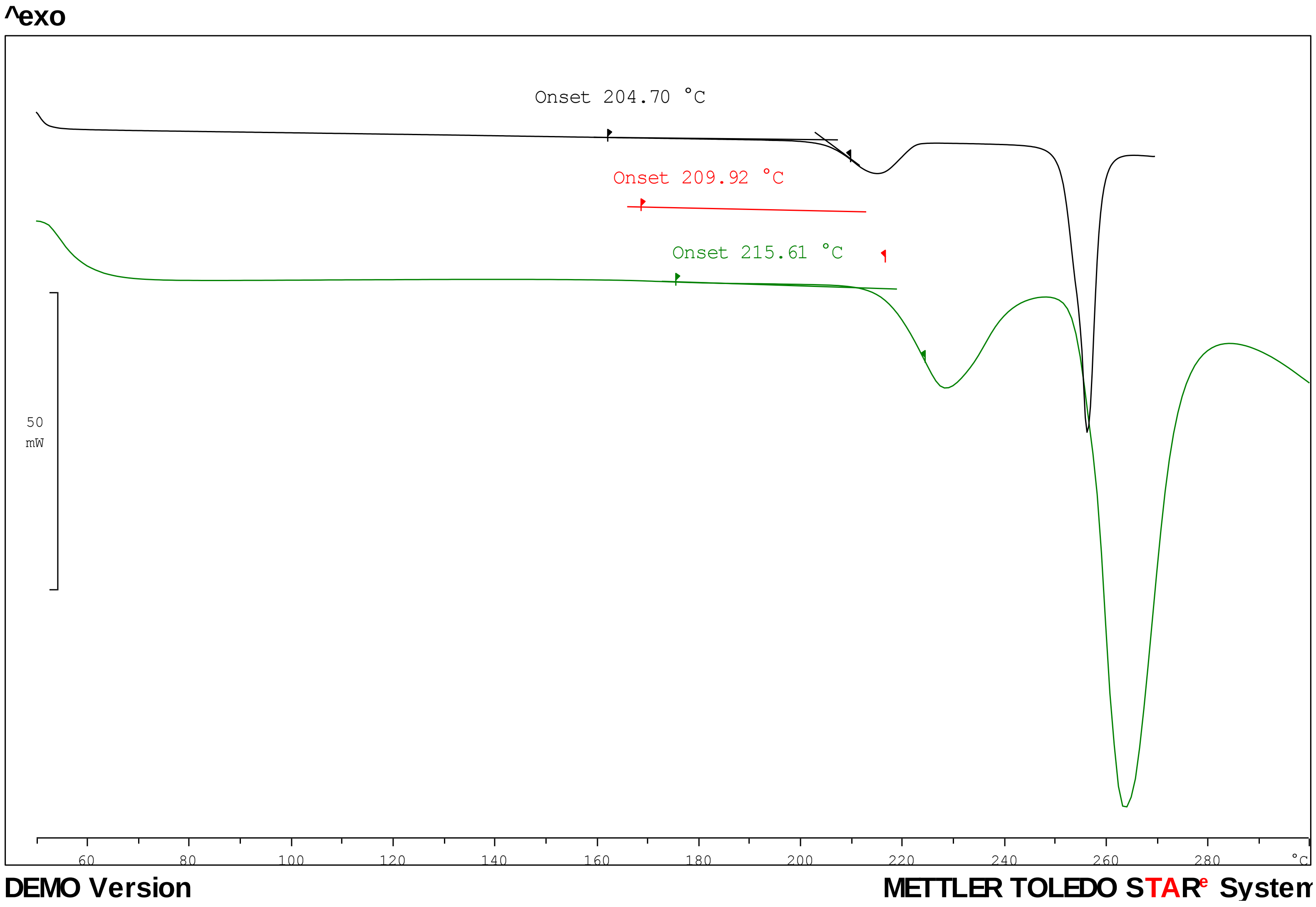
Pseudopolimorfismo



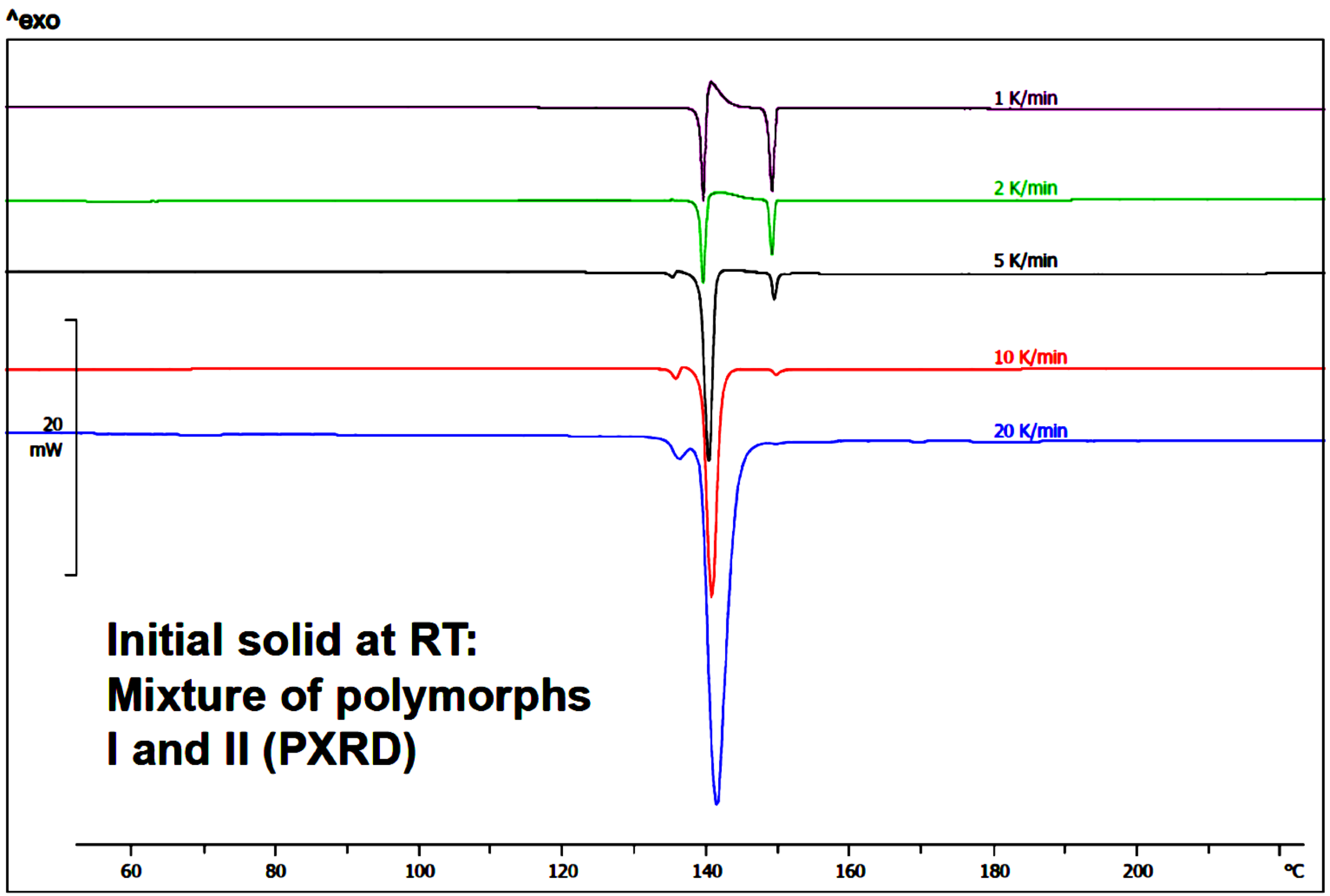
¿Fusión o transición?



¿Fusión o transición?



Efecto de la velocidad de calentamiento



Melting temperatures:

- **Polymorph I: 135ºC**
- **Polymorph II: 139ºC**
- **Polymorph III: 149ºC**

Processes observed:

- **Melting of I**
- **Melting of II**
- **Recrystallization of III**
- **Melting of III**

- Gráfica cedida por CRISFORMA (ICIQ) -

Basic equations

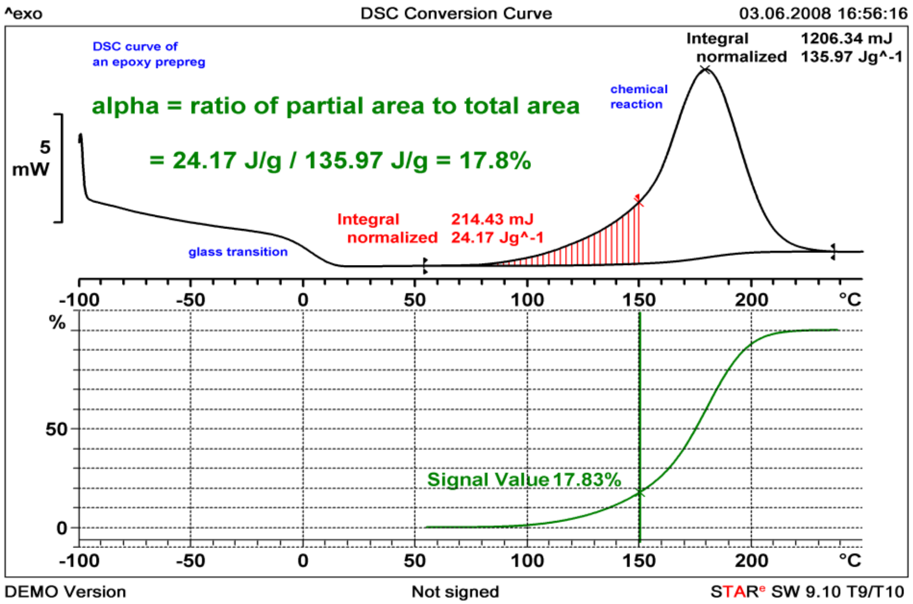
$$\frac{\mathrm{d}\alpha}{\mathrm{d}t} = k(T)\ f(\alpha)$$

$$k(T) = k_0\ e^{-E_a/RT}$$

$$f(\alpha) = (1-\alpha)^n$$

$$\frac{\mathrm{d}\alpha}{\mathrm{d}t} = \frac{\mathrm{d}H/\mathrm{d}t}{\Delta H_{tot}}$$

$$\alpha = \frac{\Delta H}{\Delta H_{tot}}$$



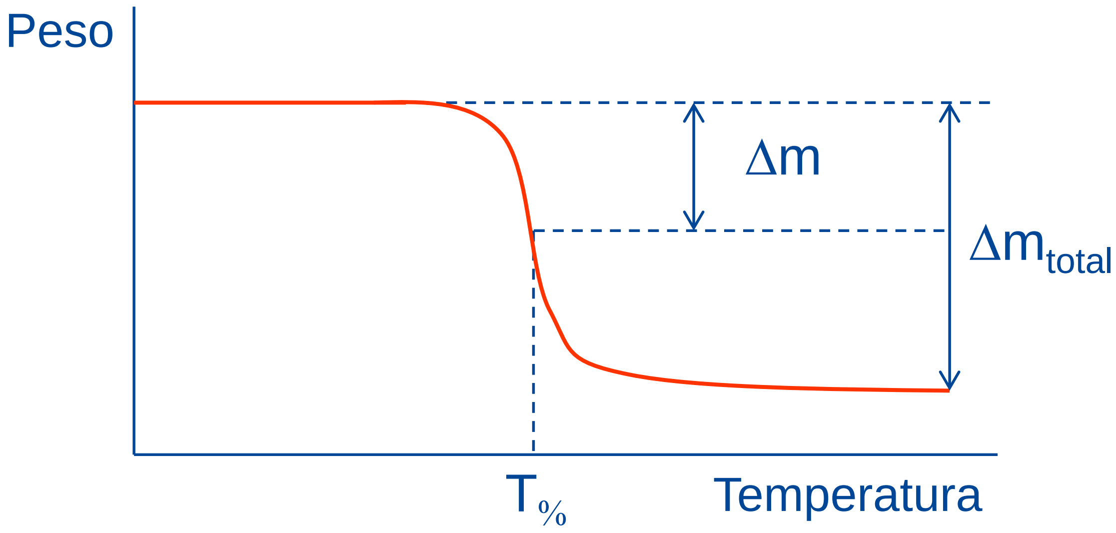
Grado de avance = dα/dt = f(concentración, temperatura)

- conversión = Salto normalizado

$$\alpha = \frac{\Delta m}{\Delta m_{tot}}$$

- grado de avance = DTG normalizado

$$\frac{d\alpha}{dt} = \frac{dm/dt}{\Delta m_{tot}}$$



La velocidad de reacción aumenta con la temperatura

Arrhenius (1889):

$$k(T) = k_0 \; e^{-E_a / RT}$$

- k: rate constant
- k_0: pre-exponential factor (rate constant at infinite temperature)
- E_a : activation energy ("temperature coefficient" of rate constant, typically 50 to 200 kJ/mol)
- R: gas constant (8.314 J/mol·K)

Modelo de orden n

A simple model is nth order kinetics (only for elementary reactions):

$$f(\alpha) = (1-\alpha)^n$$

Wilhelmy (1850)

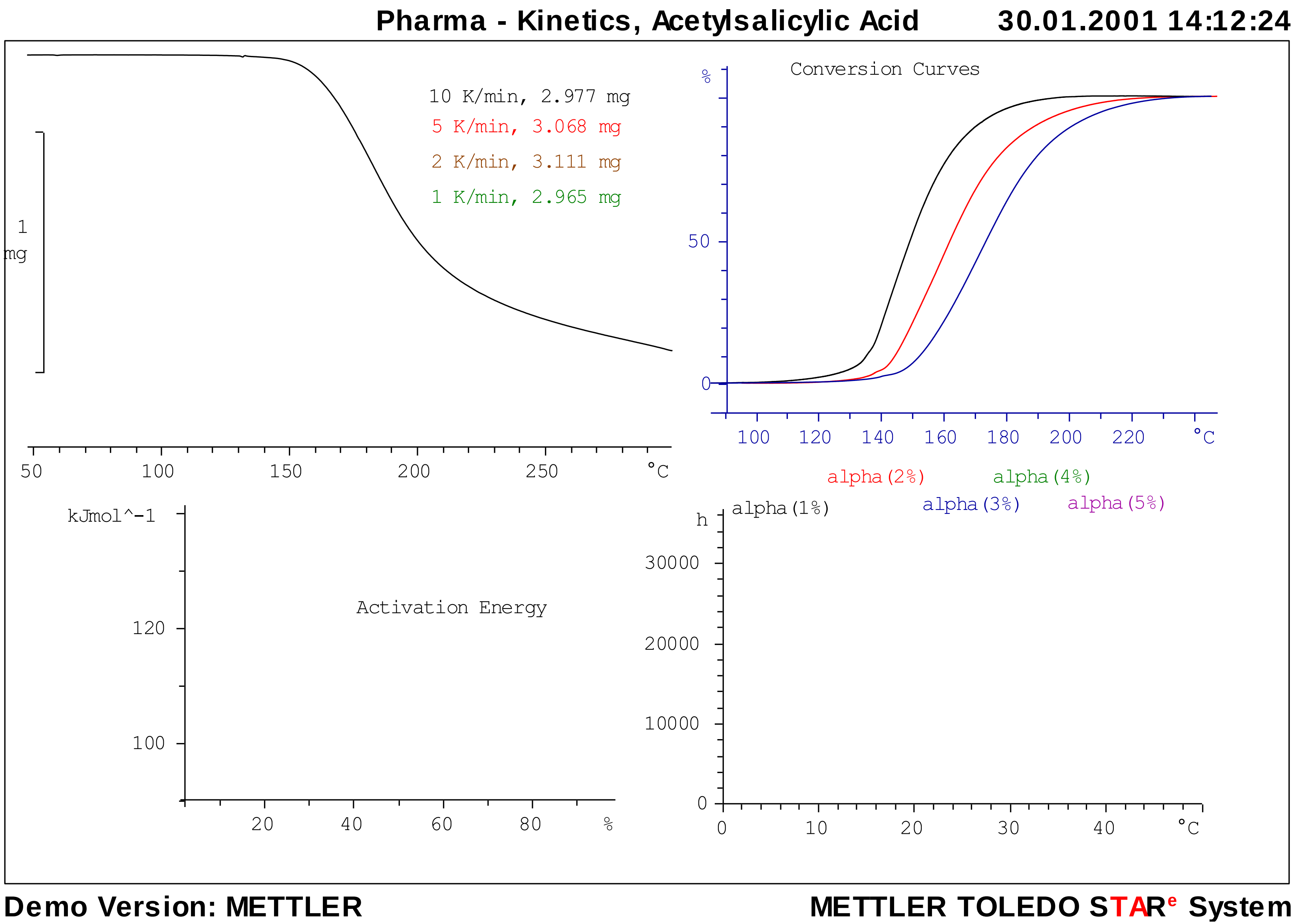
Options:

- 1 dynamic measurement
- ASTM E698 Kinetics (> 2 dynamic measurements)
- ASTM E1641 Kinetics (> 3 dynamic measurements)
- Isothermal nth order kinetics (1 or more isothermal measurements)

- Calculation of kinetic parameters k_0, E_a and n

(For a single isothermal measurement, k and n are calculated)

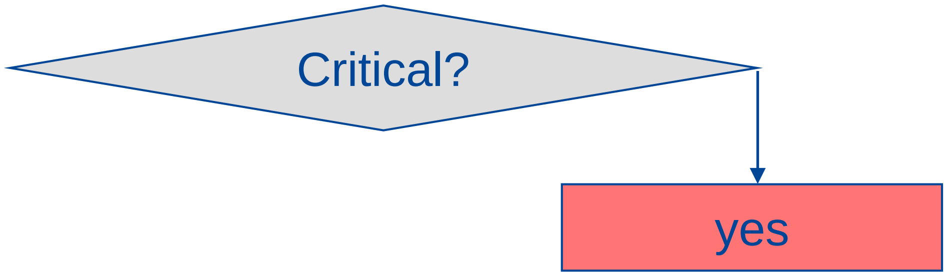
Estabilidad / Cinéticas



When is a reaction dangerous?

- \+ Heat of the reaction is big and exothermic ⇐ **DSC**
- \+ Reaction rate is fast (auto-acceleration)
- \+ Gaseous products are released ⇐ **TGA**
- \+ Apparatus is not pressure resistant
- \+ Secondary events affect the surroundings (e. g. burning, melting)

= **High risk of damage**



Fast screening

Screening

DSC: heat production, enthalpy change, rate of reaction

→ provides c_p , ΔH_r , ΔT_{adiab} , maximum power output, temperature range

→ HPDSC provides T_{decomp} = f(pressure):

TGA: weight, mass change, rate of change

→ provides amount of gas , $T_{decomp.}$

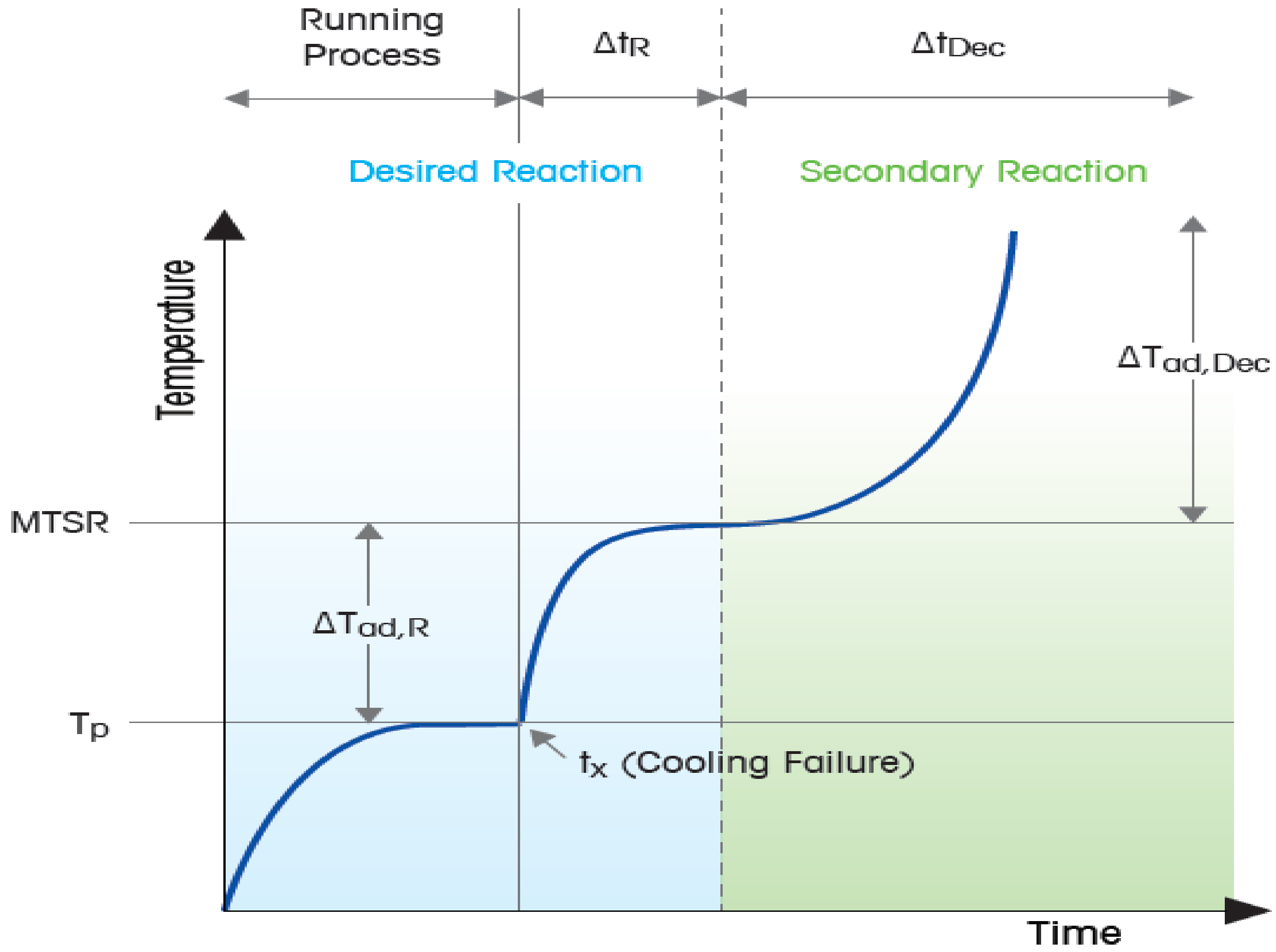
EGA: measurement of nature and concentrations of chemical species (TGA-MS, TGA-FTIR, TGA-GCMS, ...)

Risk evaluation of a chemical reaction, decomposition or other transition:

$$\Delta T_{adiabat} = \frac{\Delta h}{c_p}$$

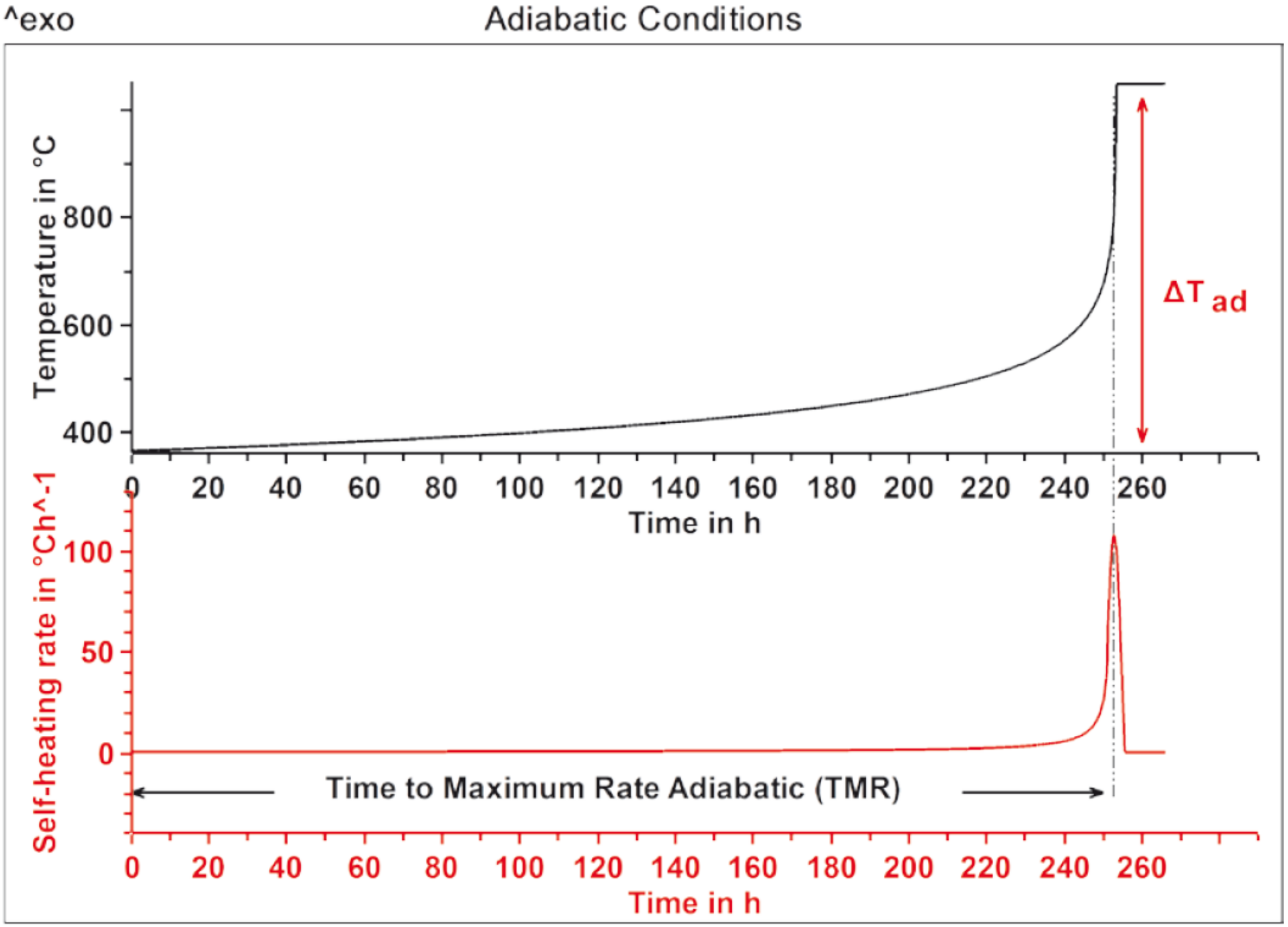
Exothermic reaction enthalpy Δh in J/g	Adiabatic temperature increase $\Delta T_{adiabat}$ in K	Hazard potential
0 … 50	less than 50	low
50 … 500	less than 200	high
500 … ca. 25 000	greater than 200	very high

Runaway Scenarios

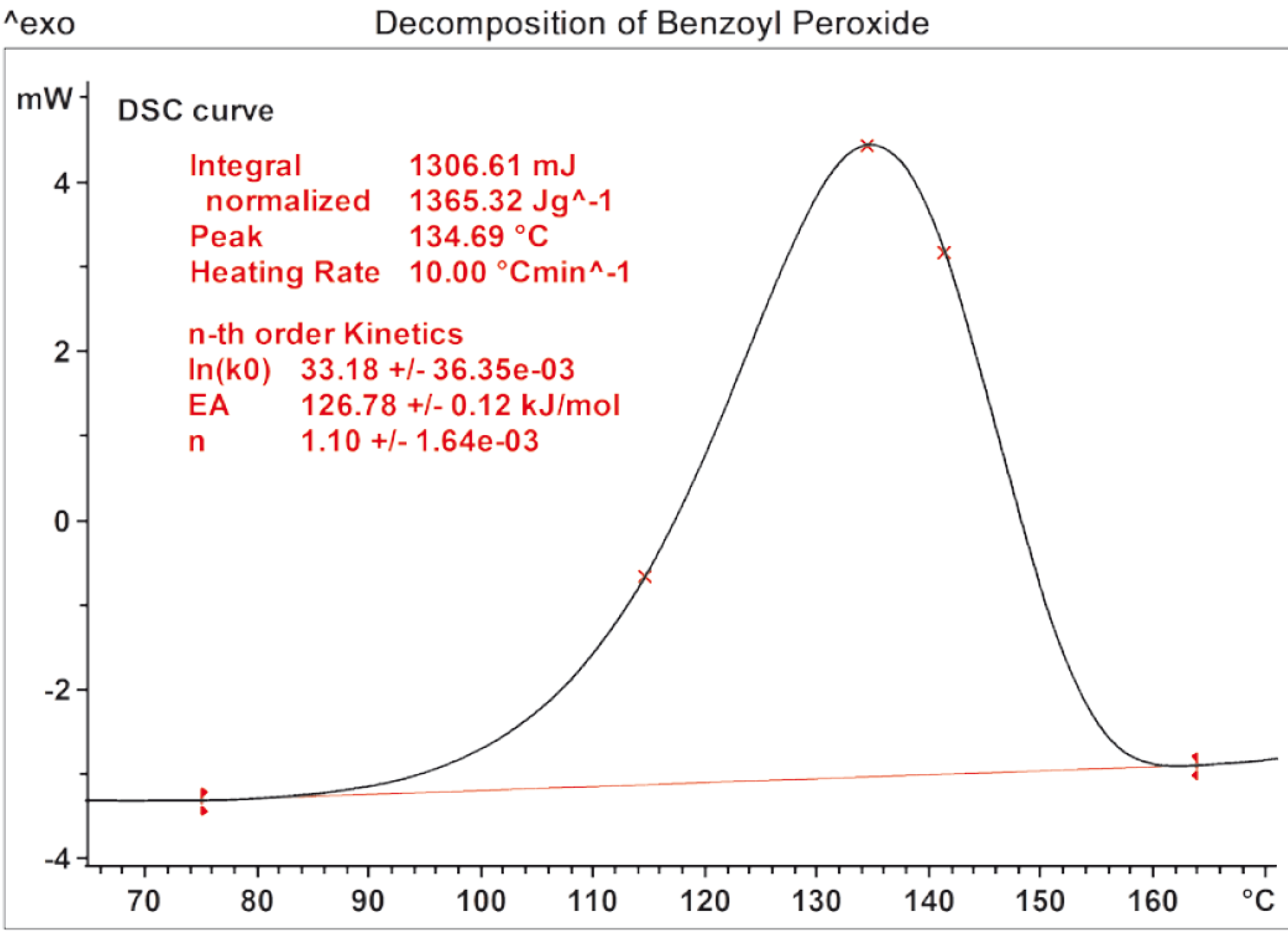


Condiciones adiabáticas

TMR: Time to Maximum Rate

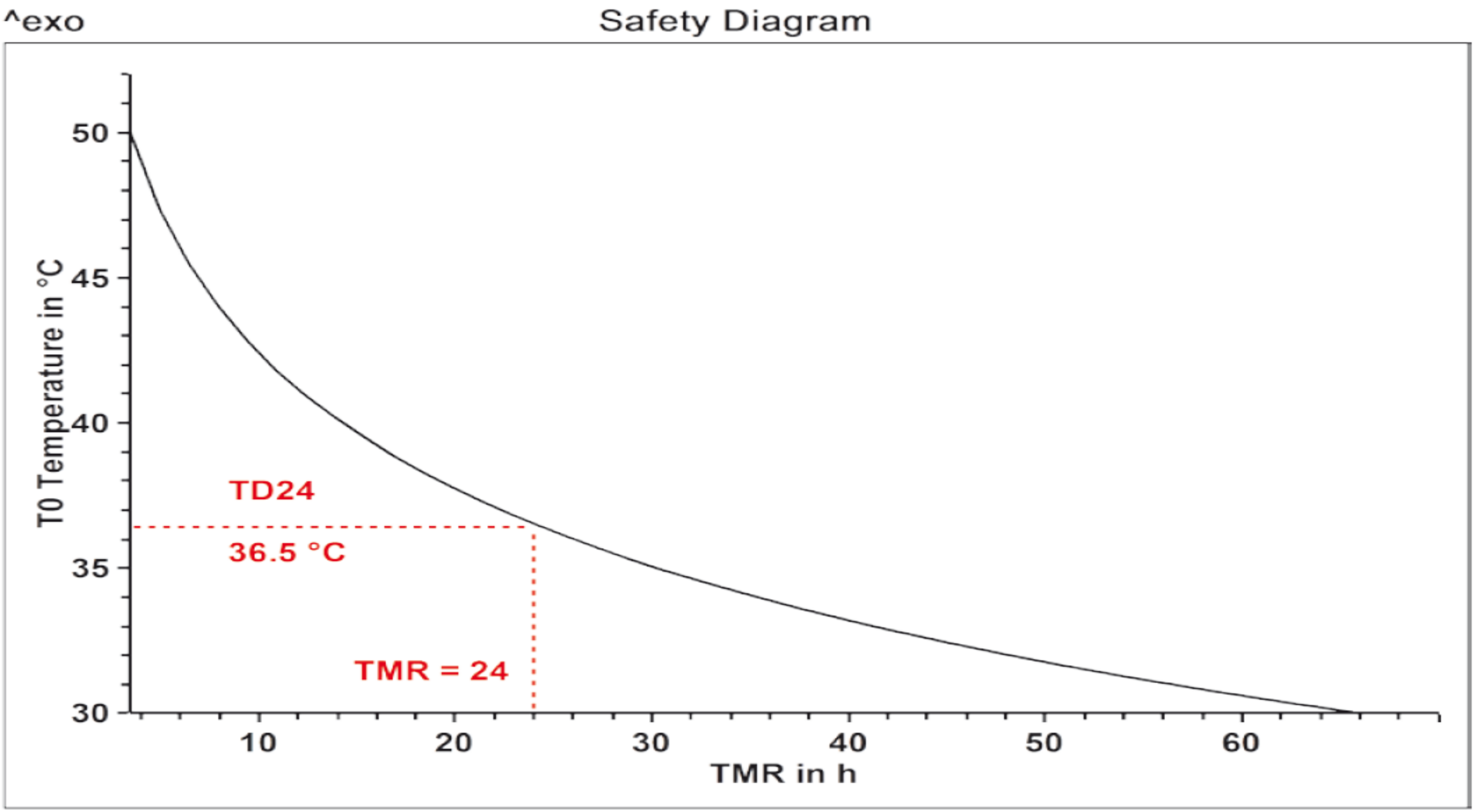


Kinetic behavior



TMR: Time to Maximum Rate

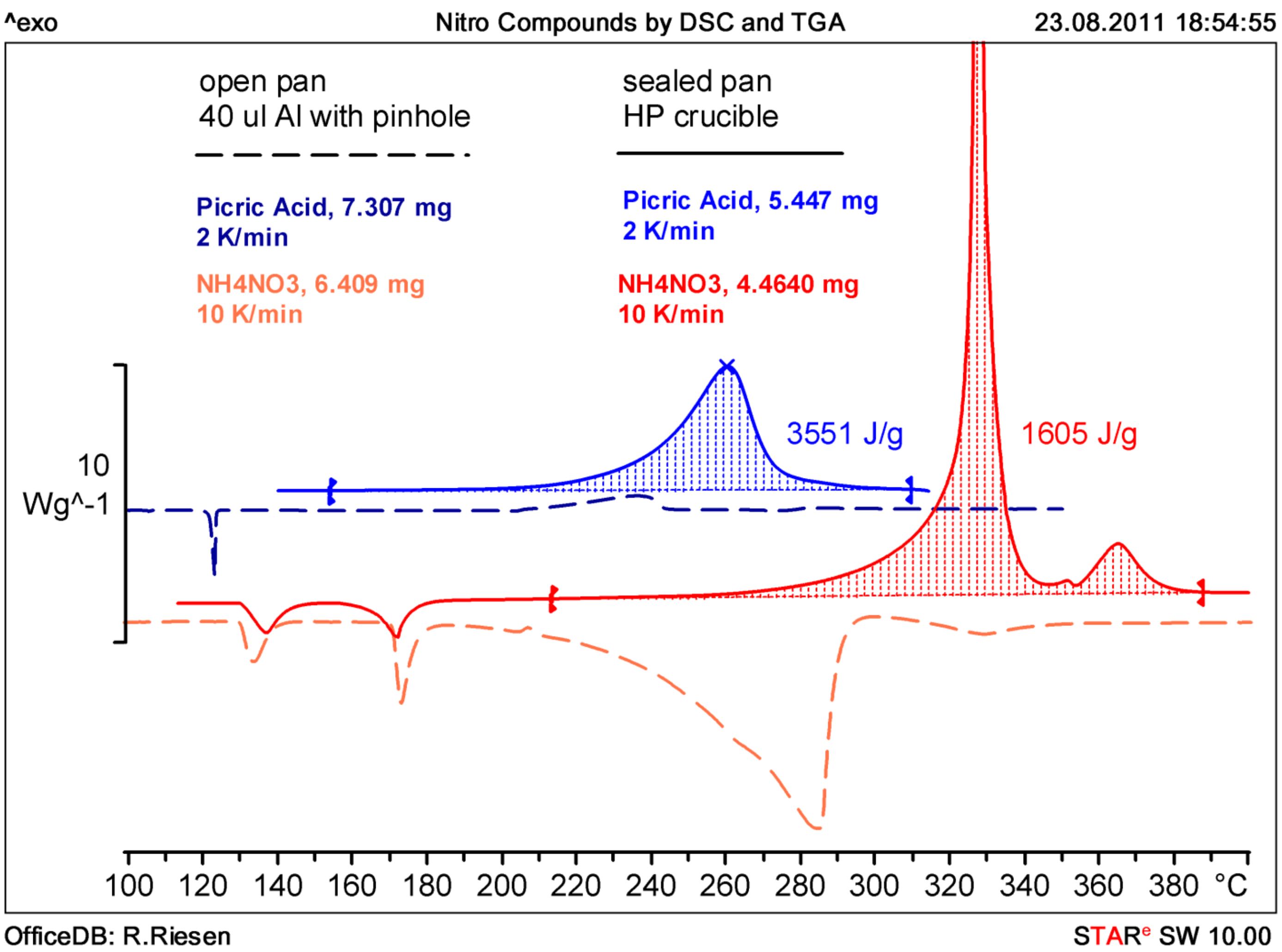
TD24: Temperatura a la cual el TMR es de 24 horas

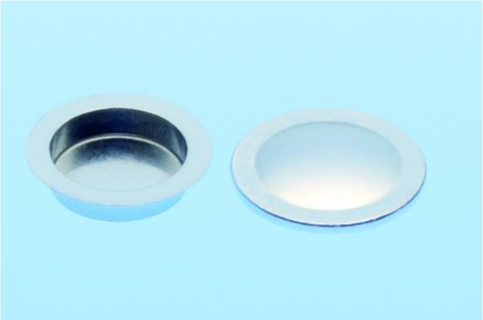


Severidad y Probabilidad

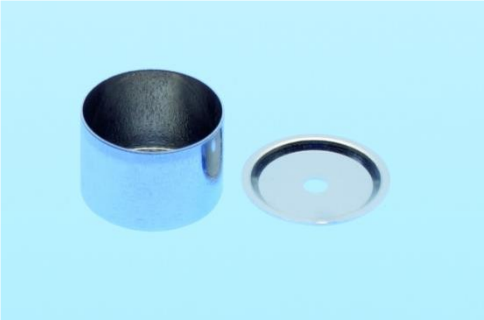
Risk/Factor	ΔT_{ad} in K	TMR in hours
High	>200	<8
Medium	50< ΔT_{ad} <200	8<TMR<24
Low	<50	>24

DSC open / closed system (pan)

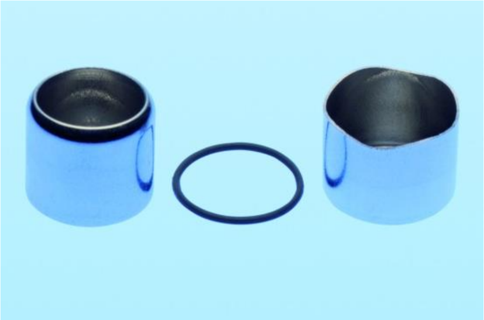




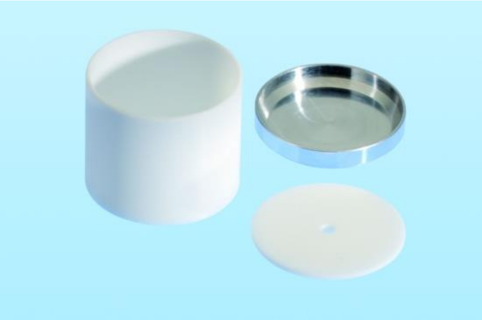
Standard crucible aluminum, 40 µL



Platinum crucible 30, 70 and 150 µL



Medium pressure crucible, steel 120 µL 2 MPa



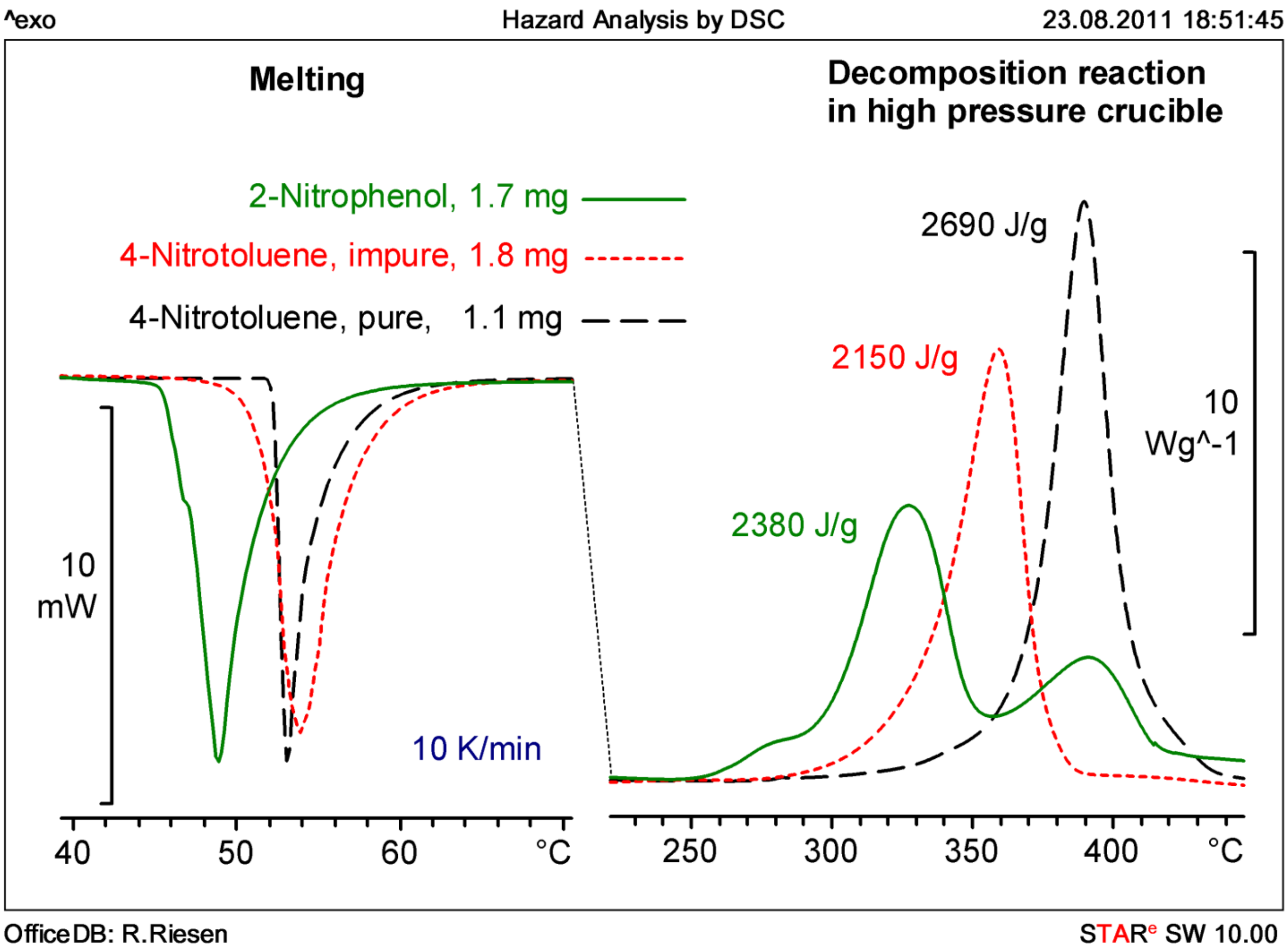
Alumina, 70 µL

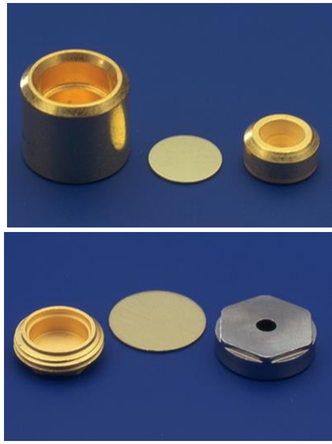
Gold, 40 µL

High pressure crucible 150 MPa, steel/gold

DSC Safety investigations: mostly high pressure pans are used

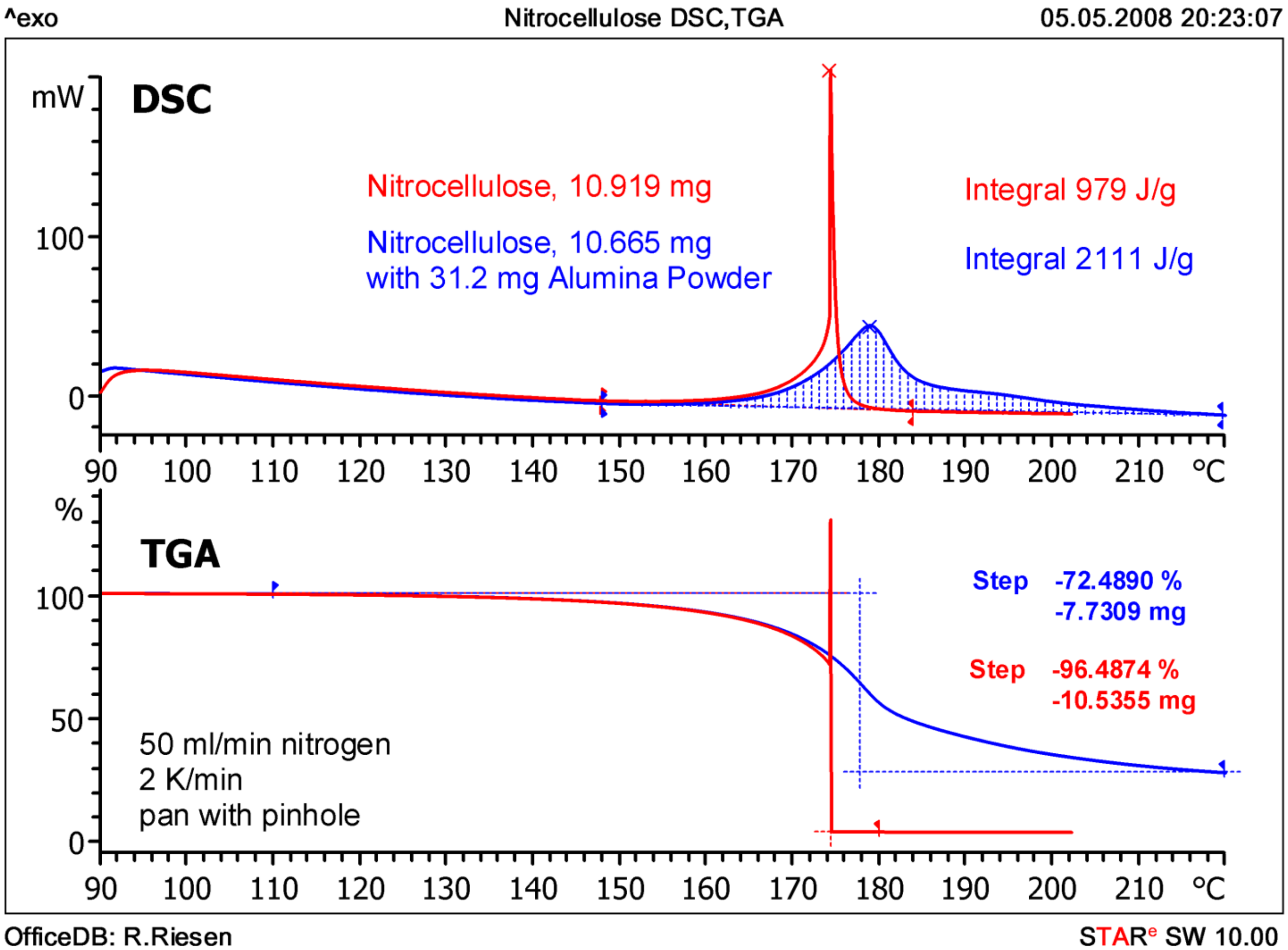
Influencia de la pureza en la temperatura de descomposición

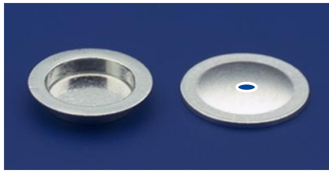




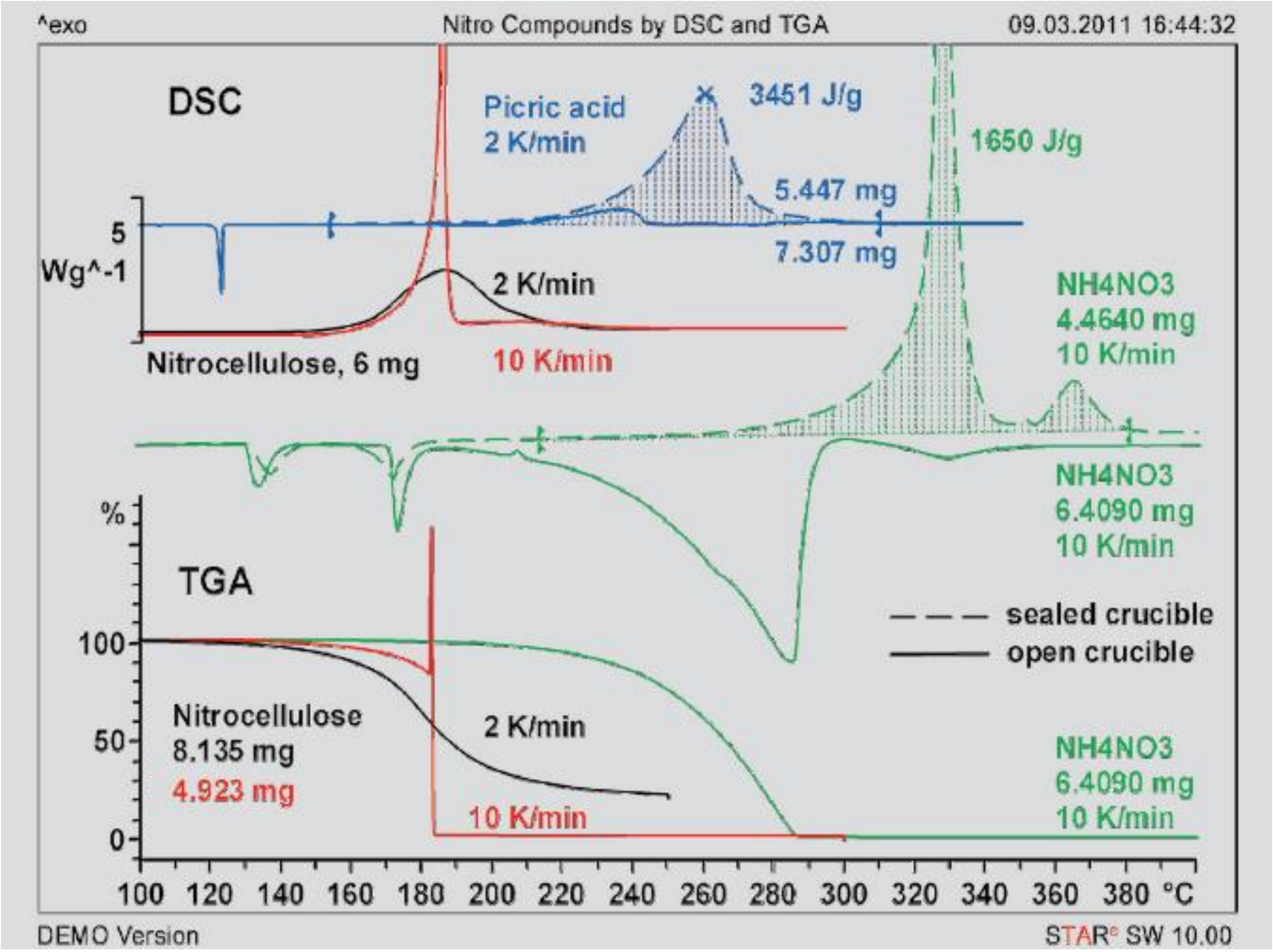
Efecto de añadir un polvo inerte en la muestra

open system:

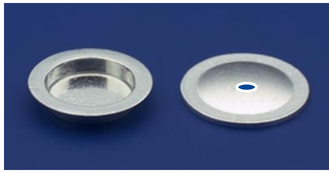




Efecto de la velocidad de calentamiento (Nitrocelulosa)



open system:



Conclusion: Choice of the Technique

	DSC	TGA	TOA
Melting point, melting range	●	•	○
Heat of fusion	●		
Polymorphism	●		○
Glass transition	●		
Thermal stability		●	◦
Kinetics of decomposition	○	●	
Purity, phase diagram	●		◦
Evaporation, desorption	◦	●	
Compositional analysis	○	○	
Pseudo polymorphism	○	○	◦
Interactions, compatibility	○		