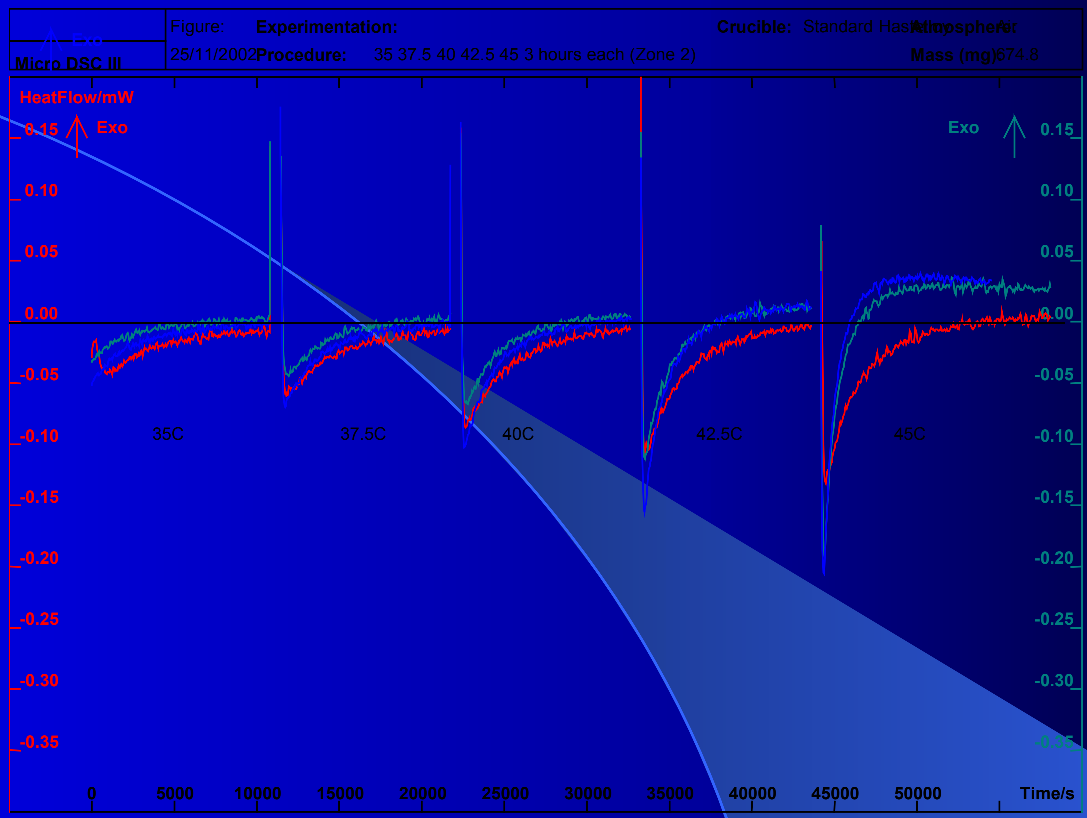
Applying Microcalorimetry to Characterize the Stability and Compatibility of Pharmaceutical Systems



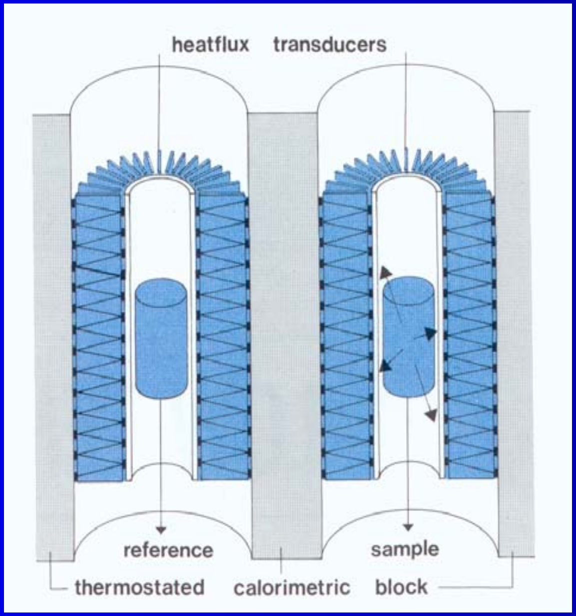
ThermalCal International

Outline

- Microcalorimetry: The Universal Detector
- Overview of Microcalorimetry Stability and Compatibility Testing
- Overview of Commercially Available Microcalorimeters

Microcalorimetry: The Universal Detector

Isothermal Microcalorimetry



Heat Flow Measured as Difference Between Sample and Reference

Isothermal Temperature Usually Maintained by Large Volume Constant Temperature Bath

Typical Detection Limit ~ +/-0.5 uJ/sec

Sample Sizes Range from 1ml to 150ml

Temperature Range ~ 5 to 90 °C

$$dQ/dt = \Delta H * dn/dt$$

$\Delta G = \Delta H - T \Delta S$

Microcalorimetry: The Universal Detector

Isothermal Microcalorimetry

Chemical Processes

Hydrolysis, oxidation, free radical, etc. all have large heats of reaction.

Ideally, degradation rates of less than 1% per year can be predicted in a matter of days.

Physical and Bio Processes

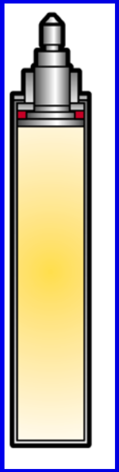
Crystallization, polymorph conversions, bacterial growth.

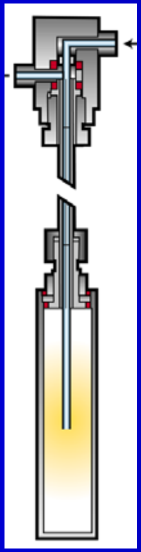
$\Delta G = \Delta H - T \Delta S$

Microcalorimetry: The Universal Detector

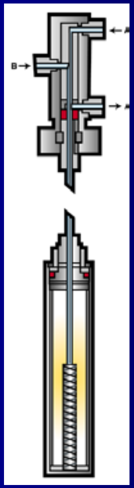
Isothermal Microcalorimetry

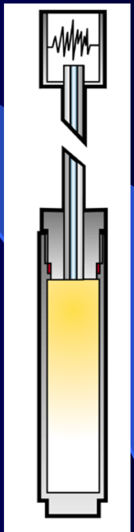
Closed or Open Systems


Batch


Fluid


Batch Mixing


Fluid Mixing


Pressure

$\Delta G = \Delta H - T \Delta S$

Microcalorimetry: The Universal Detector

Isothermal Microcalorimetry

$$Q_{ox} = \Delta H_{ox} * n_{ox}$$

$$Q_{hyd} = \Delta H_{hyd} * n_{hyd}$$

etc.

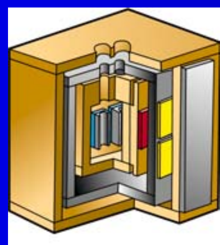
etc.

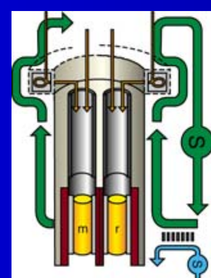
$$Q_{measured} = \Sigma_i \Delta H_i * n_i$$

Standard Addition

Microcalorimetry: The Universal Detector

Scanning Microcalorimetry (HSDSC)





Heat Flow Measured as Difference Between Sample and Reference

Temperature Ramped by Peltier Elements or Fluid Circulation. Heat/Cool. Isothermal.

Typical Detection Limit ~.2-5 uJ/sec

Sample Sizes Range from .3 ml to 1 ml

Slow Scan Rates .001 – 1 °C /min

Temperature Range ~ -45 to 120 °C

$$d(dQ/dt)/dT = \Delta H * d(dn/dt)/dT$$

$\Delta G = \Delta H - T \Delta S$

Microcalorimetry: The Universal Detector

Scanning Microcalorimetry (HSDSC)

Chemical Processes

Thermally induced chemical reactions.

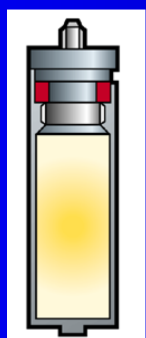
Physical and Bio Processes

Glass transitions, thermally induced crystallization and polymorph conversions, protein denaturation.

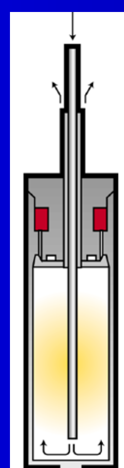
Microcalorimetry: The Universal Detector

Scanning Microcalorimetry (HSDSC)

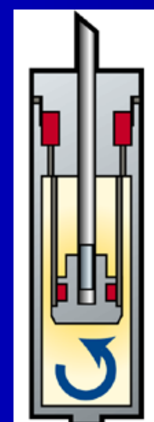
Closed or Open Systems



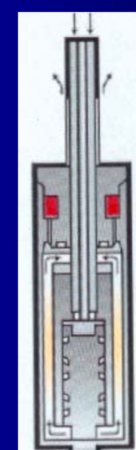
Batch



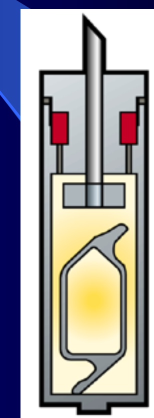
Fluid



Batch Mixing



Fluid Mixing



Wetting

$\Delta G = \Delta H - T \Delta S$

Microcalorimetry: The Universal Detector

Detection Limits

- If a significant signal of 1 μW is detectable, and if it is assumed that the reaction enthalpy ΔH_R, is 50 kJ/mole for the compound, it is possible to estimate the rate of reaction x :
- $x = (10^{-6}$ J/s / $50x10^{3}$ J/mole) = $2x10^{-11}$ mole/sec,
  or $1.2x10^{-9}$ mole/min,
  or $1.7x10^{-6}$ mole/day,
  or $6.3x10^{-4}$ mole/year

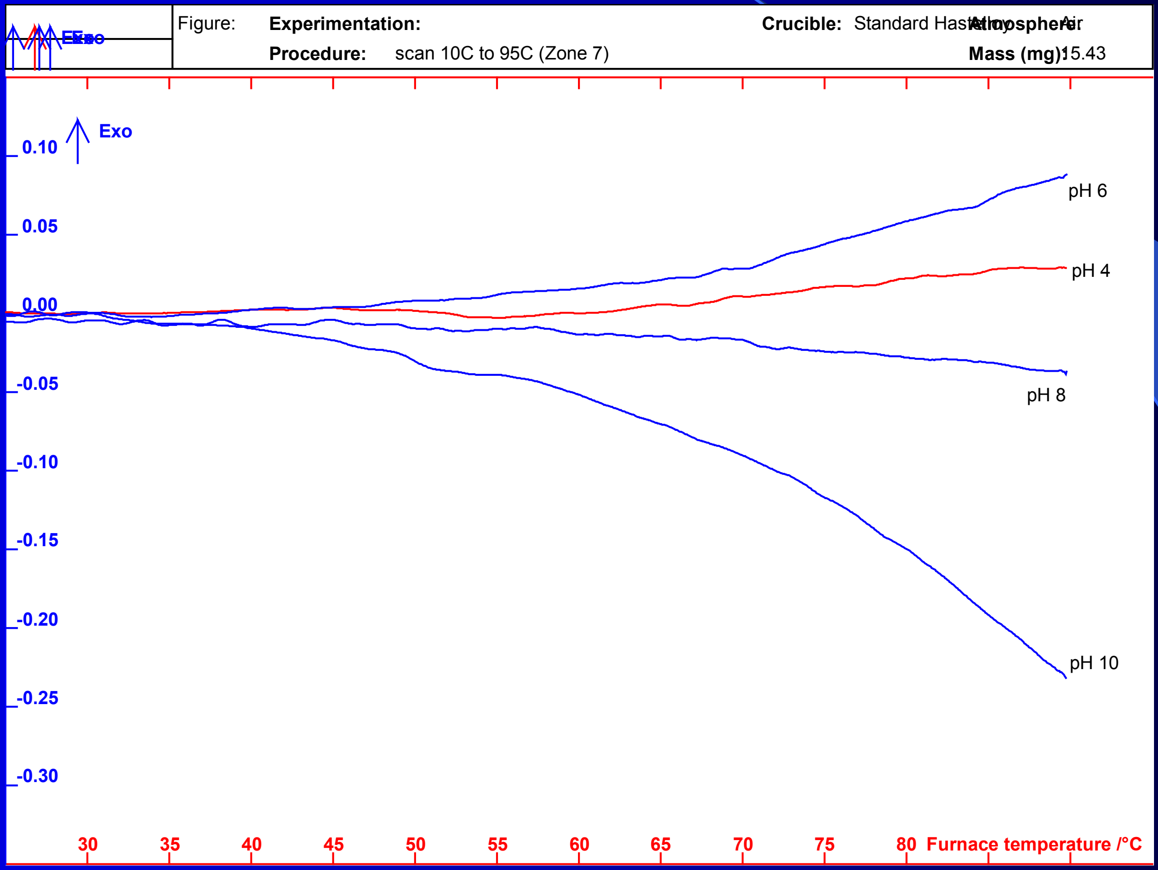
- It is also possible to use the Arrhenius law for different temperatures :

$$d\alpha/dt = k\,(1-\alpha)^n = k0\,\exp(-E/RT)\,(1-\alpha)^n$$

- $d\alpha/dt$ is proportional to the calorimetric signal (dH/dt)
- Plotting Log(dH/dt) versus 1/T yields the kinetic parameters of the reaction.

Microcalorimetry: Stability Testing

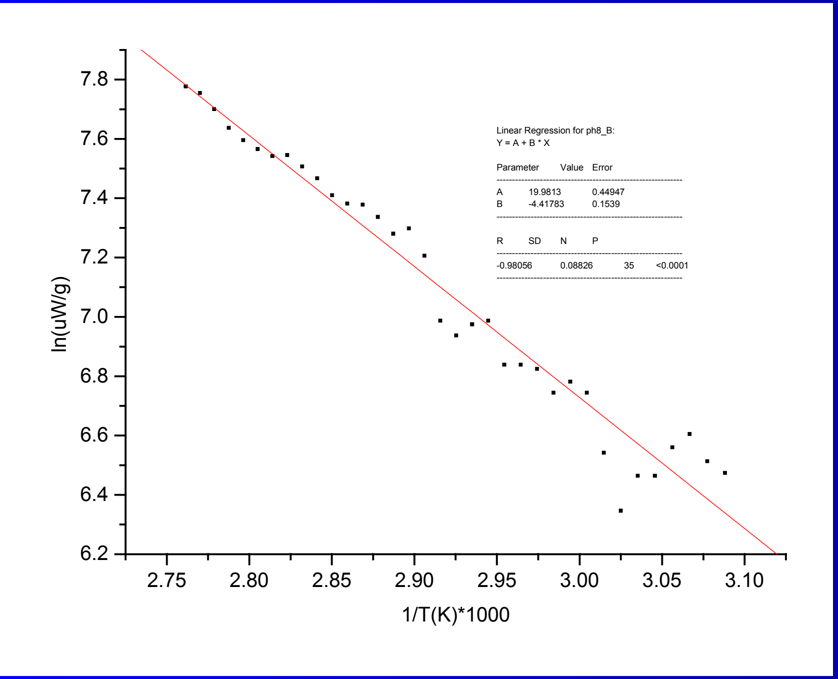
Reaction in Solution: pH Effect

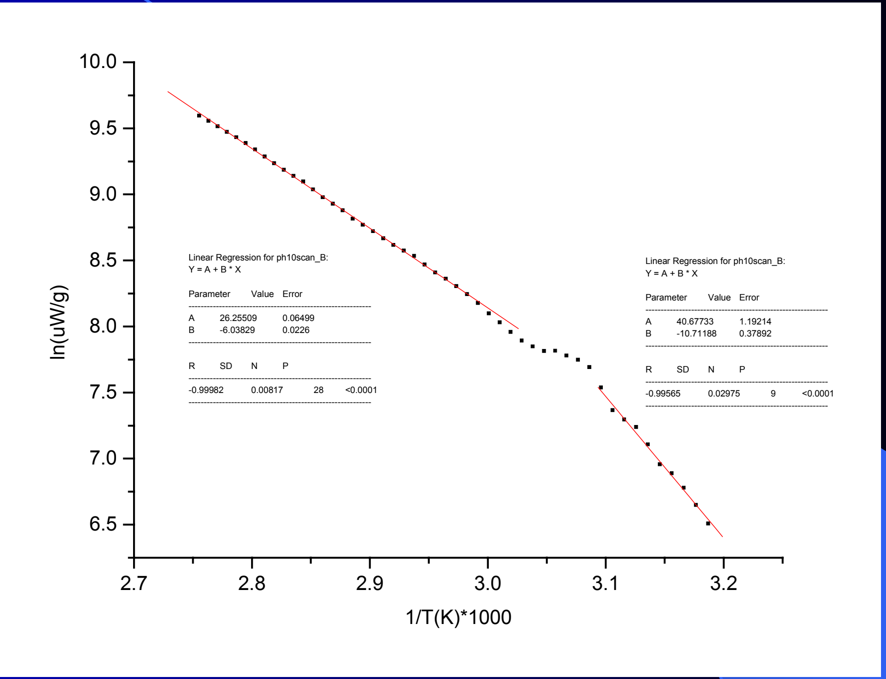


$\Delta G = \Delta H - T \Delta S$

Microcalorimetry: Stability Testing

Reaction in Solution: pH Effect

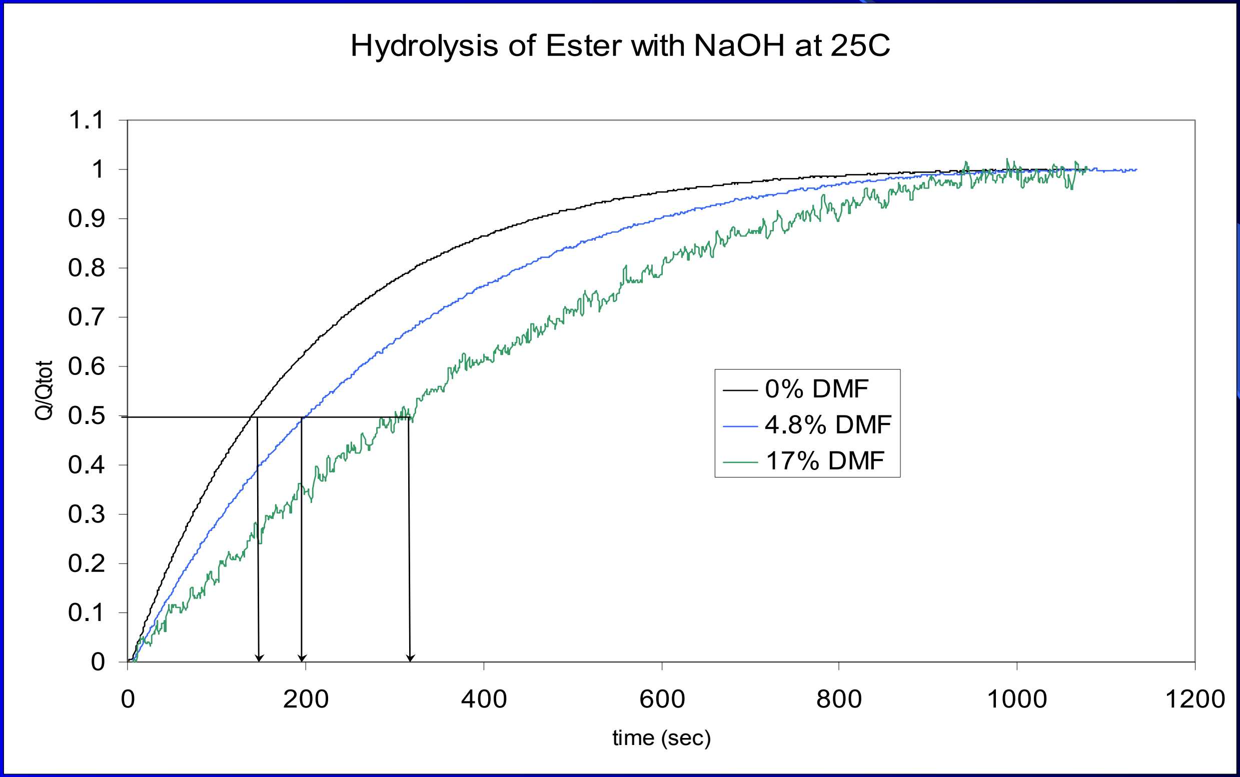




$\Delta G = \Delta H - T \Delta S$

Microcalorimetry: Stability Testing

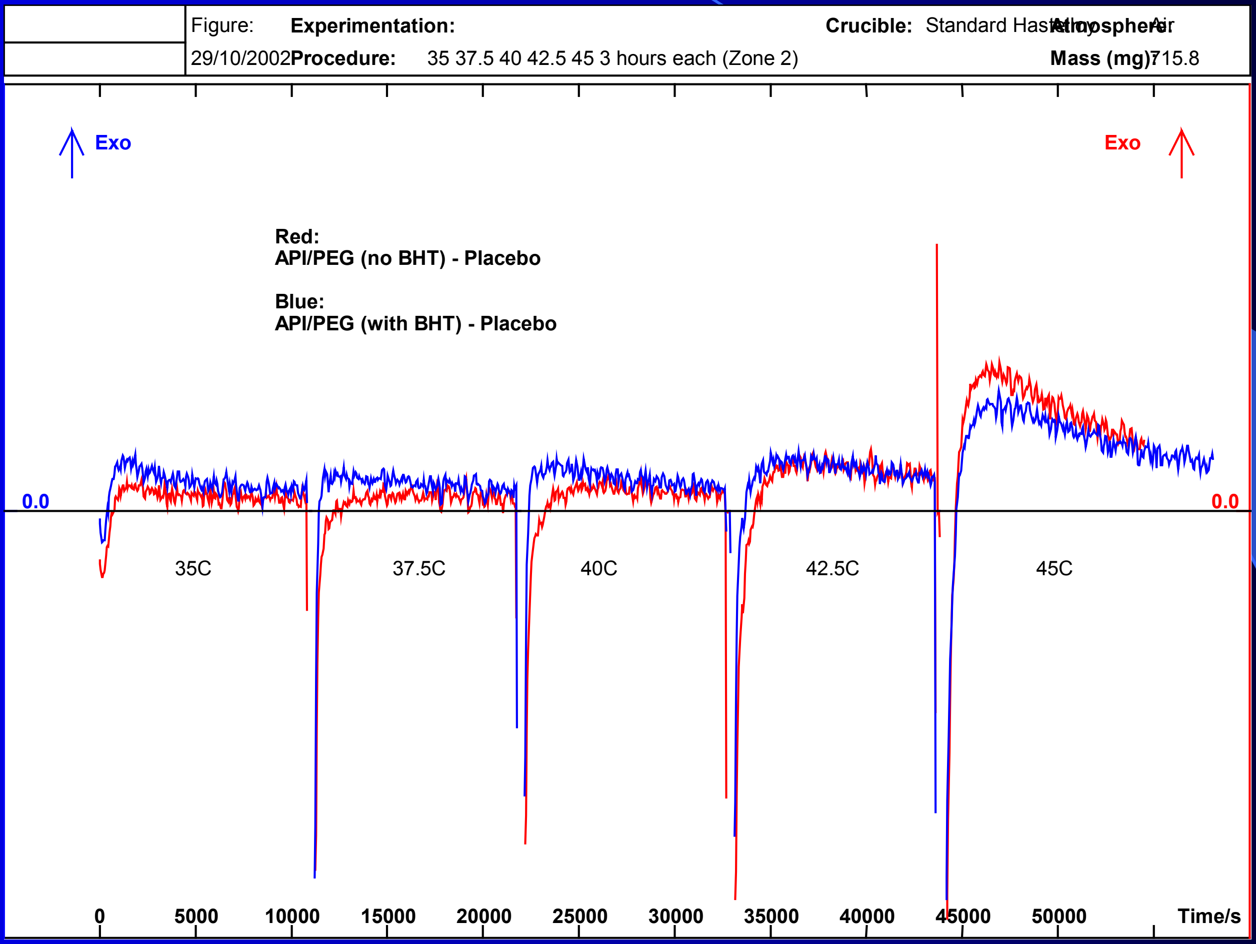
Reaction in Solution: Solvent Effect



$\Delta G = \Delta H - T \Delta S$

Microcalorimetry: Stability Testing

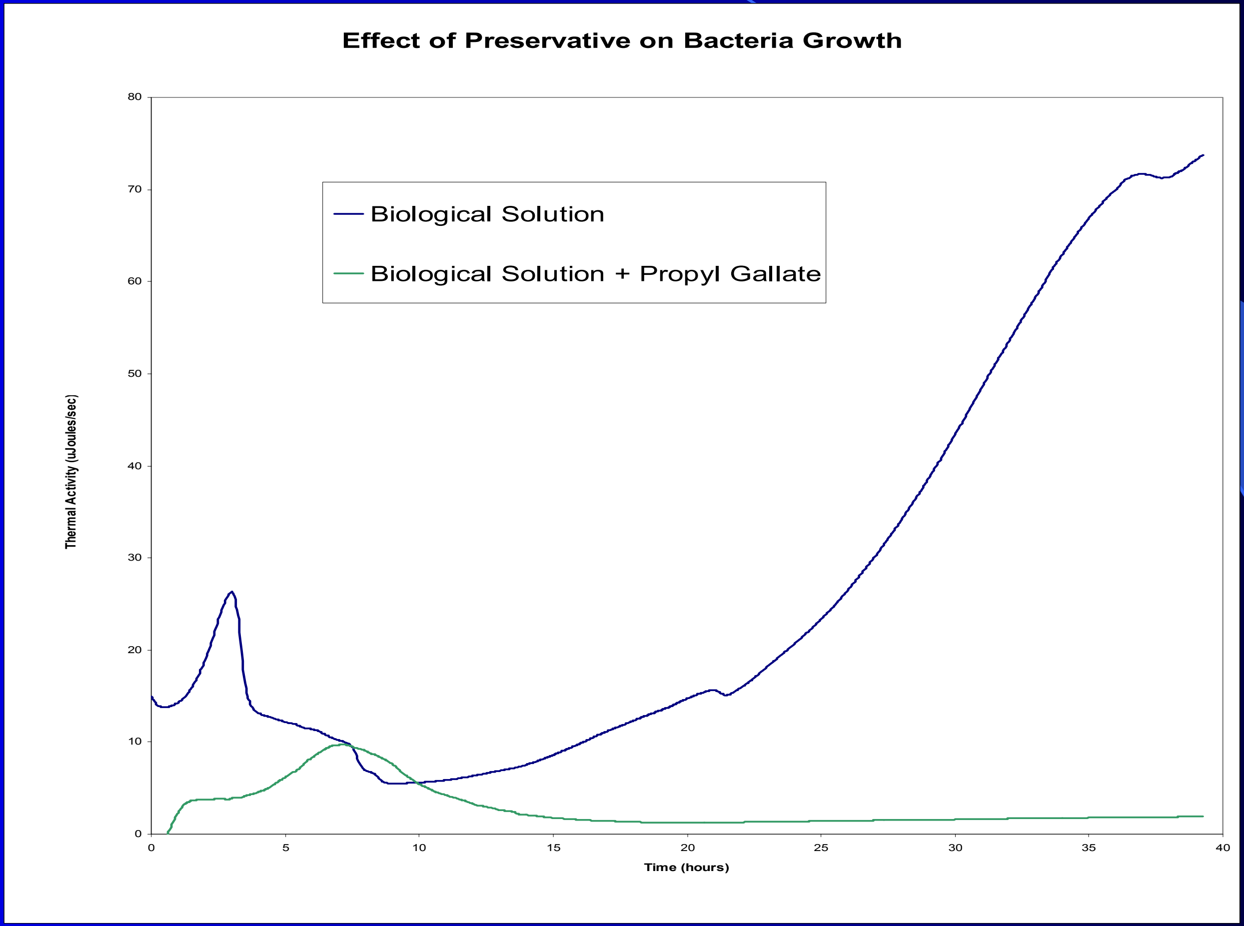
API Stability in PEG: Effect of BHT



$\Delta G = \Delta H - T \Delta S$

Microcalorimetry: Stability Testing

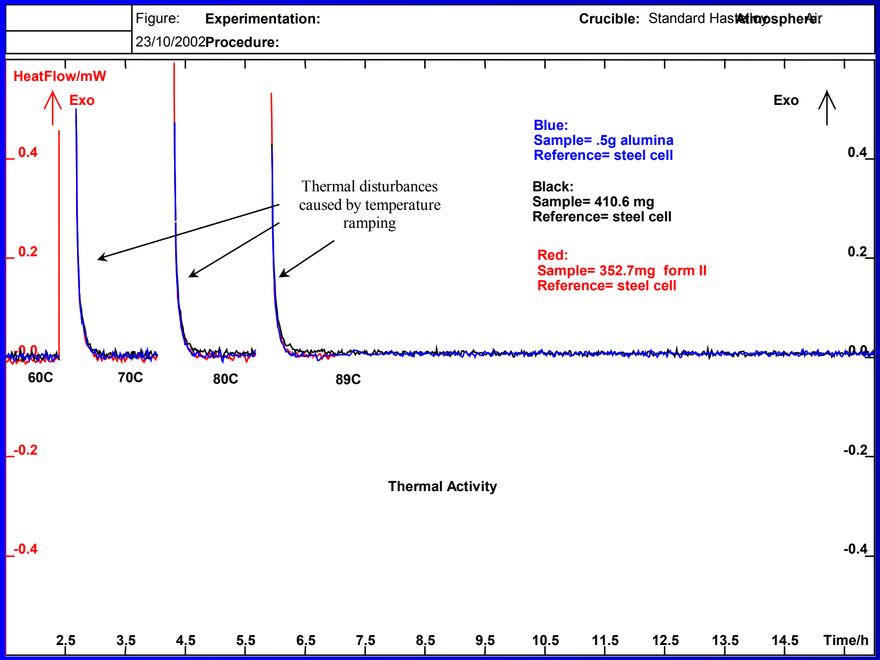
Solution Stability: Impact of Preservative

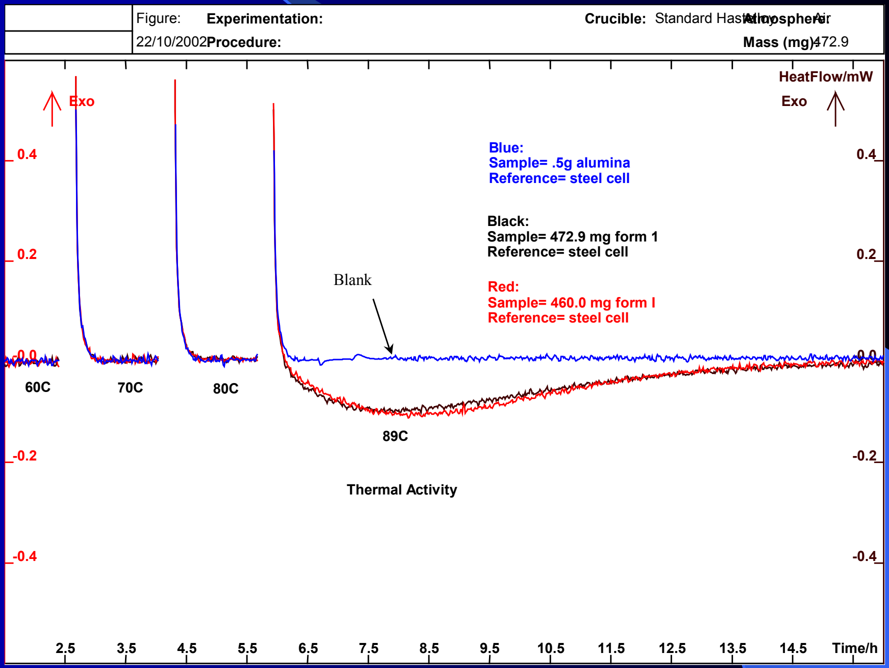


$\Delta G = \Delta H - T \Delta S$

Microcalorimetry: Stability Testing

Solid State Stability: Real-time Monitoring of Polymorph Conversion

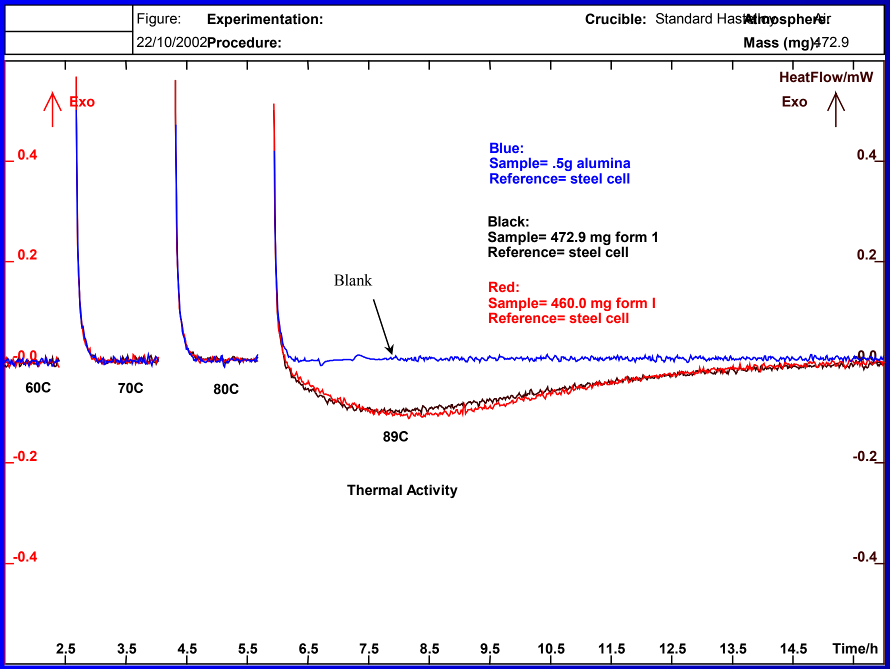


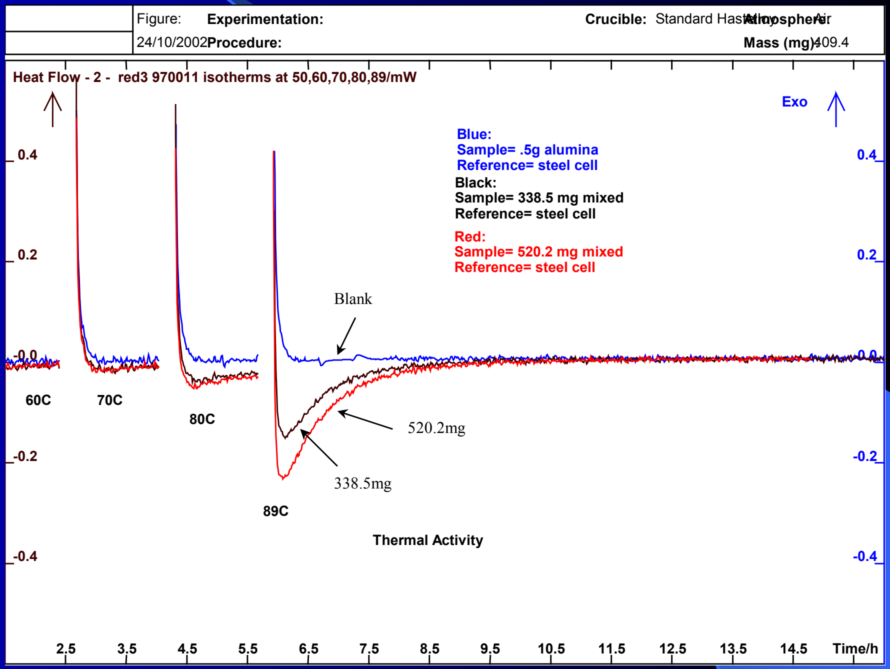


$\Delta G = \Delta H - T \Delta S$

Microcalorimetry: Stability Testing

Solid State Stability: Real-time Monitoring of Polymorph Conversion

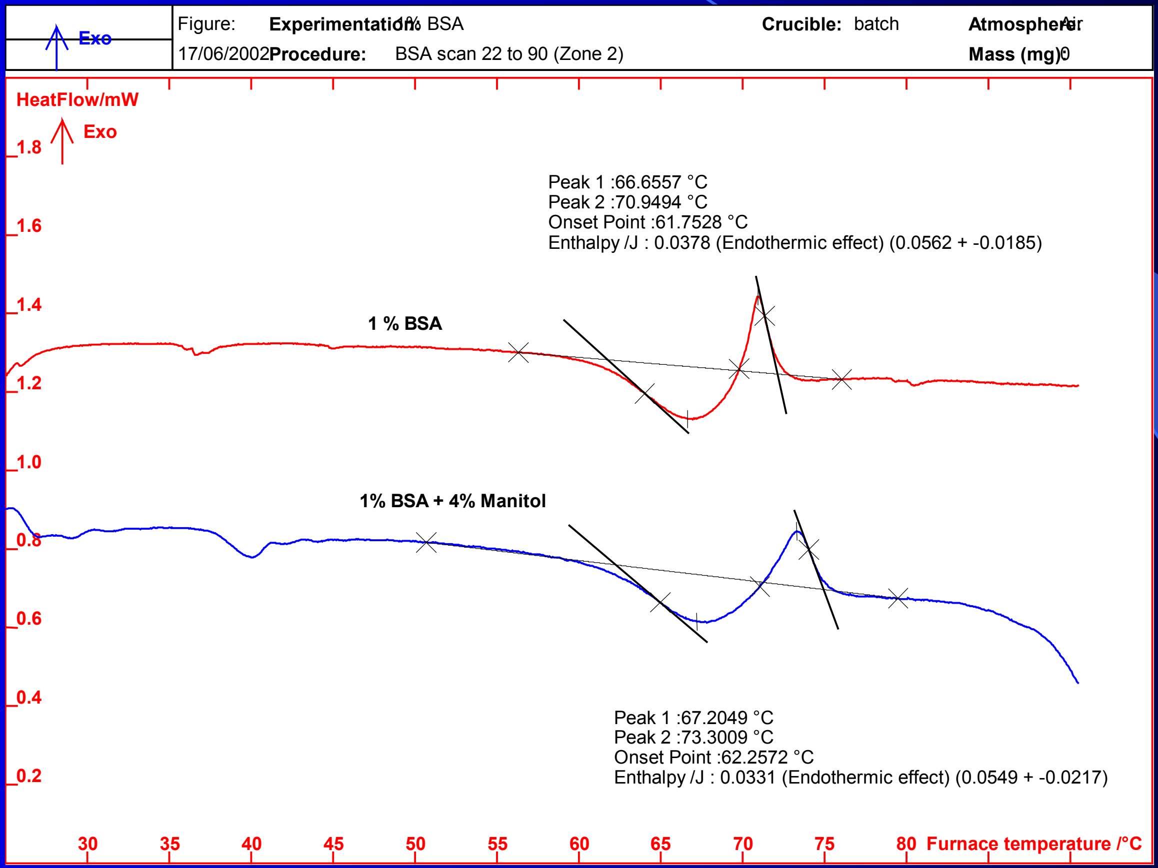




$\Delta G = \Delta H - T \Delta S$

Microcalorimetry: Stability Testing

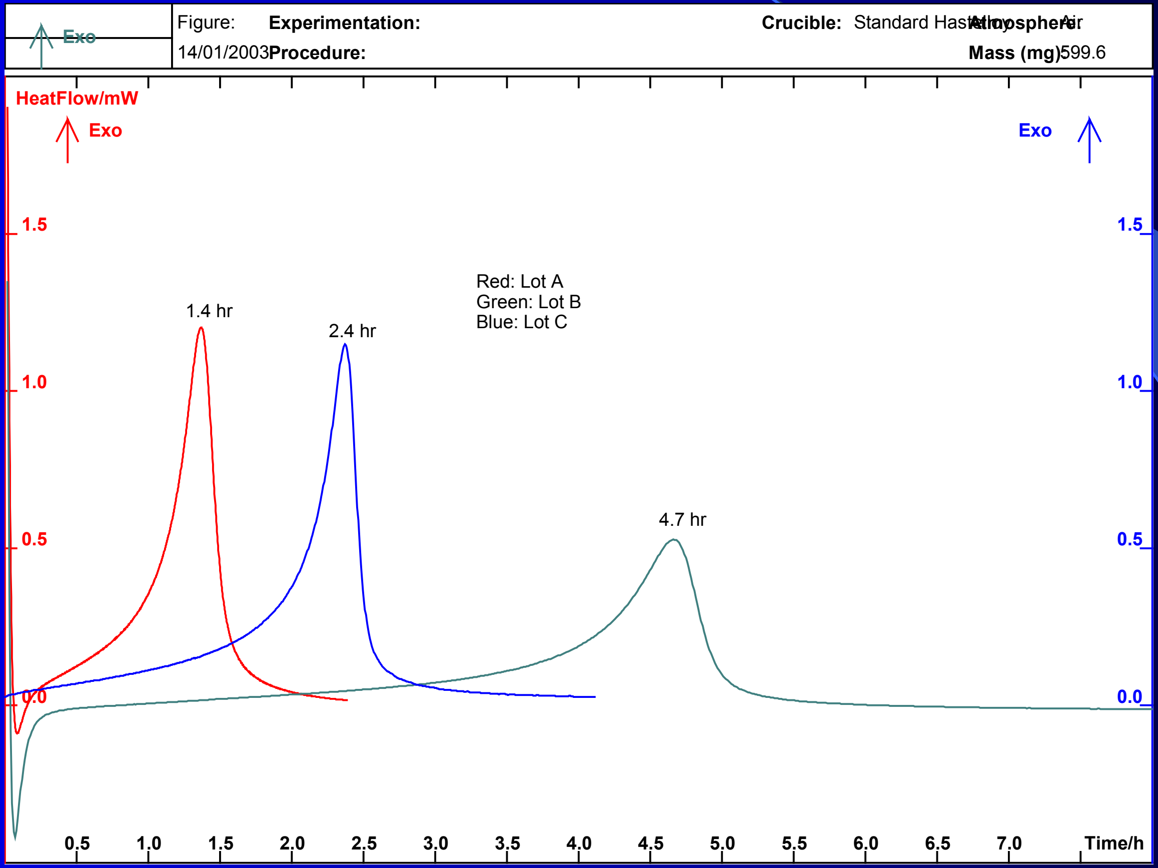
Protein Stability: Impact of Stabilizer



$\Delta G = \Delta H - T \Delta S$

Microcalorimetry: Stability Testing

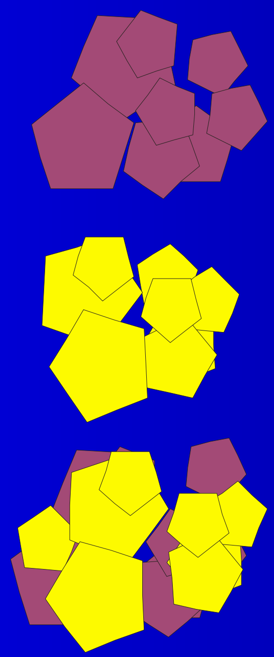
Solid State Stability: Influence of Humidity



$\Delta G = \Delta H - T \Delta S$

Microcalorimetry: Compatibility Testing

General Concept



+Time ---> TA of API q_1

+Time ---> TA of Excipient q_2

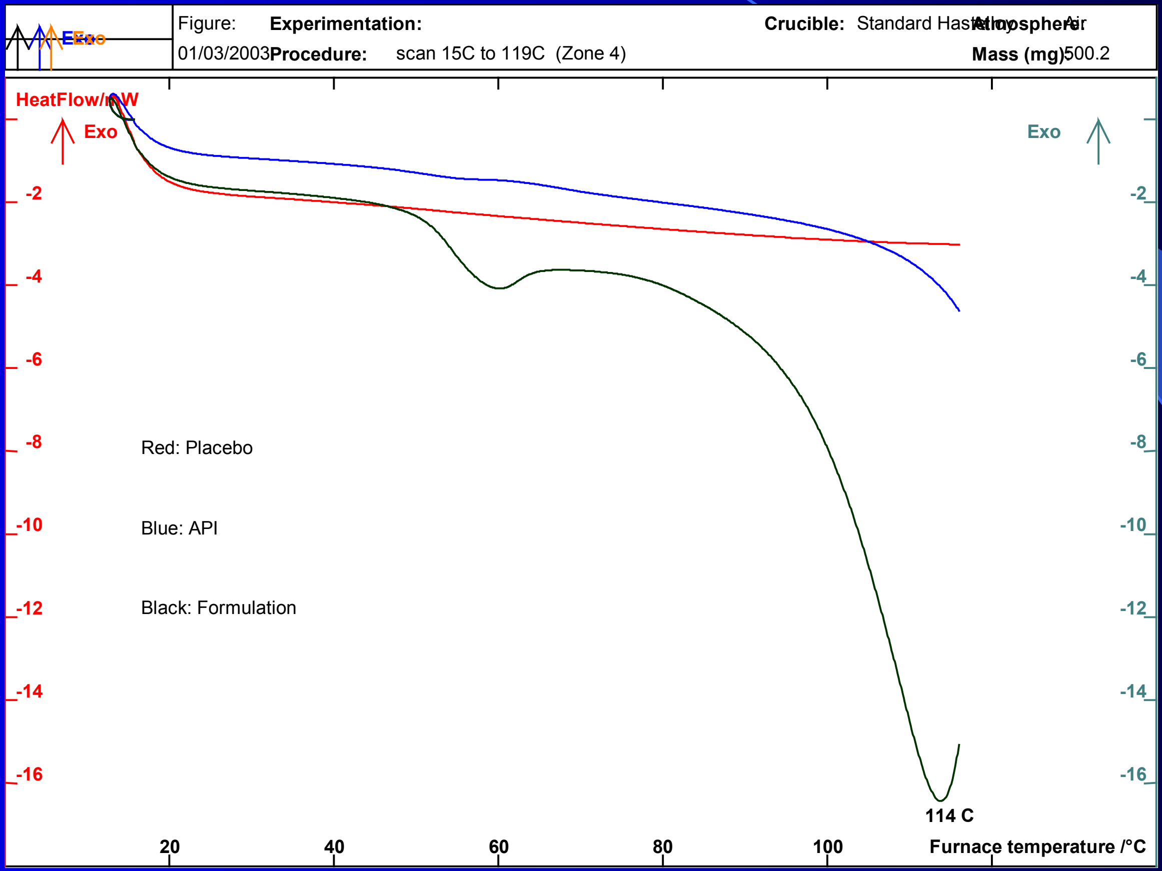
+Time ---> TA of Mix q_{mix}

$$q_{mix} = x_1 q_1 + x_2 q_2 \ ?$$

$\Delta G = \Delta H - T \Delta S$

Microcalorimetry: Compatibility Testing

HSDSC



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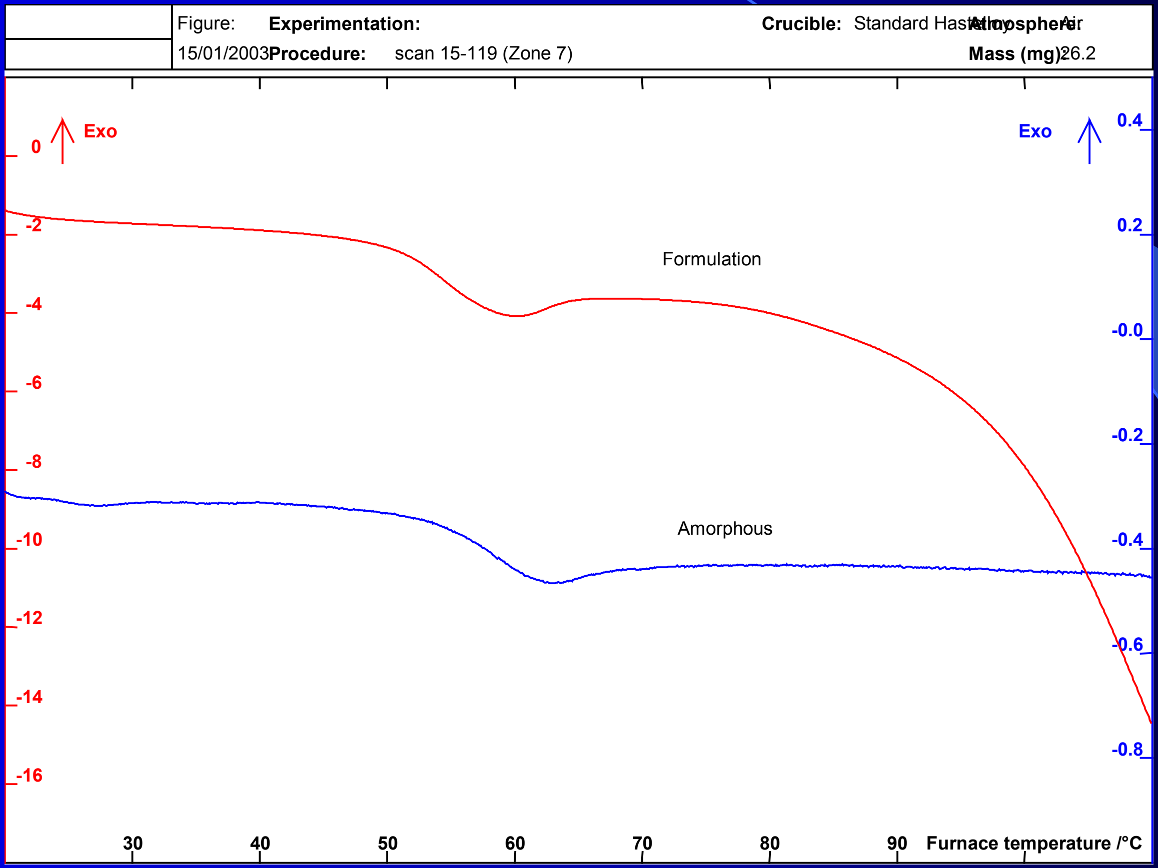
Microcalorimetry: Compatibility Testing

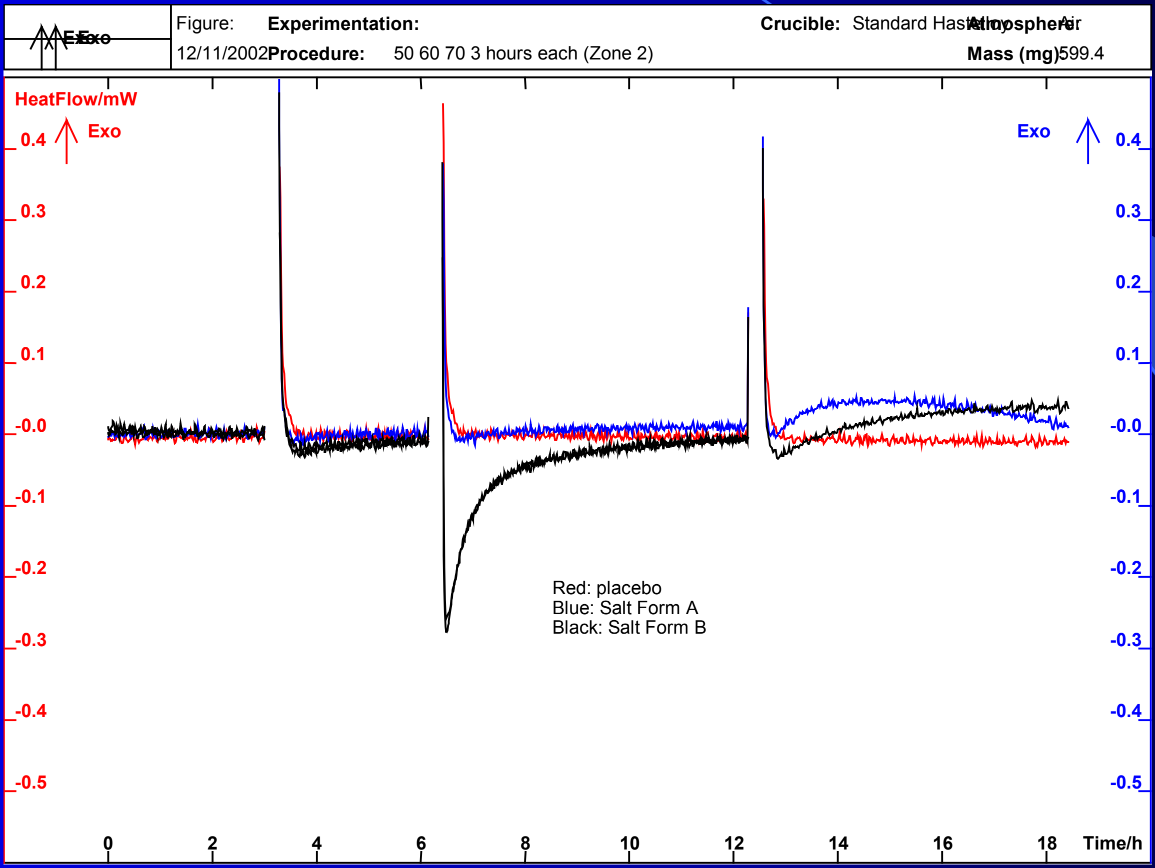
HSDSC



$\Delta G = \Delta H - T \Delta S$

Microcalorimetry: Compatibility Testing

Isothermal Thermal Activity



$\Delta G = \Delta H - T \Delta S$