Solid State Analysis of Multicomponent Pharmaceutical Powders by Red-Excitation, Dispersive Raman Spectroscopy

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Raman Spectroscopy Targets

- Detect crystallization, or polymorph transitions in stability tests
  - Detect changes as early as possible = Low detection limits, good long term repeatability
  - No measurement induced changes in the sample = Minimal laser sample interaction, environmental control
- Analyze solid state make-up of formulations
  - Deconvolution of multicomponent systems = High resolution, good signal-to-noise ratio
  - Measure response to temperature and humidity stress = Environmental control

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Raman System Requirements

Top requirements for intended applications:

Environmental Control:

0 – 95 % RH, -50 – 200 ^{o}C

Sensitivity:

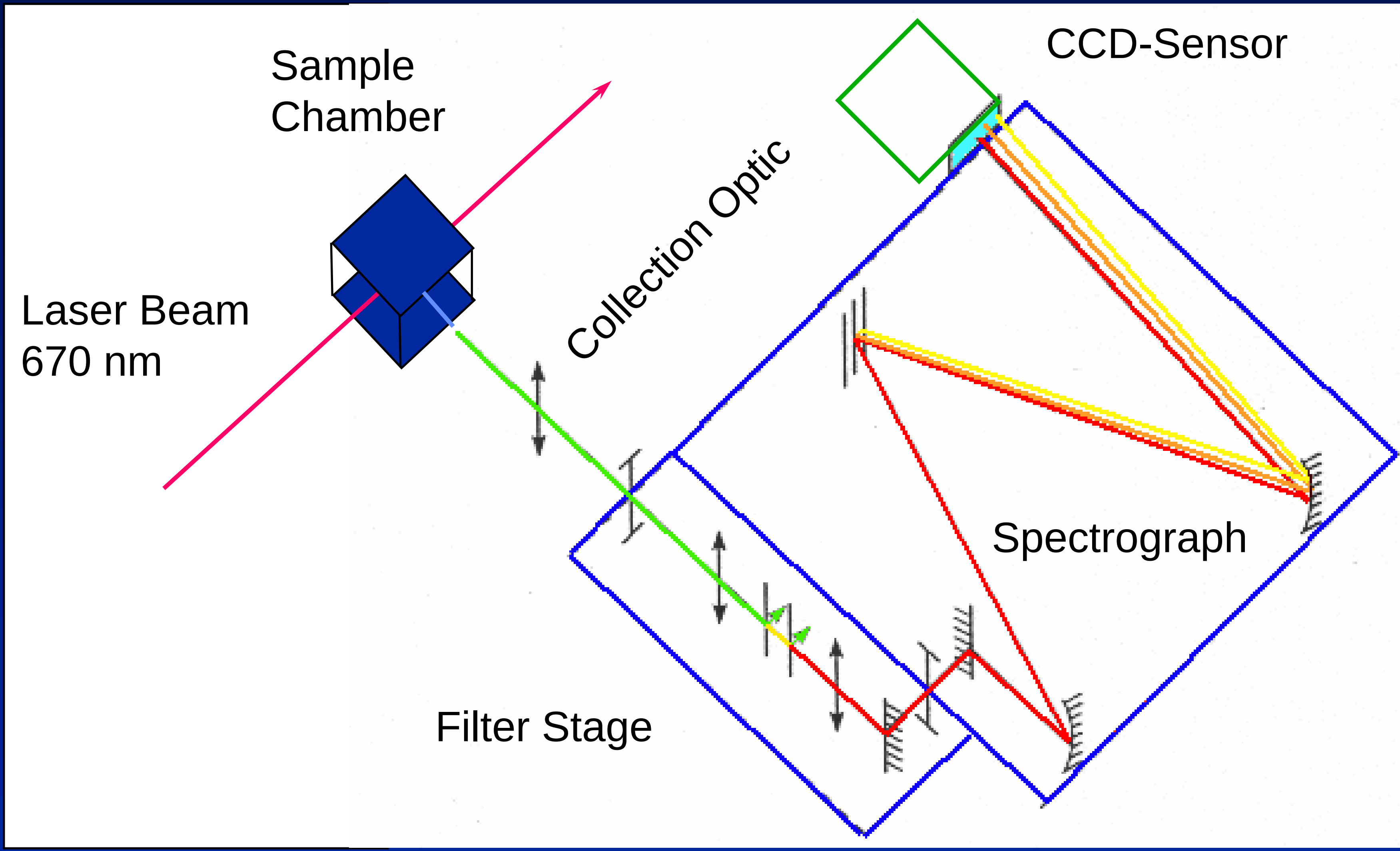
~1 % detection limit, SN ratio > 100

Minimal laser-sample interaction:

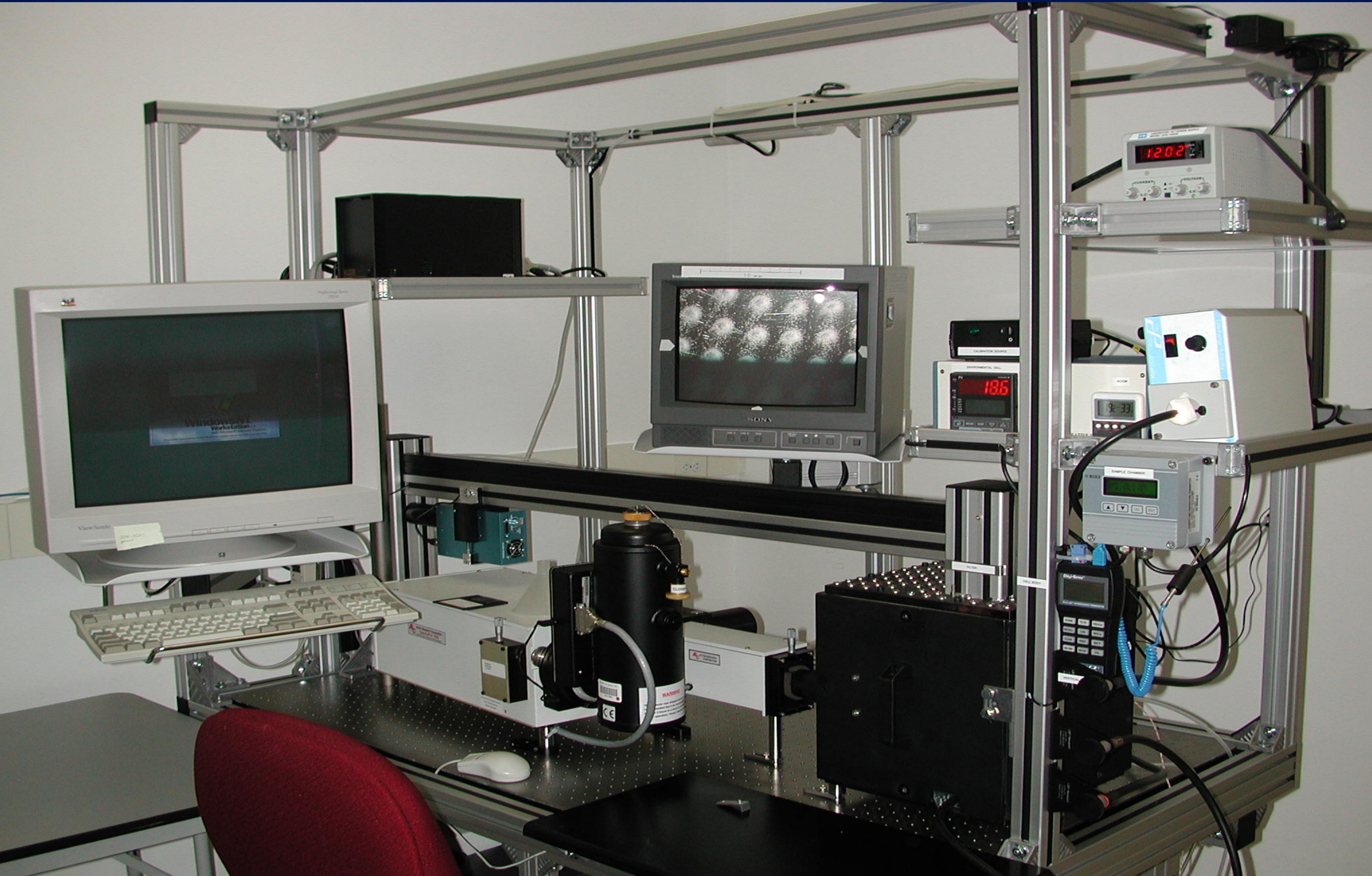
Visible excitation, moderate focusing

***Solution:* Custom-built Raman system**

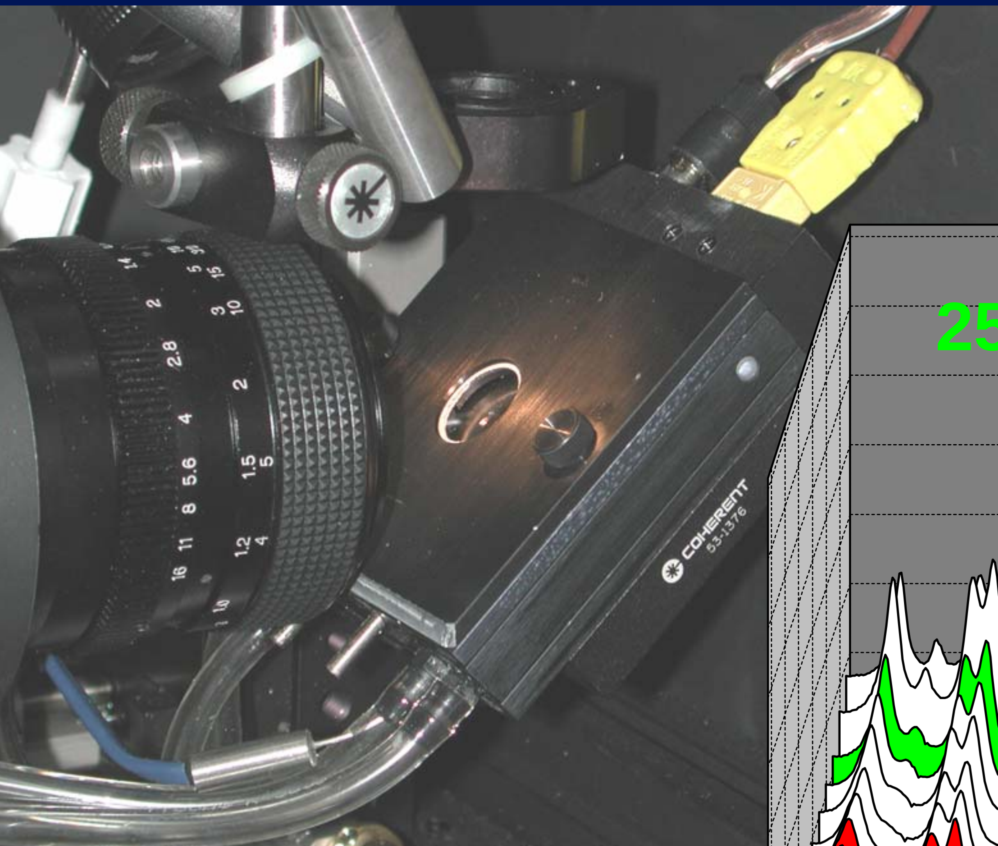
Dispersive Raman with Red Excitation



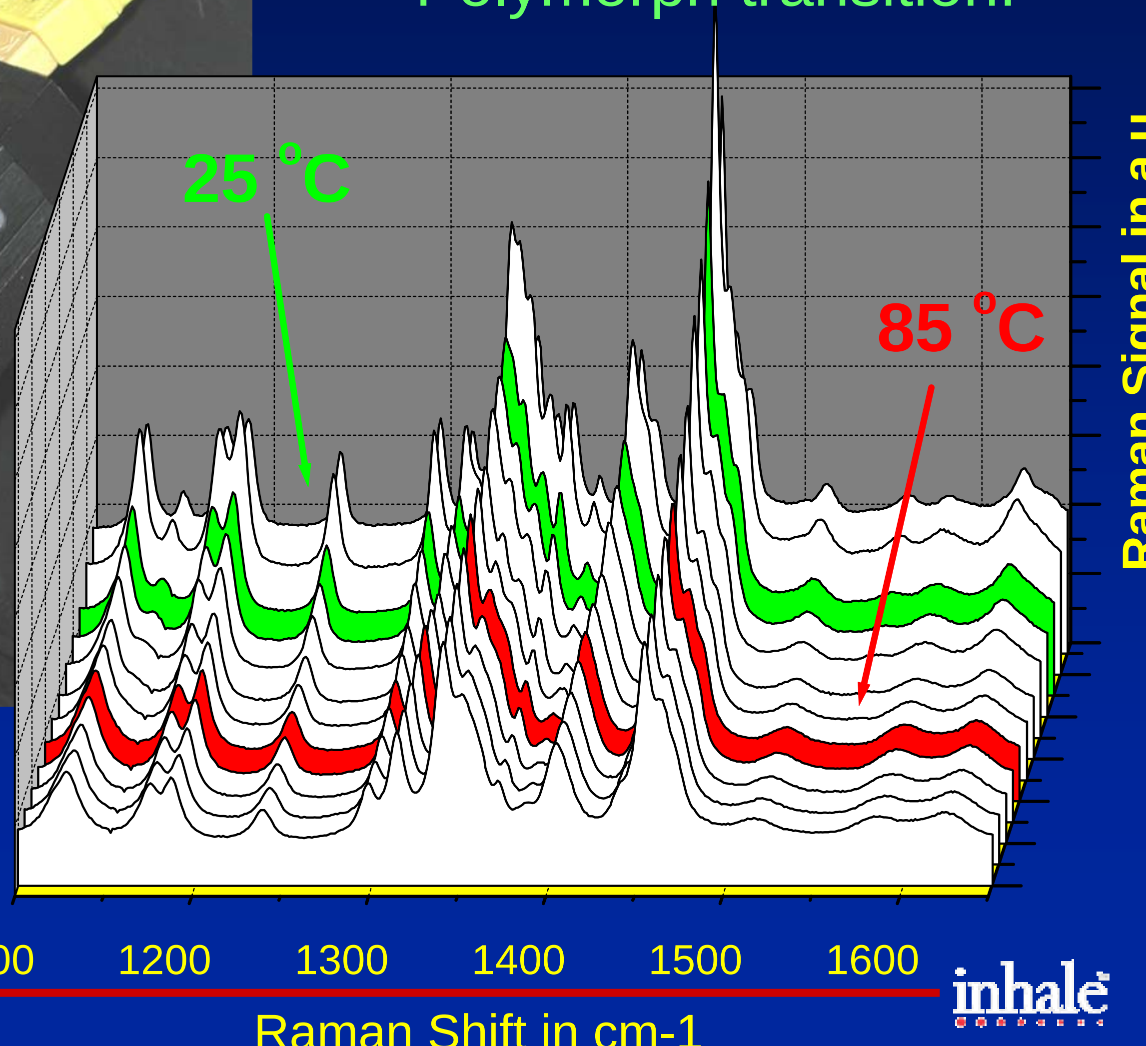
Inhale's Research Raman System



Environmental Control: –50 to 400 ^{o}C, 0 to 95 % RH



Example:
Polymorph transition:



Transition temperatures agree with published data
= No sample heating

High Sensitivity Achieved

Measurements on low sample mass possible!

In this example: 10 μg

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Stability Studies with Diode Laser Spectroscopy

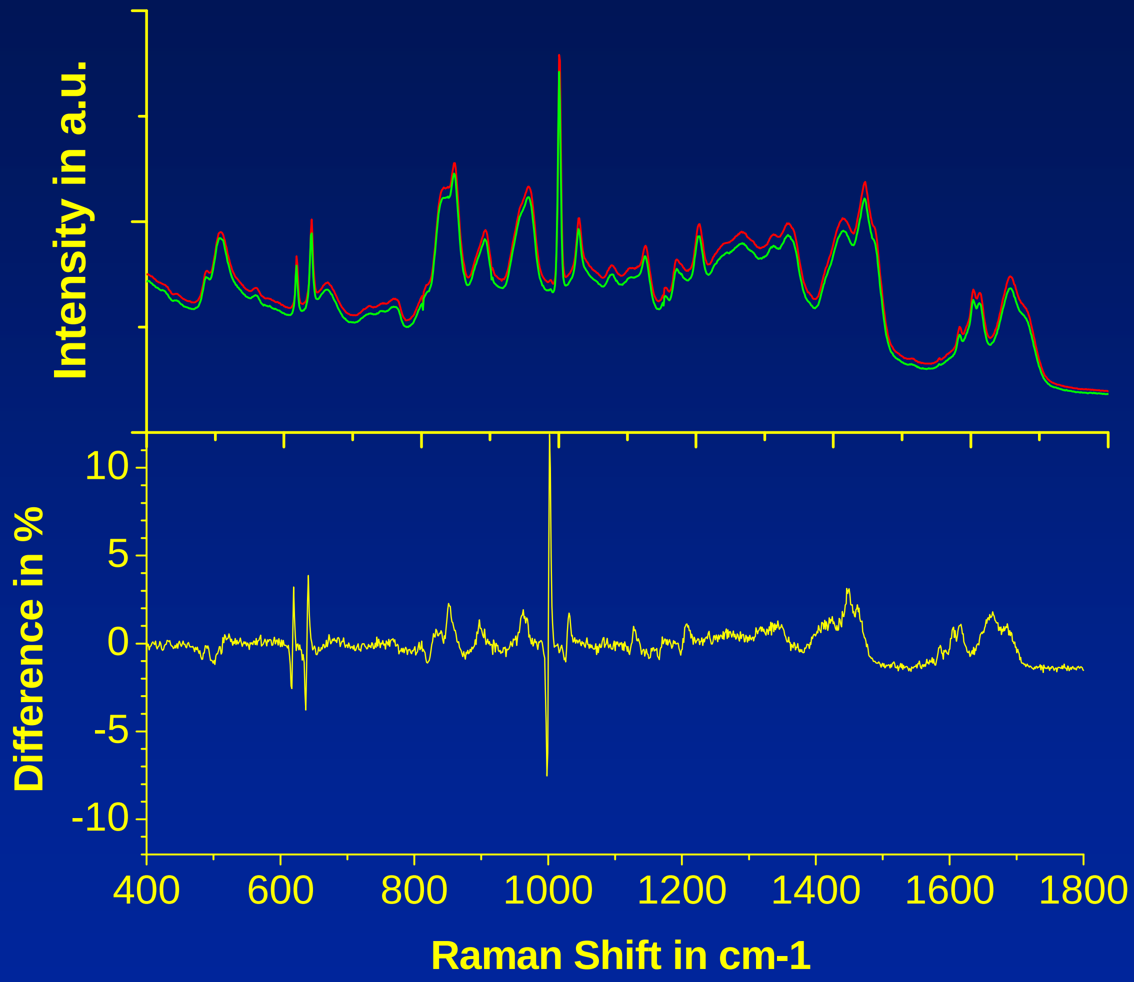
- Problem:

  Variable laser wavelength causes artifacts in difference spectra

- Solution:

  Calibration or Correction ?

Artifacts caused by shifts in laser wavelength:



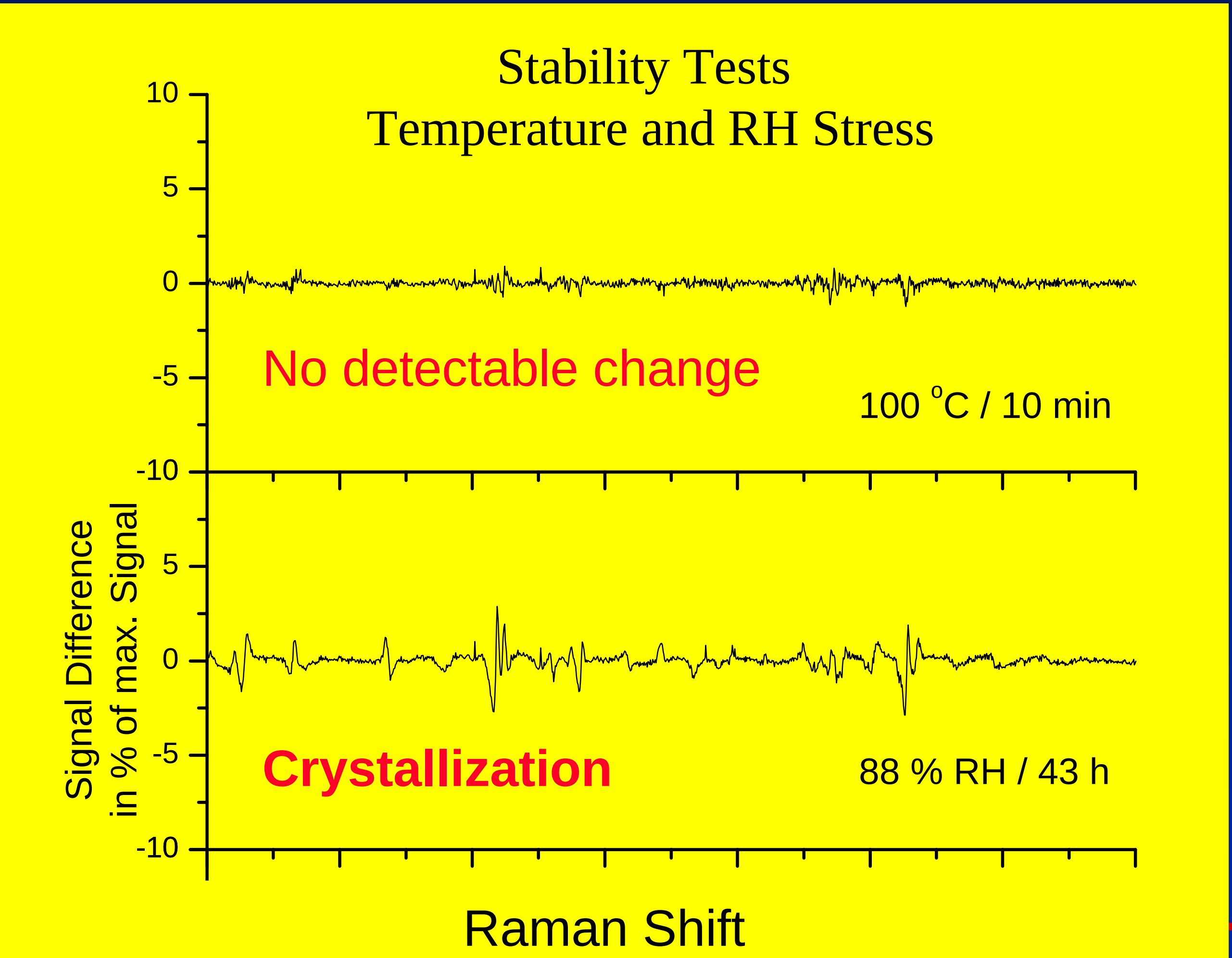
Two consecutive measurements with a laser wavelength shift of 0.3 cm^{-1}

Artifacts were found for shifts as low as 0.1 cm^{-1}

Required calibration accuracy: 10 x instrument resolution !

Artifacts removed by correction procedure:

Shifted spectra relative to each other by fractions of pixels



Excellent detection limits allowing early detection of stability problems

Calibration of laser wavelength unnecessary !

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Deconvolution requires Quantitative Measurements

The Raman signal is proportional to concentration, but the proportionality constant is unknown

Solution: Measure relative to an internal standard

Raman signal, Φ_A, of a substance *A*:

$$\Phi_A = \phi \cdot c_A N_a V \cdot E(\lambda) M(\lambda) \cdot \sigma_A$$

$$\Phi_A / \Phi_{Ref} = c_A \sigma_A / c_{Ref} \sigma_{Ref}$$

ϕ	Radiant flux density	c_A	Molar concentration of substance A
N_a	Avogadros Number	V	Sample volume
σ_A	Scattering cross section	$E(\lambda)$	Instrument Efficiency
$M(\lambda)$	Morphology factor		

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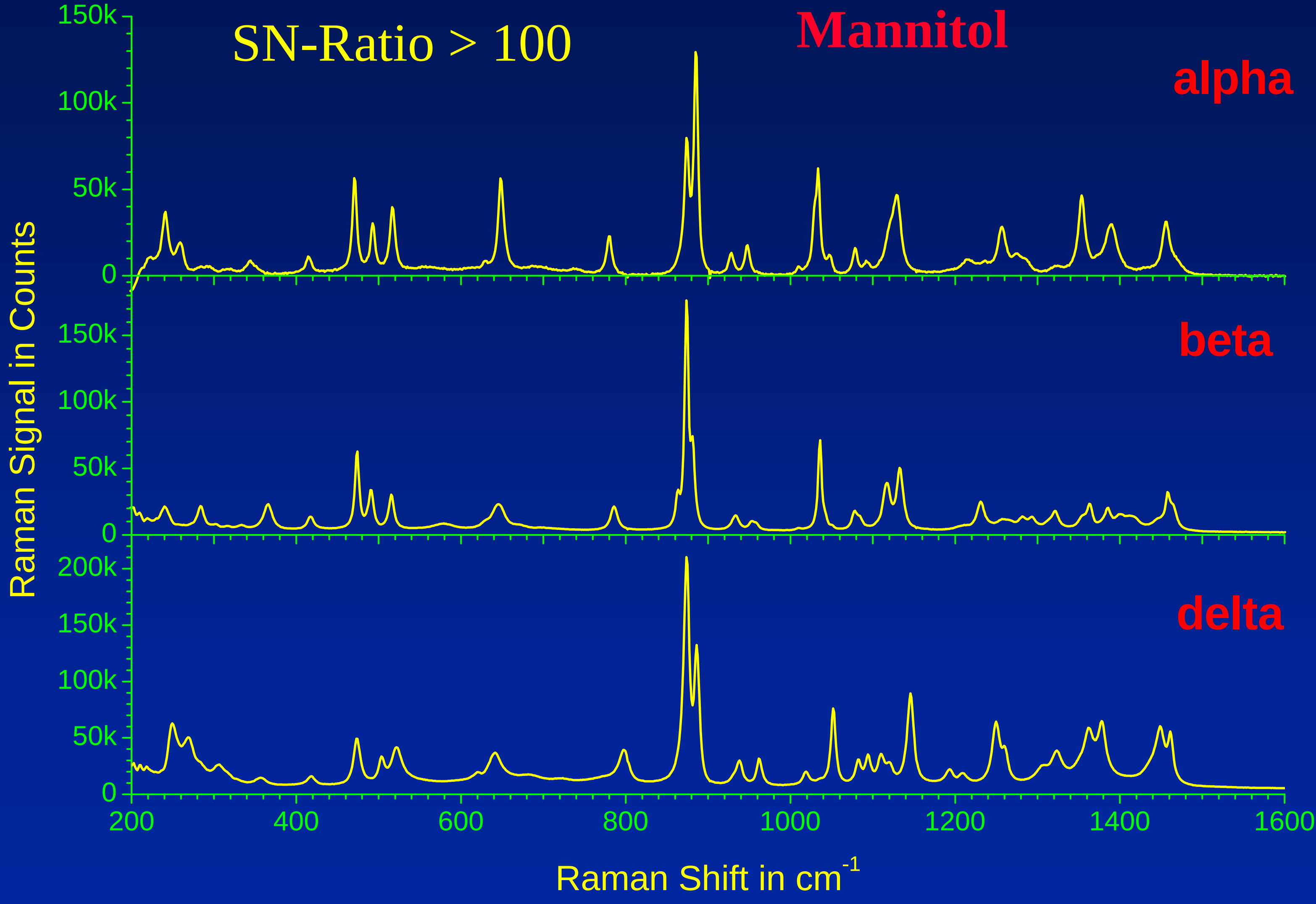
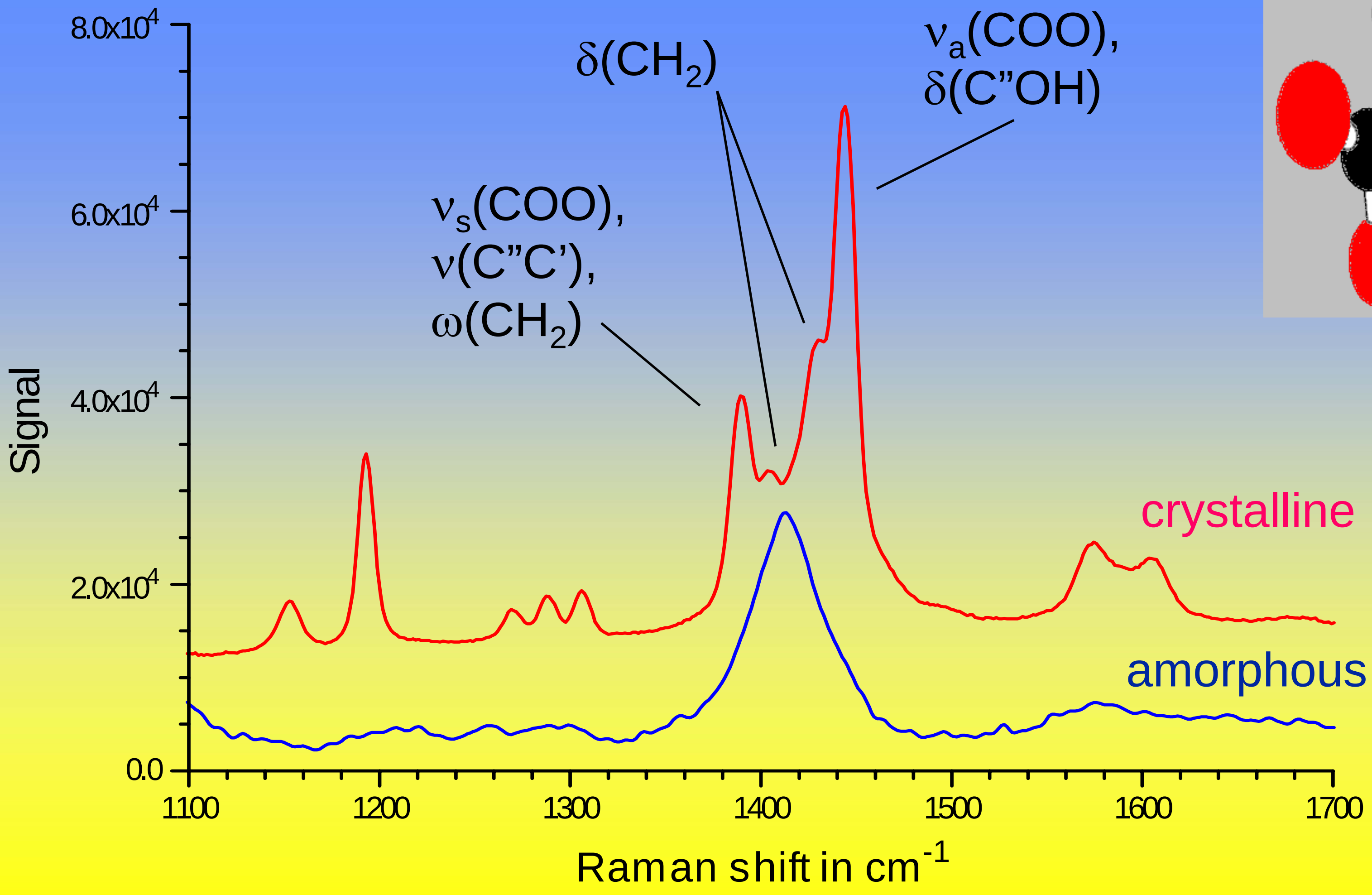
Specificity: High-Quality Fingerprints of Polymorphs

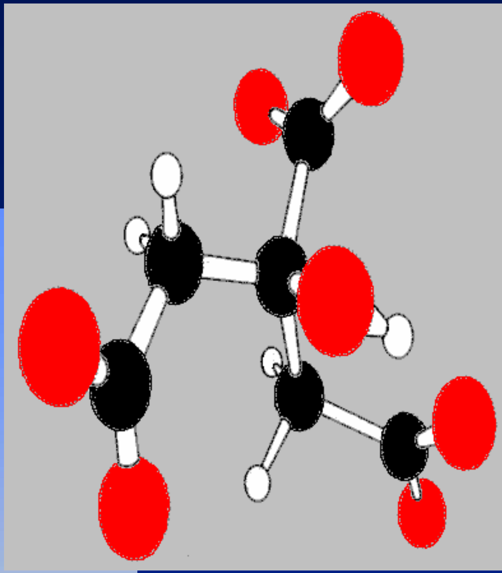


Specificity: Amorphous vs. Crystalline

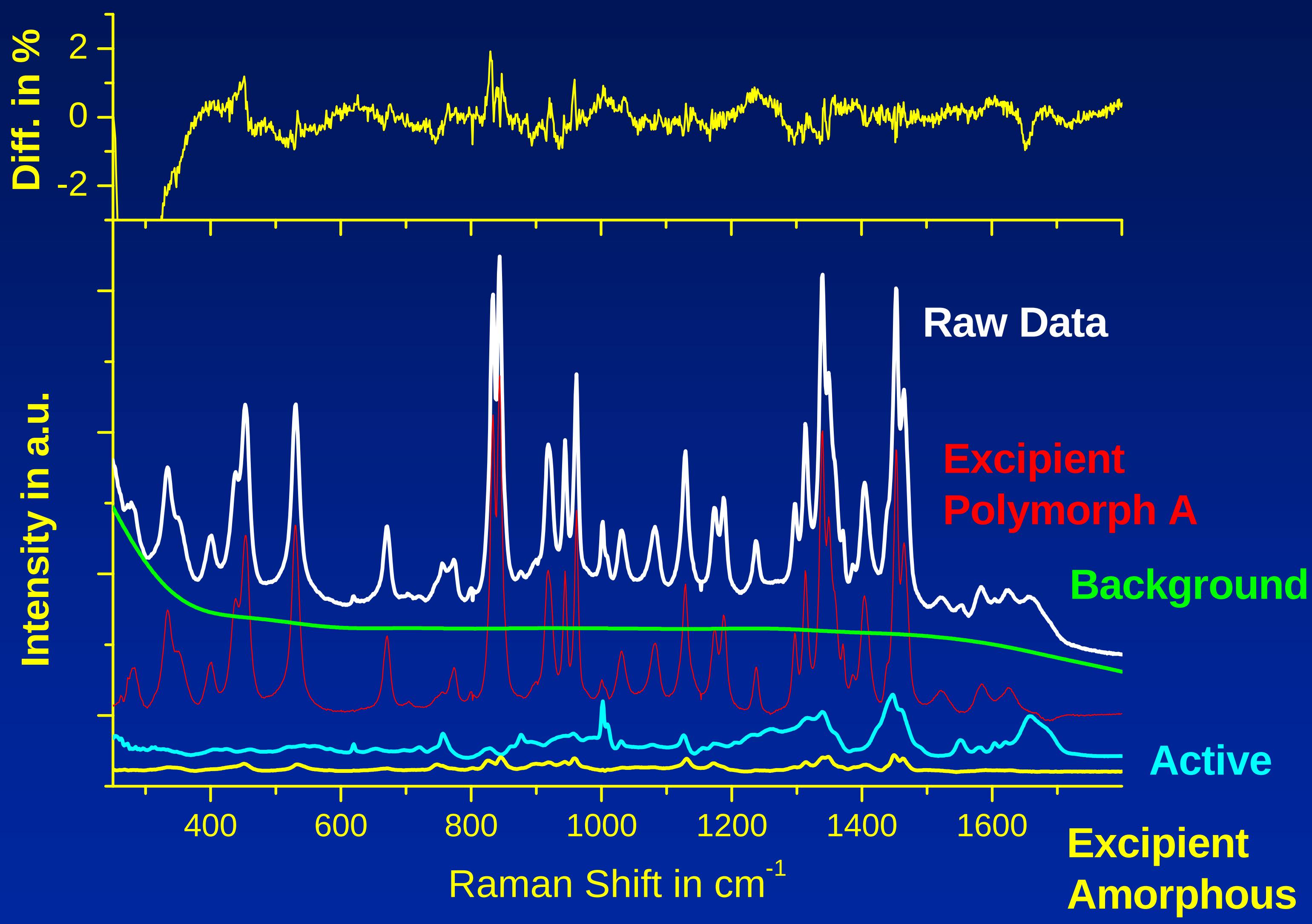
Example: Citrate

Clear differences allow easy identification





Deconvolution Procedure



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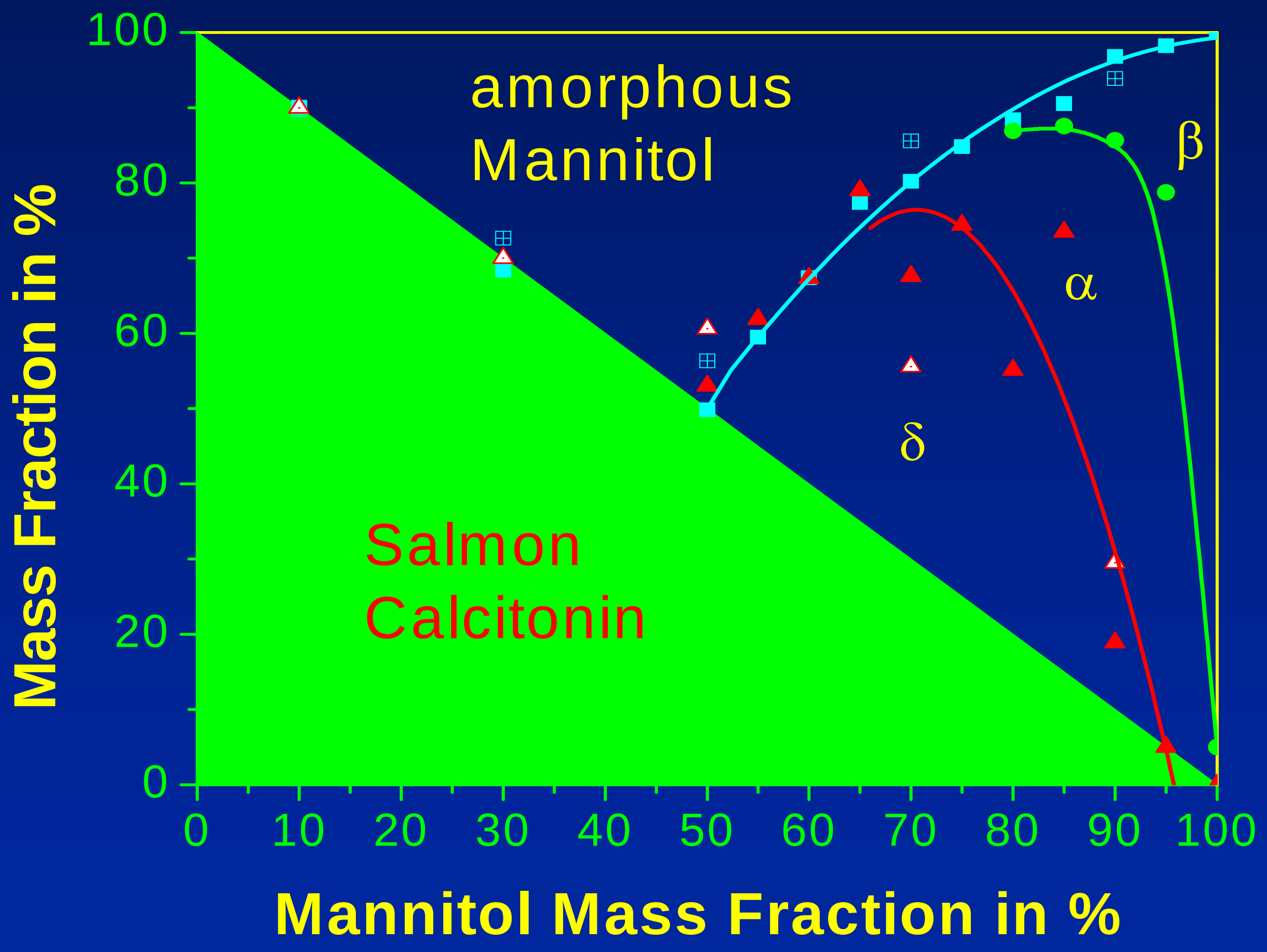
Solid State Analysis in Multicomponent Systems

Spray-Dried Salmon Calcitonin – Mannitol System



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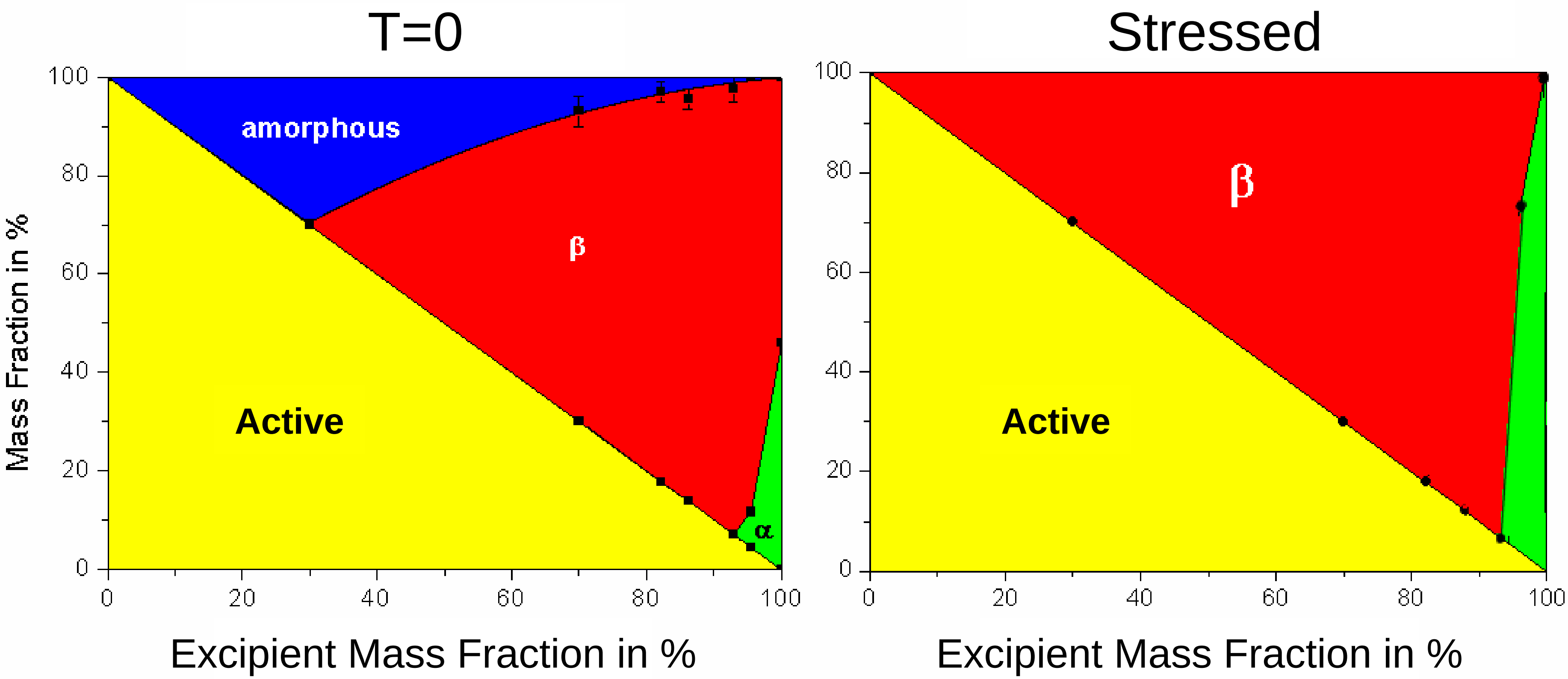
Analyzing Solid State Changes caused by RH Stress



The method helps select formulations and processing conditions which lead to favorable solid state properties.

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Summary

Inhale has developed a custom Raman instrument and data processing methods which allow early detection of stability problems and sophisticated analysis of multicomponent pharmaceutical formulations.

These capabilities contribute to shorter development times and optimized product performance.

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