晶云药物第一届晶型专题技术培训

课程六：药物固态表征方法及其在药物研发和生产中的应用

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提纲

- 药物固态表征方法简介
- X射线粉末衍射及应用
- 热分析及应用
- 动态气相吸附
- 激光散射粒度分布分析
- 比表面积测量
- 拉曼光谱分析

固态表征方法

All variants of spectroscopy, microscopy, scattering etc. are used

Structure, order and dynamics of the solid state probed

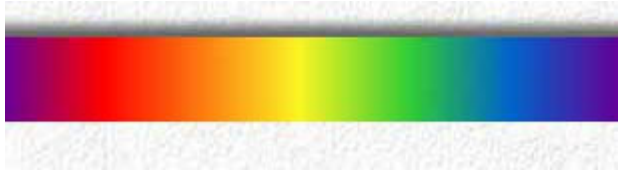
Spectroscopy	**ssNMR**, IR, **Raman**, Terahertz…
Microscopy	SEM, Optical, AFM…
Scattering	**X-ray**, **Laser**, …
Thermal analysis	**DSC**, **TGA**, Microcalorimetry, DMA, DEA…
Physio-Mechanical analysis	Bulk density, Solubility, Surface area, PSD…
Computer Modeling	Quantum, DFT, MD/MC, …

X 射线衍射
(X-ray Diffraction, XRD)

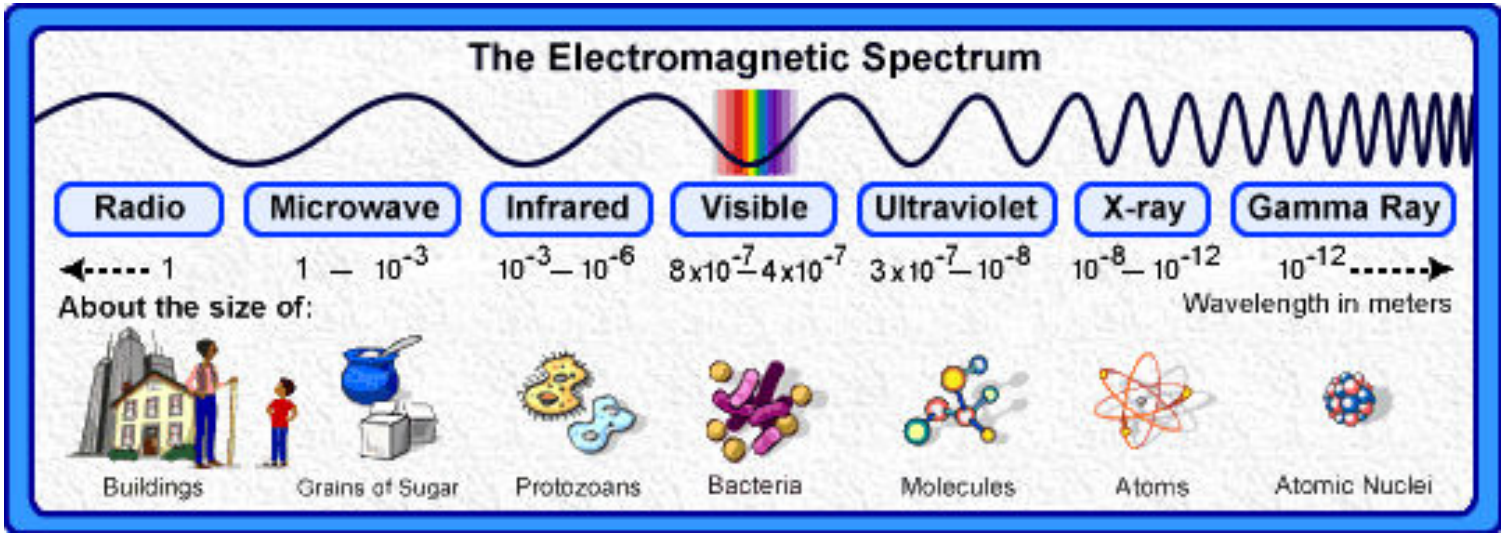
X射线衍射

- X射线衍射原理
- X射线衍射仪
- X射线衍射在制药行业的应用
  - 固相（晶相和无定形）的检测和定量分析
  - 晶型转变和其它相变的研究
  - 药物制剂的表征
  - 晶体结构的解析

X射线是电磁光谱的一部分



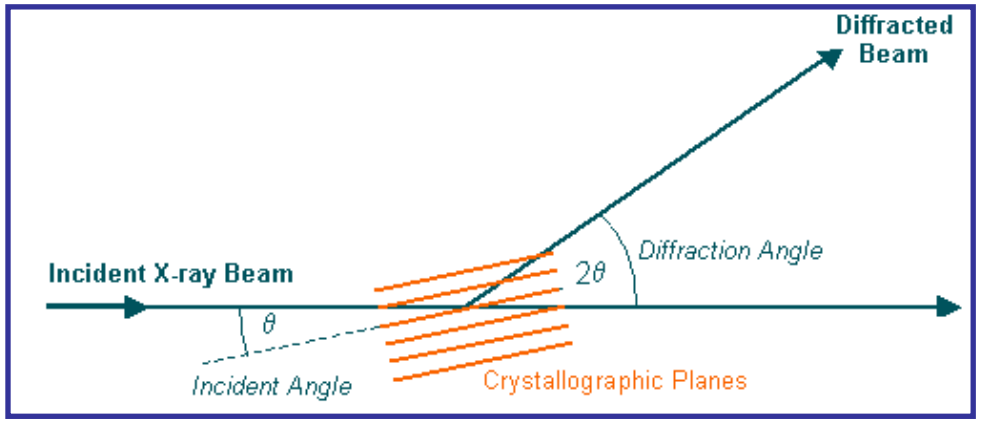
A rainbow of colors



X-rays：wavelength of 0.1 Å to a few Å.
Ideally suited for probing structural arrangements of molecules

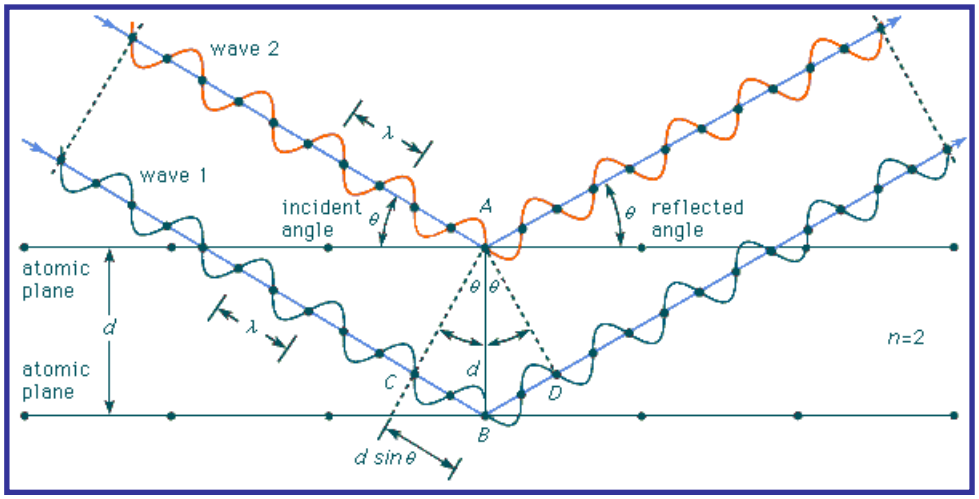
X射线衍射：实验原理

Basic set-up



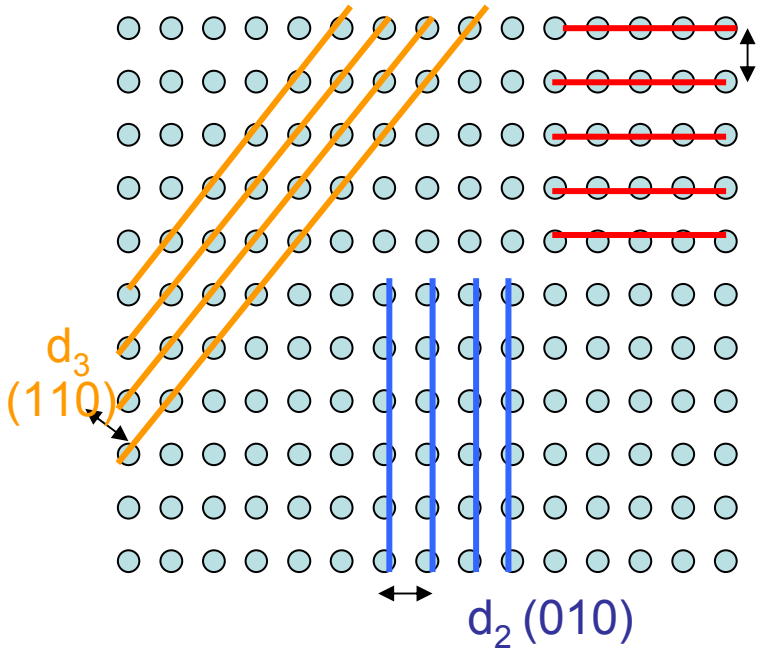
Bragg's law:

$$n\lambda=2d\sin\theta$$



d: Interplanar spacing
l: wavelength of X-ray
q: Incident angle

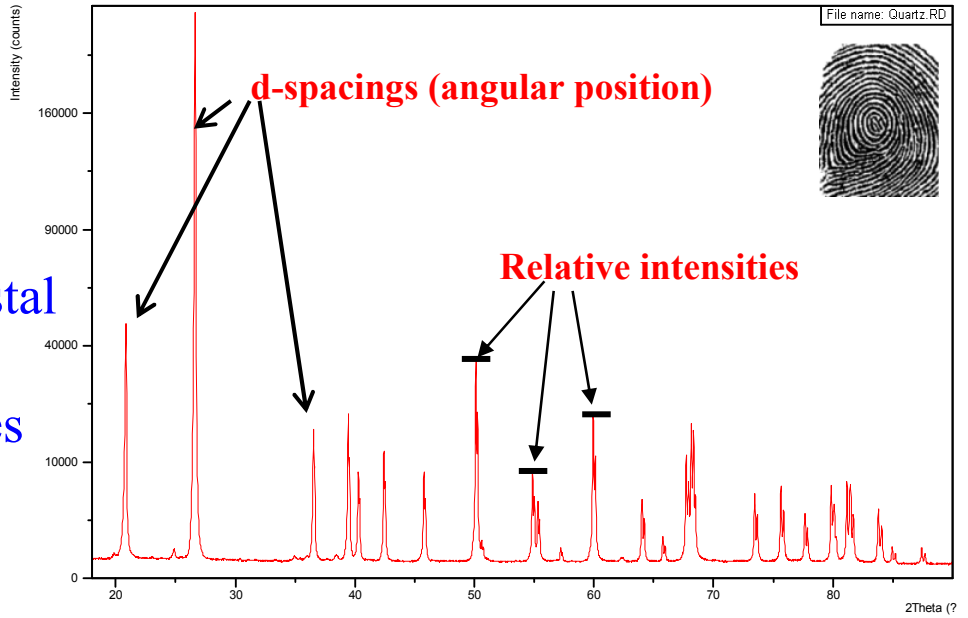
X射线衍射：晶体结构



Various lattice planes are available

Intensities expected at different q's

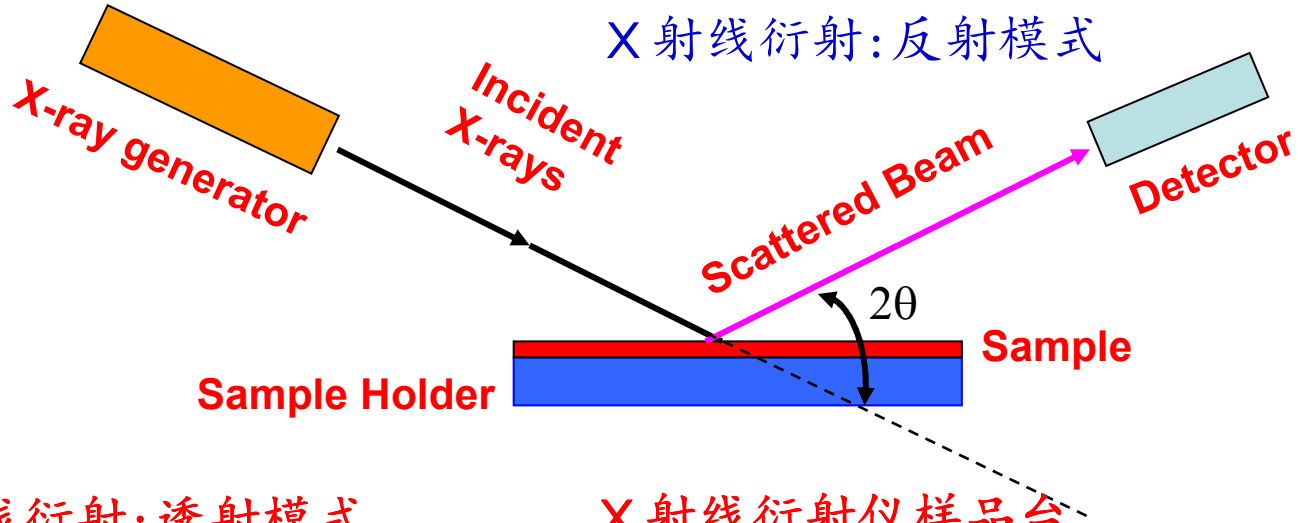
典型的X射线衍射图谱



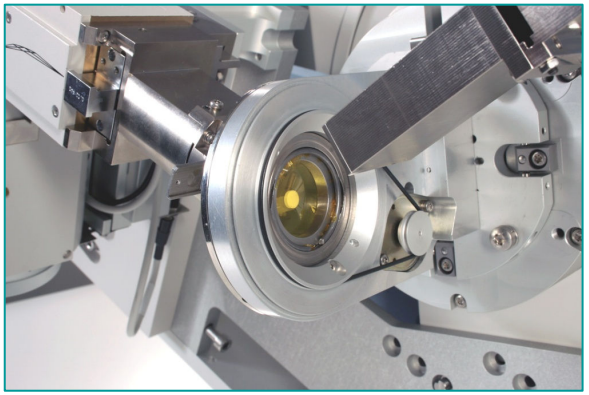
- XRPD pattern is the fingerprint of the crystal
- Used to identify different crystalline phases

X射线衍射仪

X射线衍射:反射模式



X射线衍射:透射模式

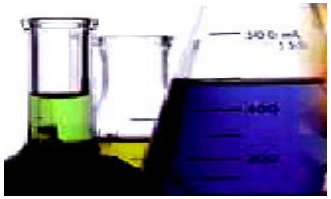


X射线衍射仪样品台

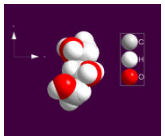
- Spinner stage (For routine sample analysis)
- Temperature/humidity stage
- Auto-sampler stage
- 96-well high-throughput stage
- Capillary stage

X射线衍射在制药行业的应用

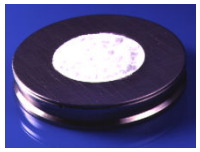
RESEARCH
-New crystal forms
-New chemical entities
-Atomic Structure
-Patents



Molecules



Powder

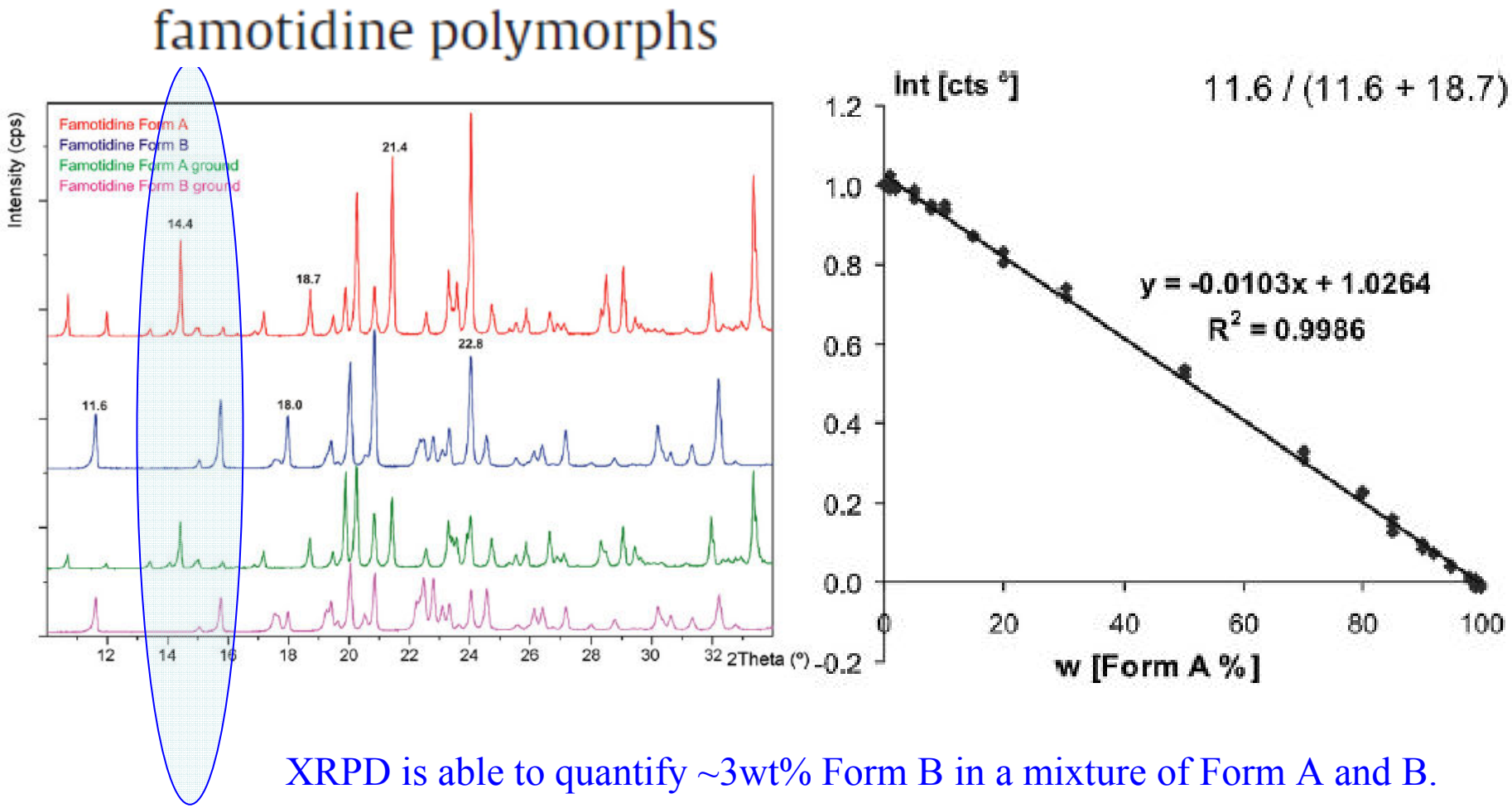


Formulation

DEVELOPMENT
-Polymorphs screening
-Crystallinity
-Pre-formulation
-Formulation
-Stability
-etc

PRODUCTION QUALITY CONTROL
- Raw Materials
- Process Control
- Batch Uniformity
- etc

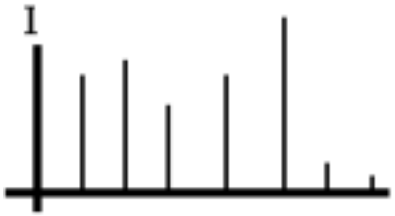
多晶型的检测和定量分析



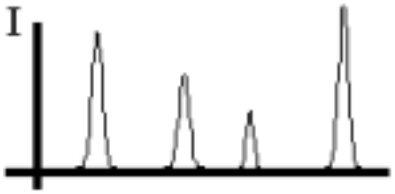
XRPD is able to quantify ~3wt% Form B in a mixture of Form A and B.

Zoltan et al, Journal of Pharmaceutical and Biomedical Analysis 49 (2009) 338–346

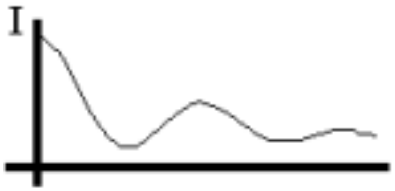
晶型/无定形的检测和定量分析



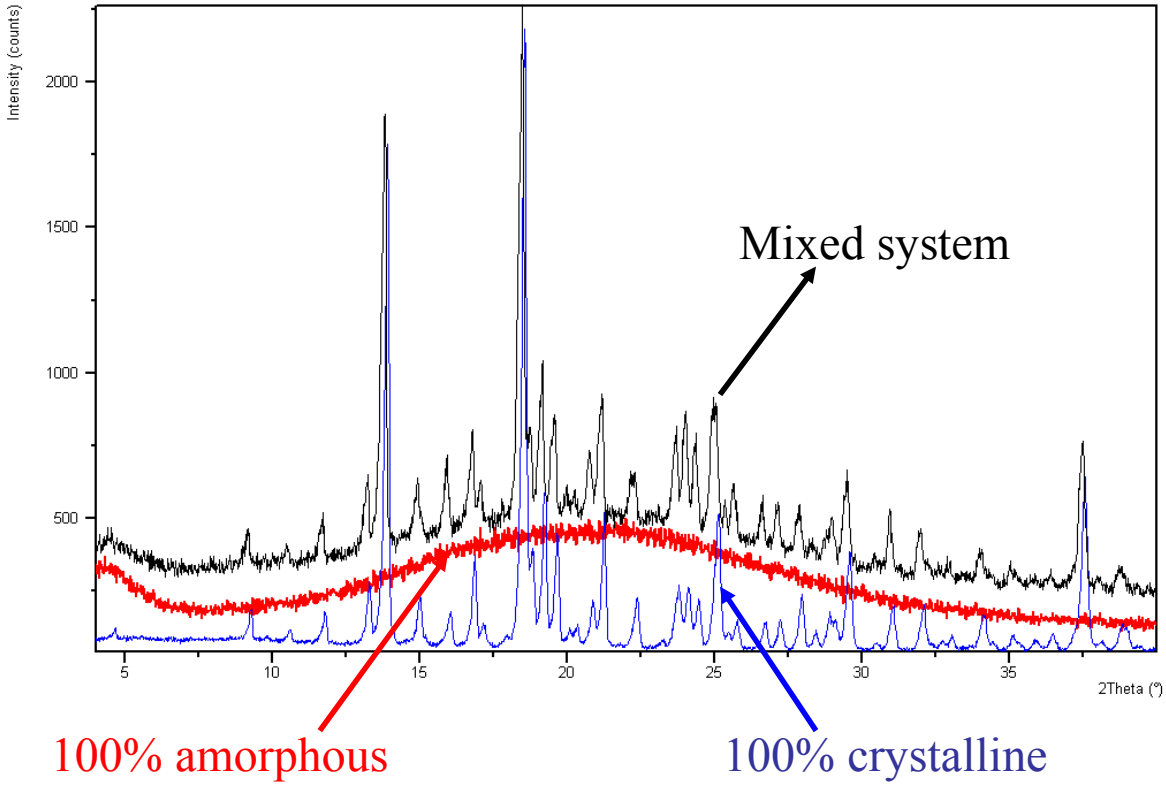
Perfect crystal



Imperfect crystal

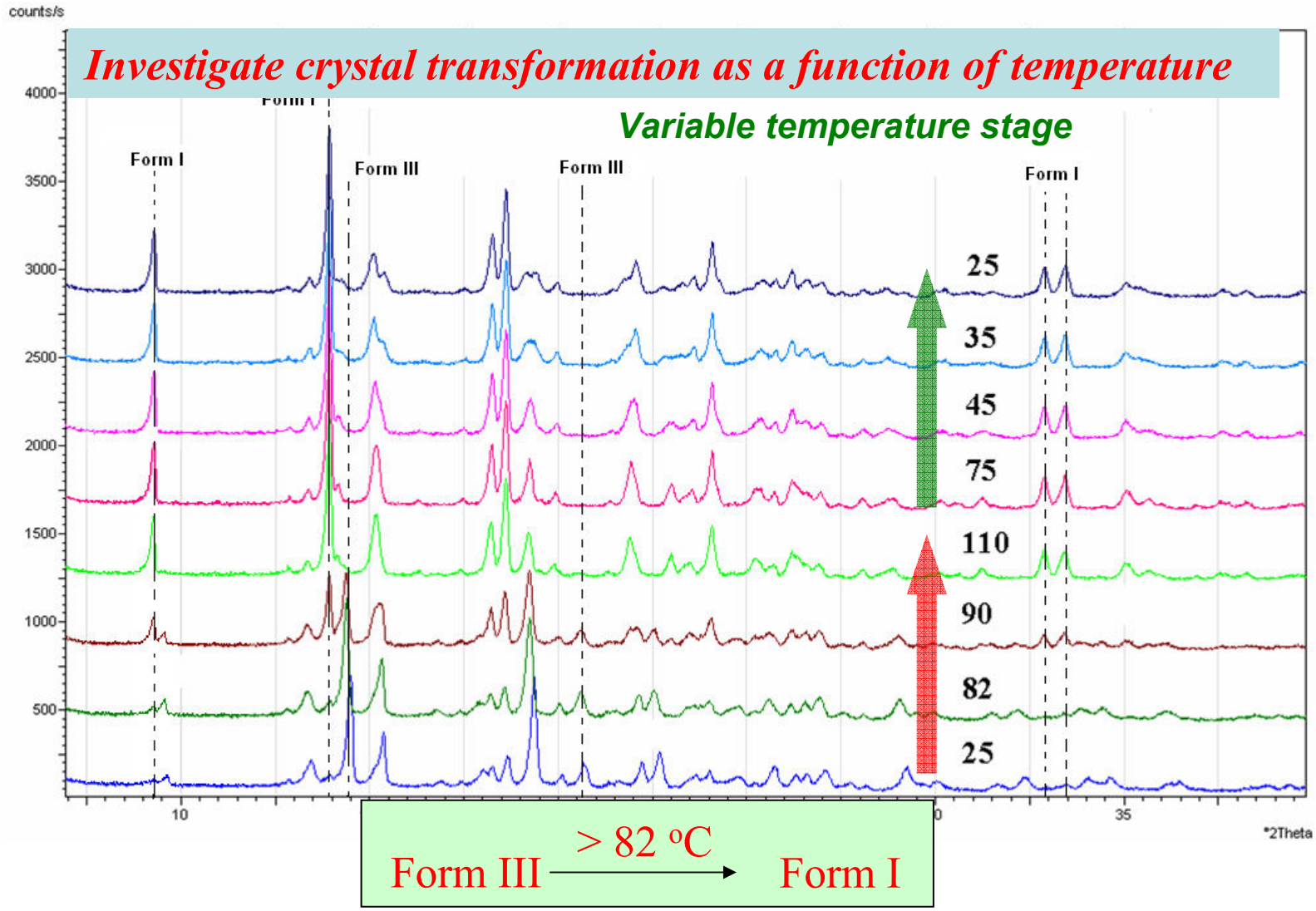


Amorphous material



Amorphous system: Broad halo
Mixed system: Crystalline peaks superimposed on the halo

不同温度下晶型转变的研究



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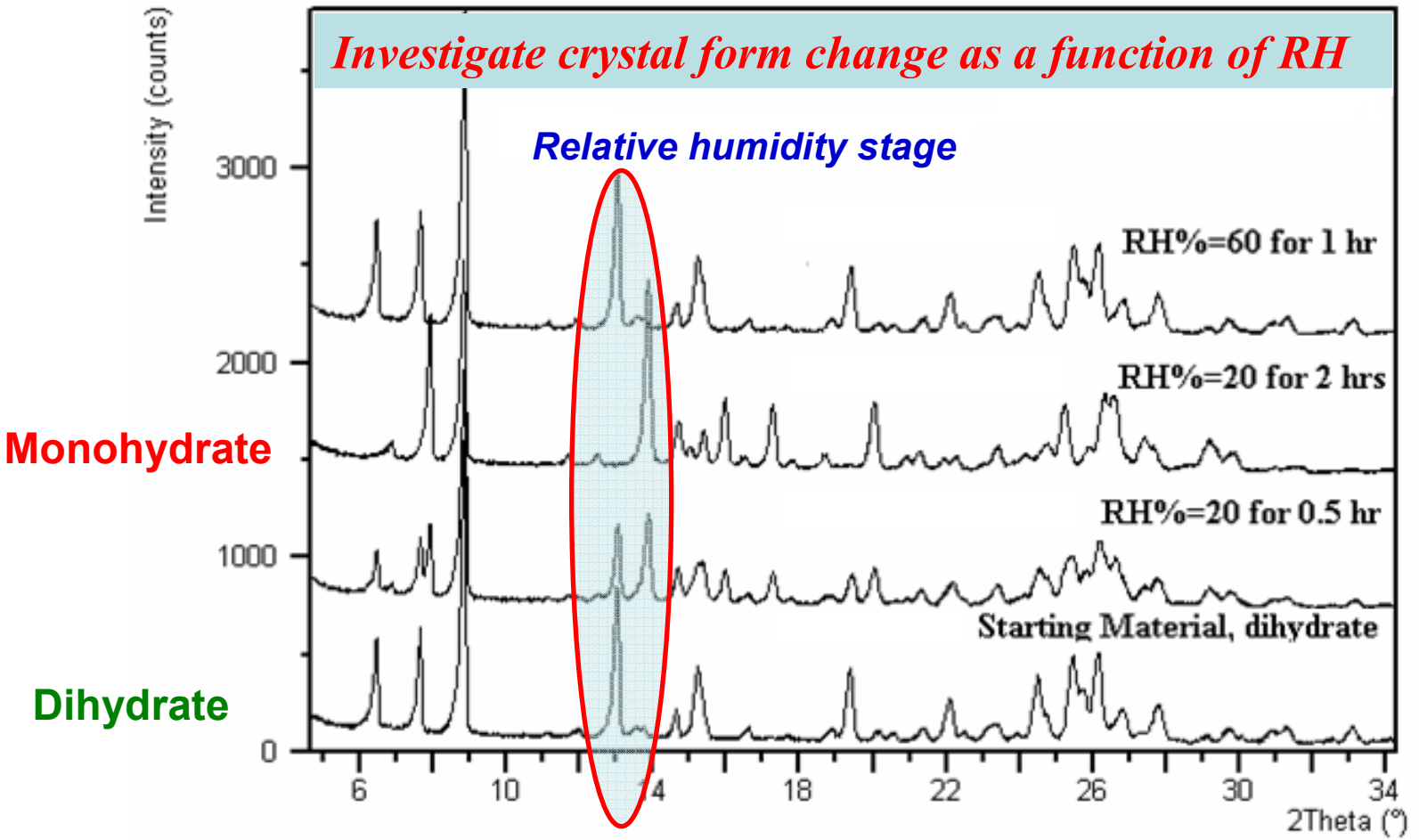
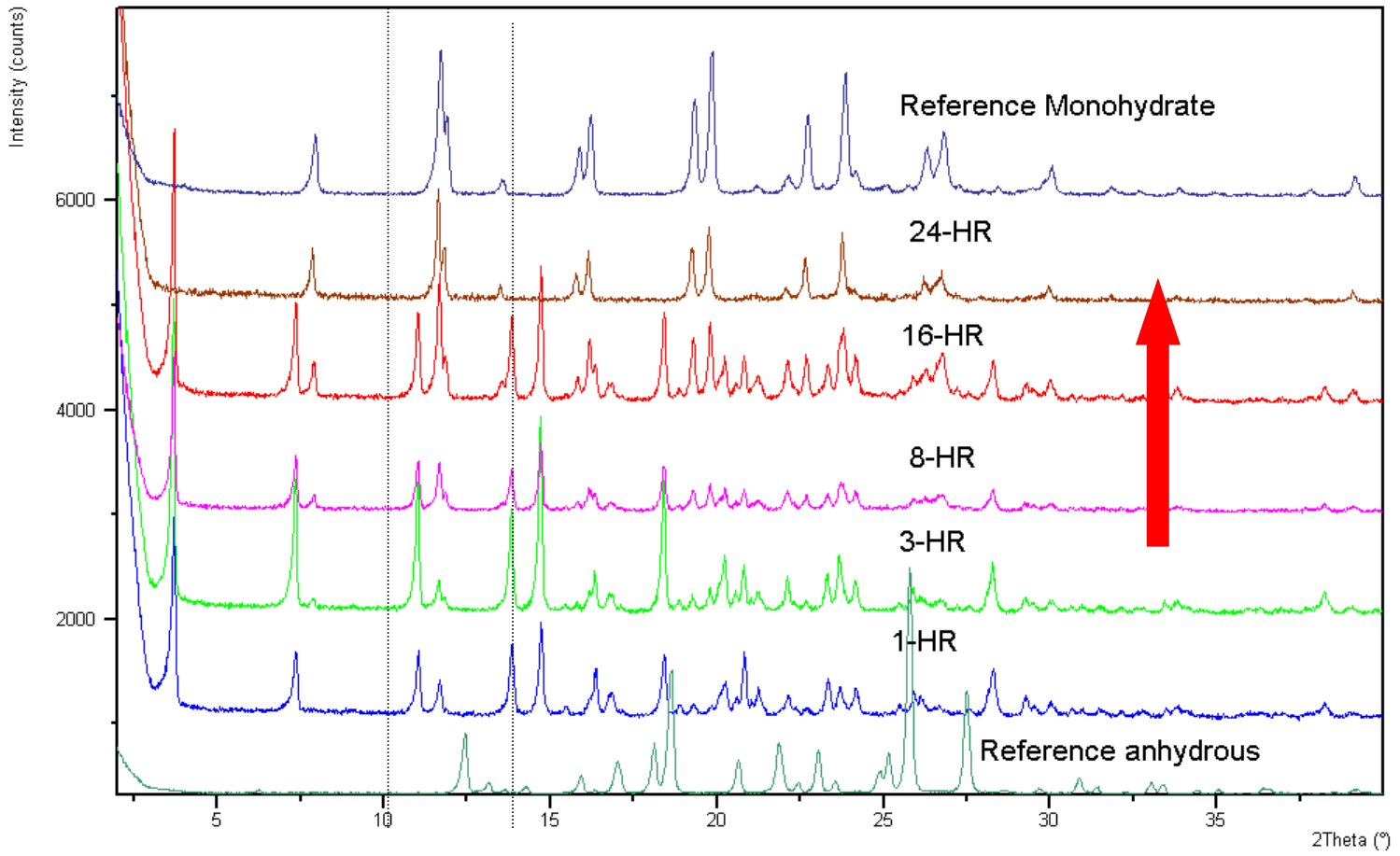
不同湿度下水合物的相互转变



Dihydrate —20% RH, 2 hours→ **Monohydrate** —60% RH, 1 hour→ **Dihydrate**

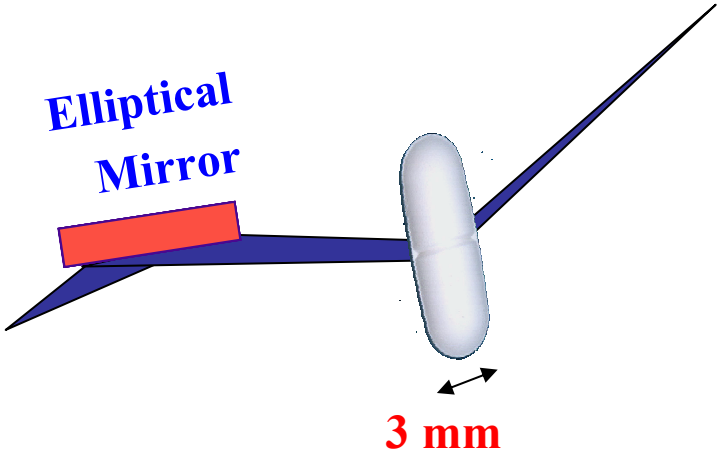
歧化反应的动力学研究

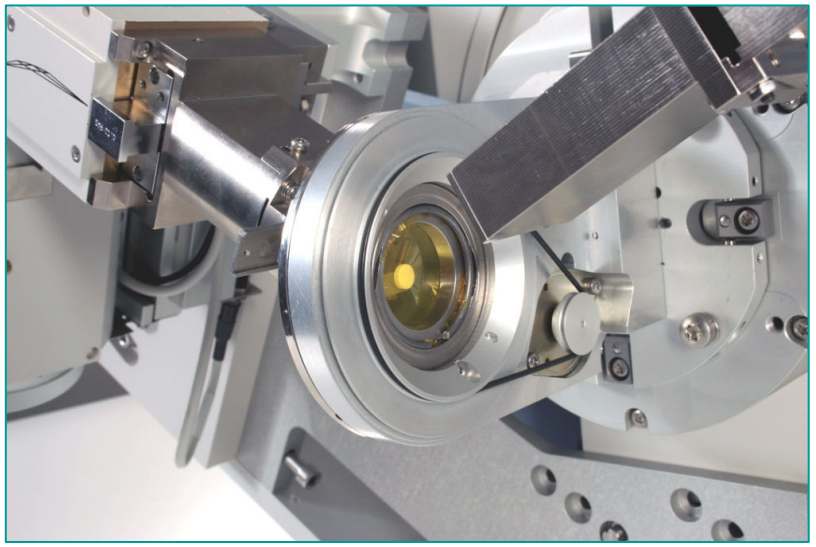


Free acid

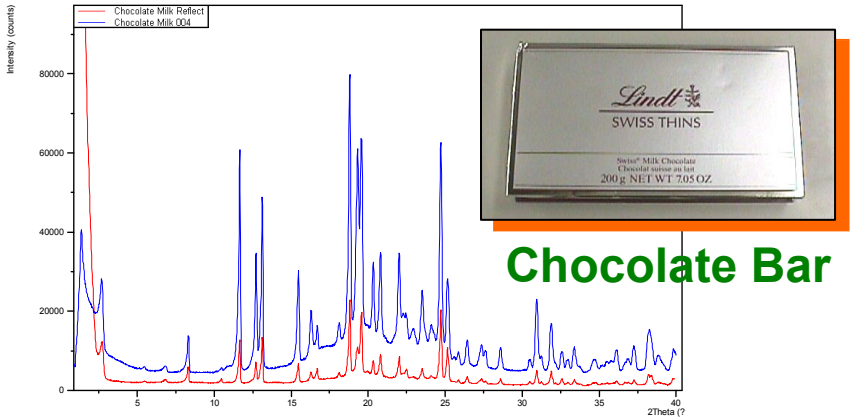
K-salt

透射XRPD：制剂表征中的全新应用

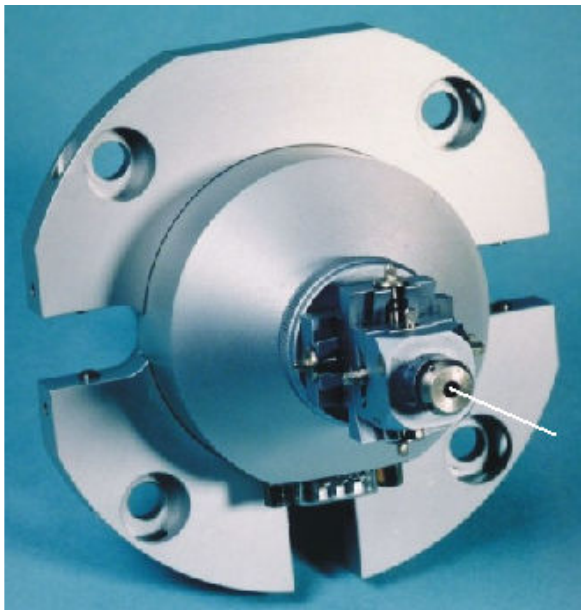




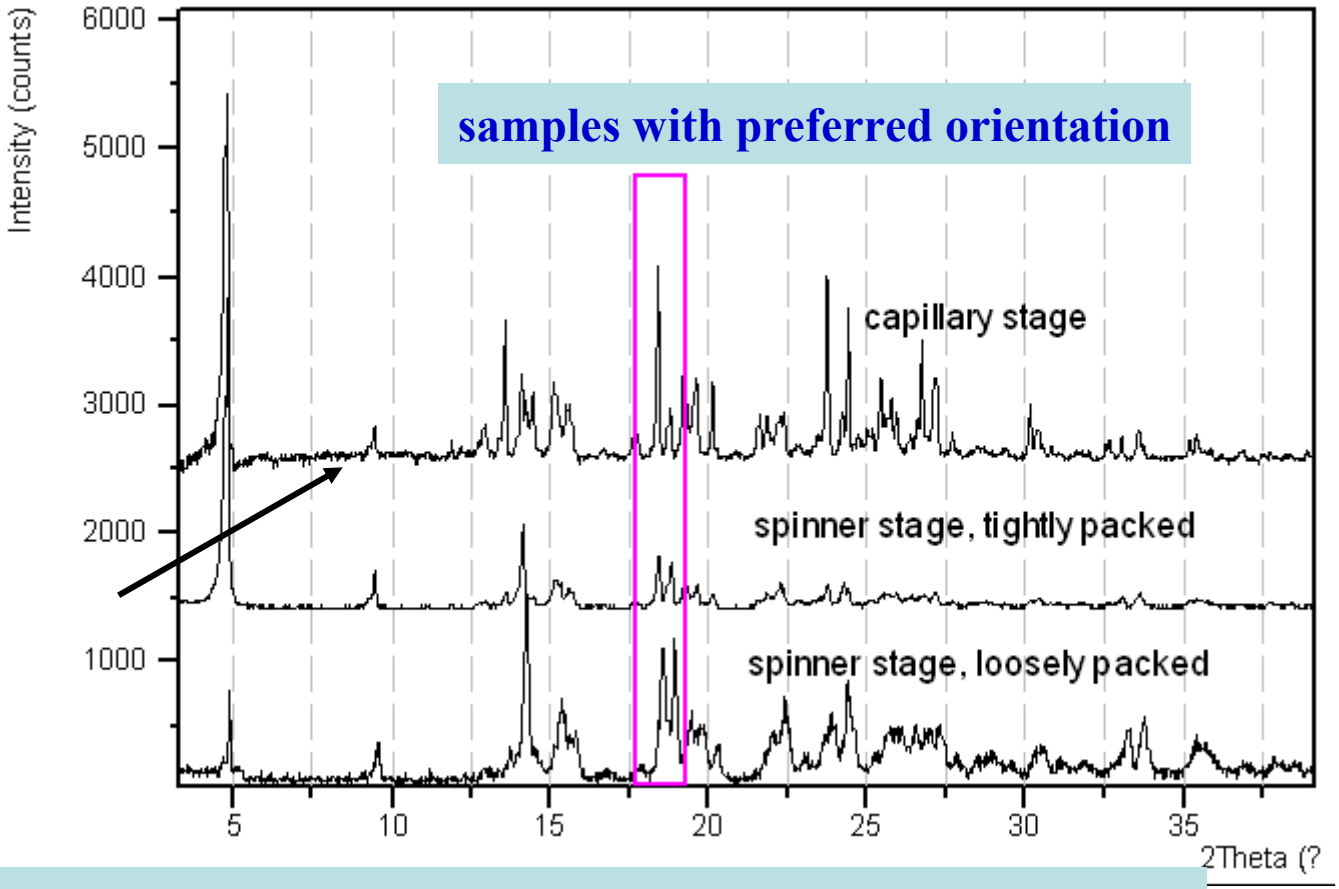
- Significant increase in non-destructive testing of complete formulations (tablets)



Capillary XRPD:
药物晶型研究中的应用

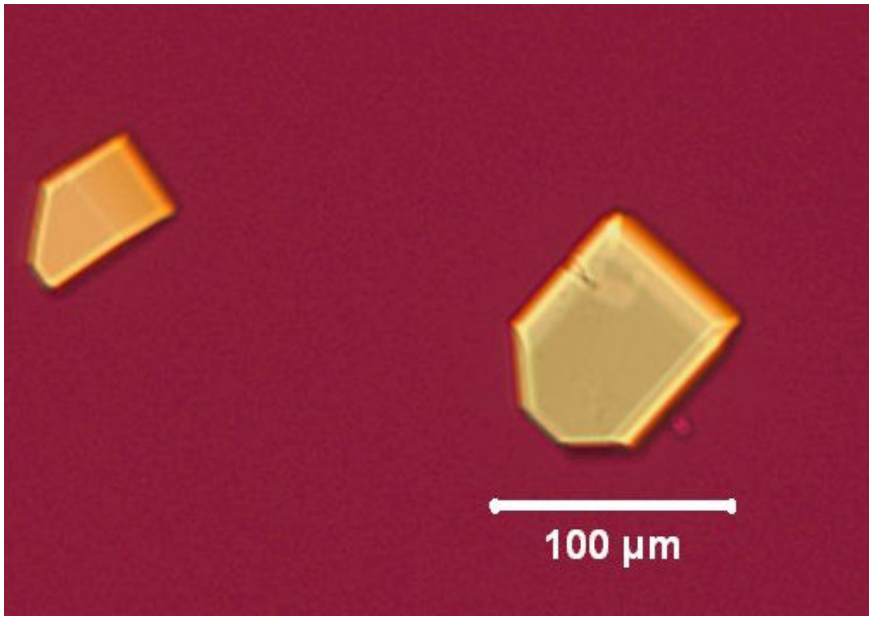


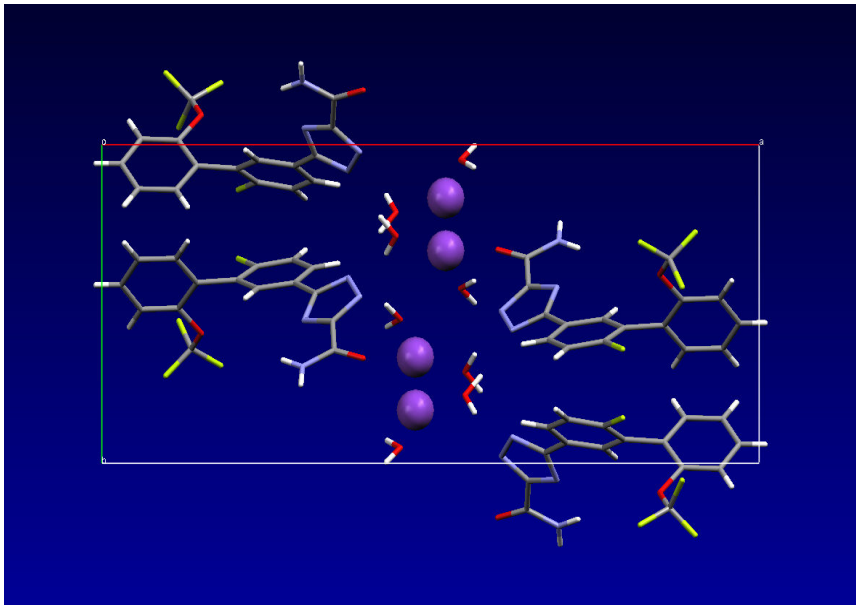
Capillary Stage



Capillary stage gives accurate relative intensities, very useful for (1) samples with preferred orientation, such as needles; (2) crystal structure determination from XRPD

单晶X射线衍射：结构解析





Crystal Structure very important in

- Stereochemistry
- Deep understanding at the atomic/molecular level
- Study of structure-property relationship
- Molecular modeling for drug and process desgin

热分析（Thermal Analysis）

热分析 (Thermal Analysis)

- 热分析方法简介
- 热重分析法(TGA)及应用
- 差示扫描量热法(DSC)及应用
- 介电弛豫分析仪 (DEA)及应用

热分析(Thermal Analysis)简介

Thermal Analysis: techniques whereby certain physical property of the sample is monitored as a function of temperature or time.

- Weight loss: TGA, TGA-MS, TGA-IR
- Heat flow: DTA, DSC(mDSC), microcalorimetry
- Dielectric: DEA
- Mechanic: DMA

DSC

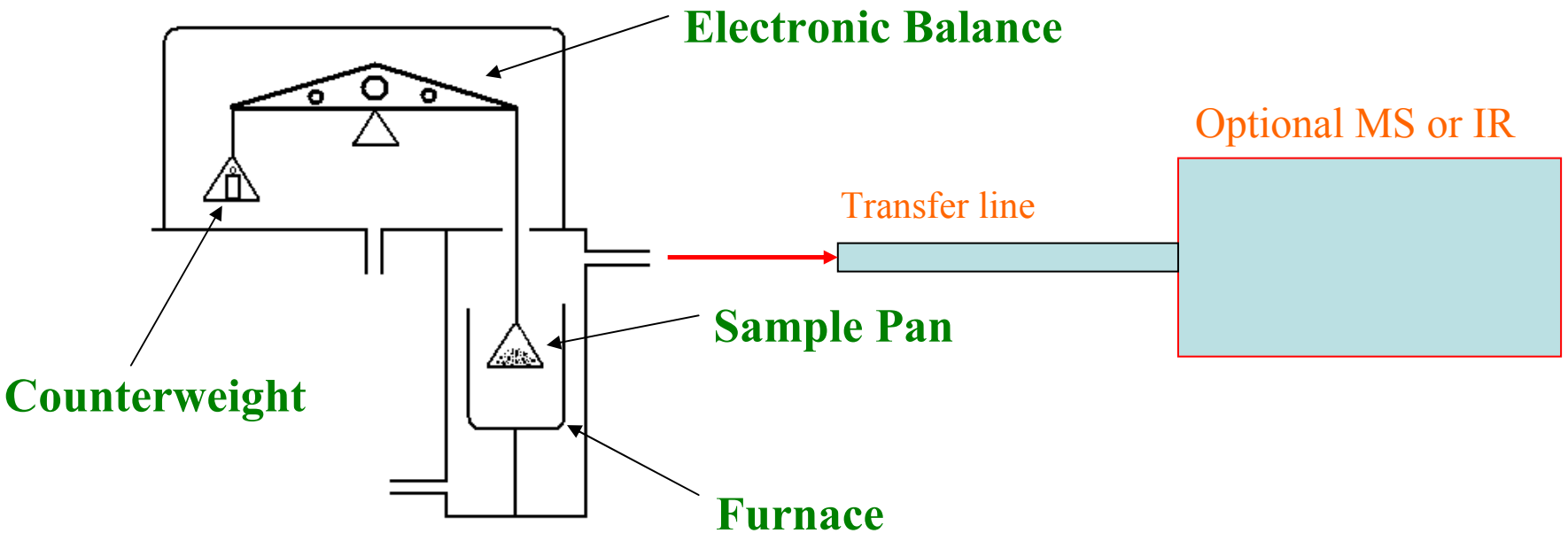
TGA

热重分析法(TGA)及应用

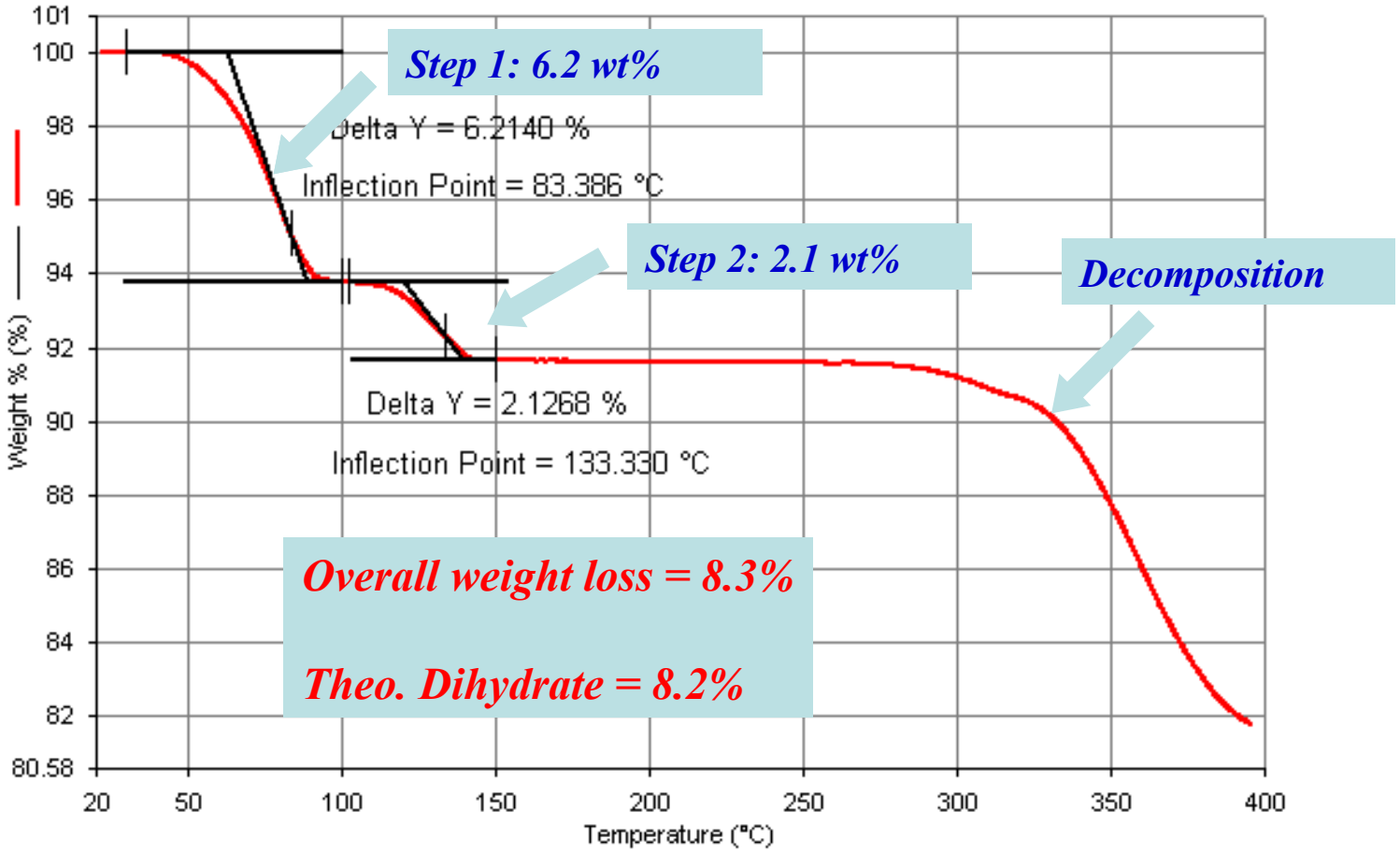
热重分析

•Measure weight changes of sample as a function of time or temperature.

•Can measure evolution of solvents, sublimation or evaporation of sample, or evaluate decomposition to volatile products

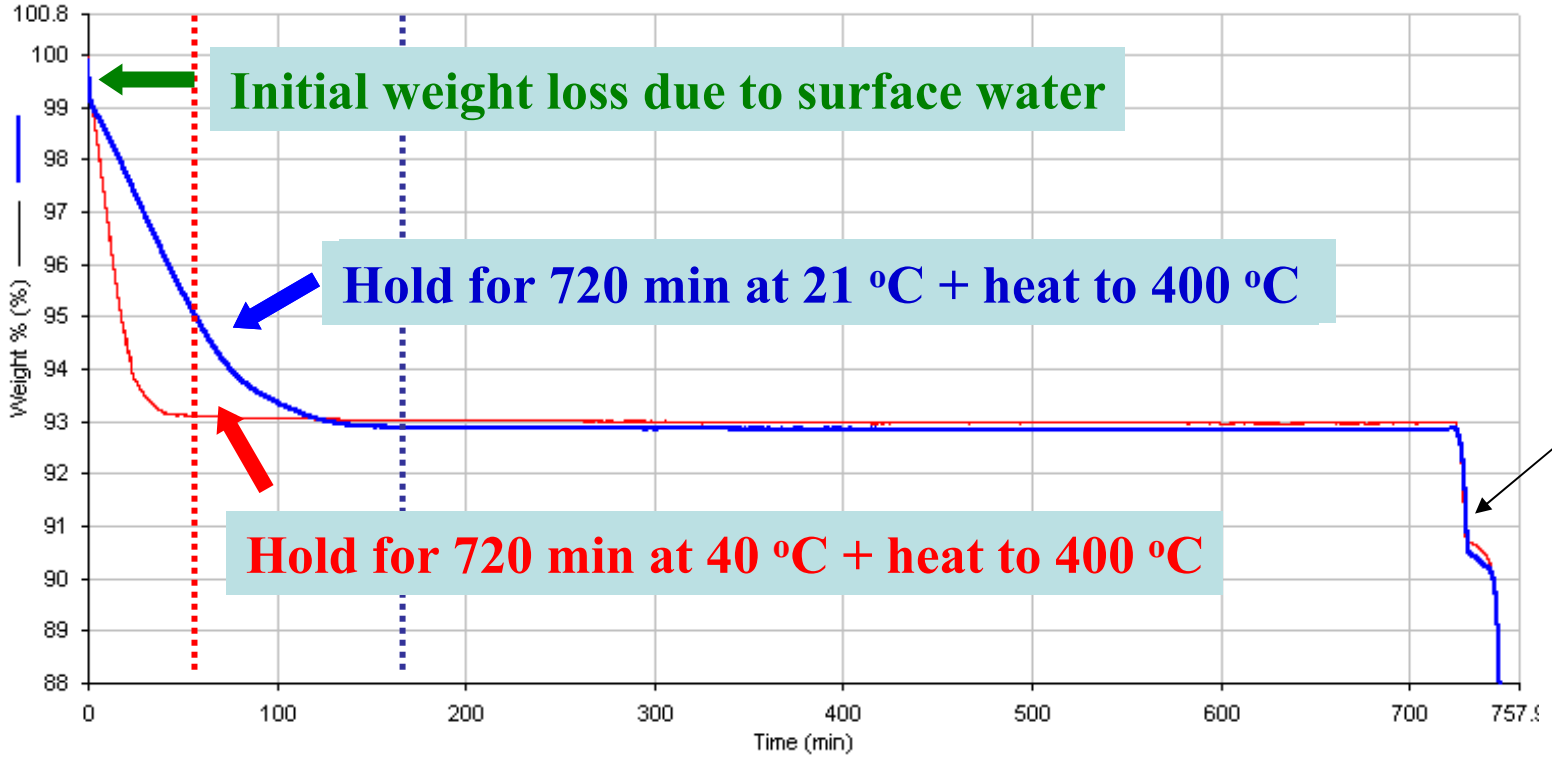


热重分析应用：水合物的检测



Two step weight loss process indicating two types of hydrated water (3:1)

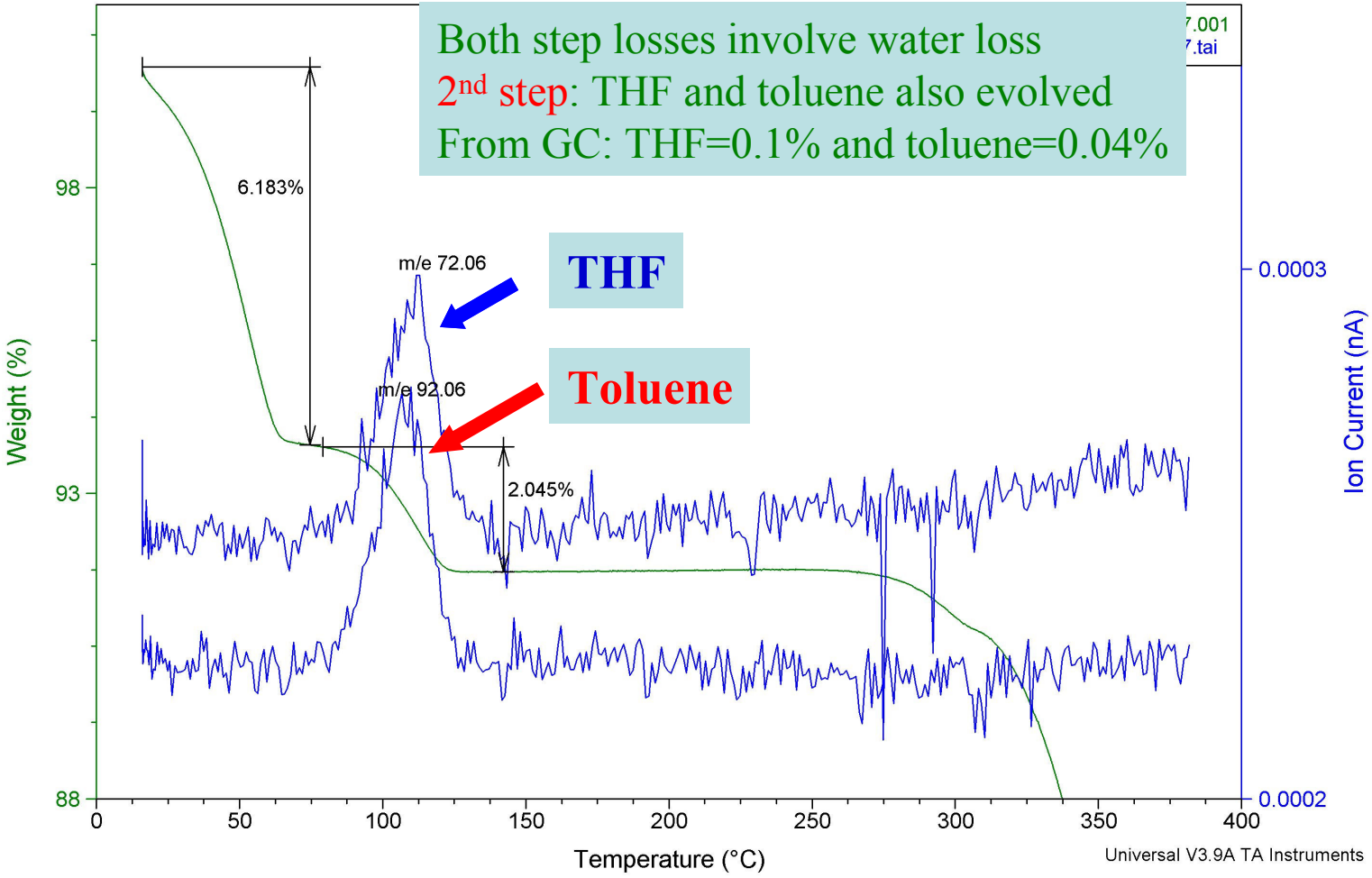
热重分析应用：
水合物中不同类型水分检测



Temperature	Initial loss	Holding loss	Heating loss
21	1.0%	6.0%	2.5%
40	1.0%	5.8%	2.4%

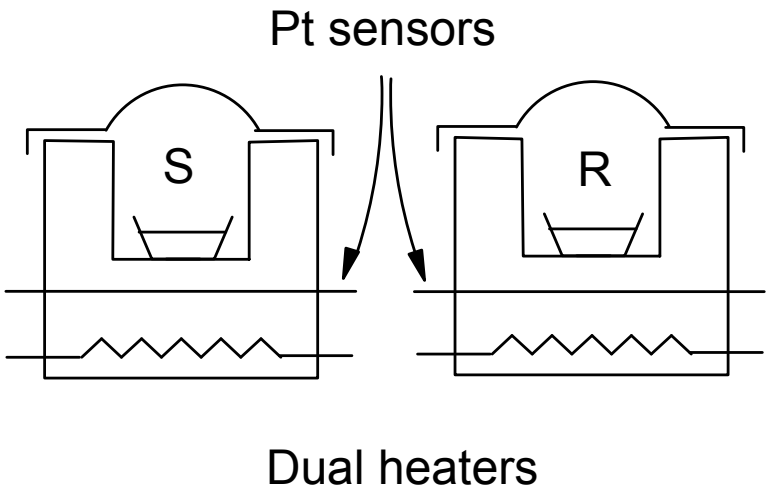
~ 1.0% surface water, ~ 5.9% loosely held water, ~2.5% tightly held water

TGA-MS应用：样品中溶剂成分的检测

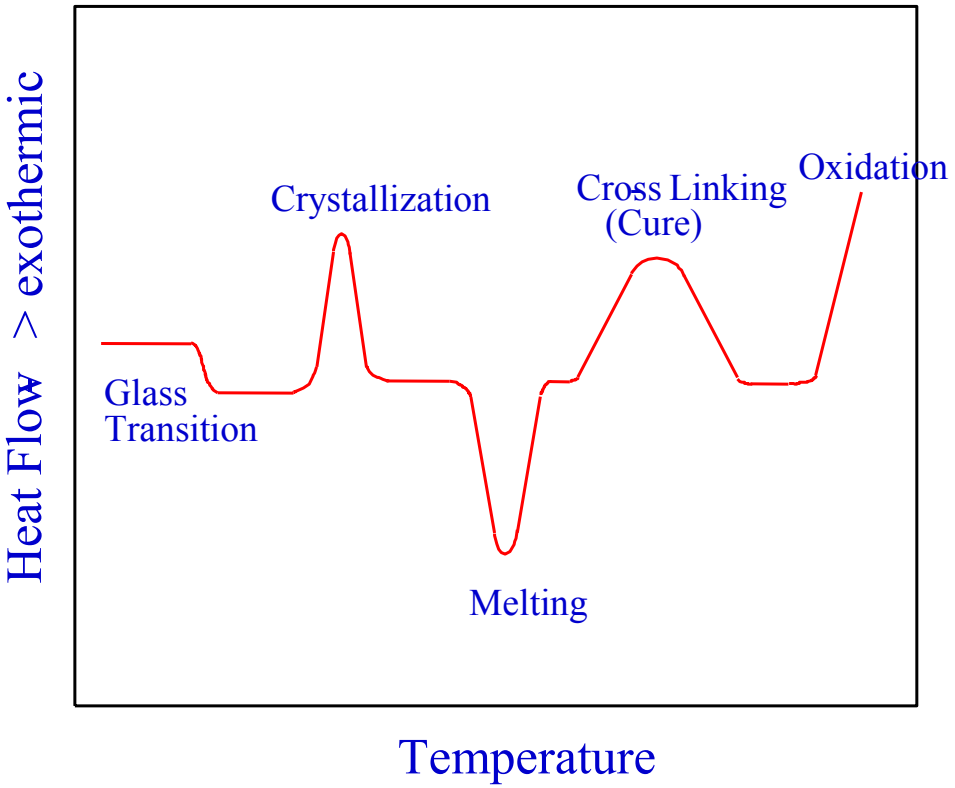


差示扫描量热法(DSC)及应用

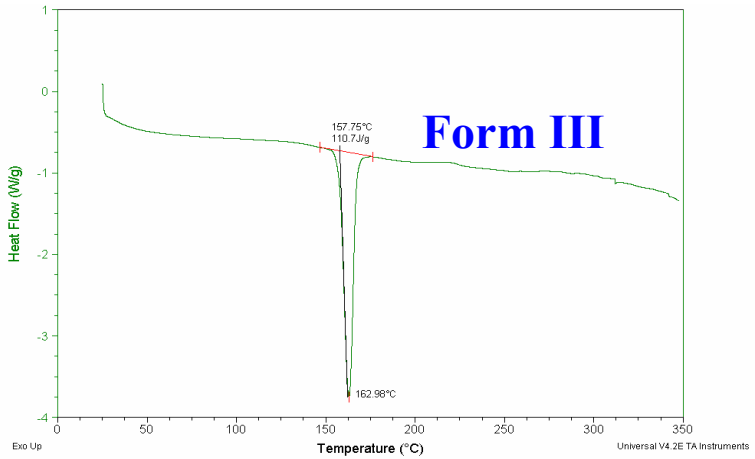
差示扫描量热法(DSC)

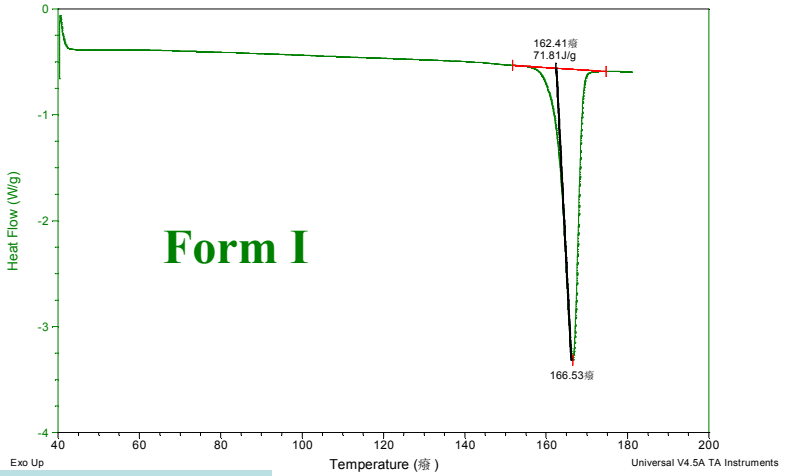


Measure heat flow to or from a sample

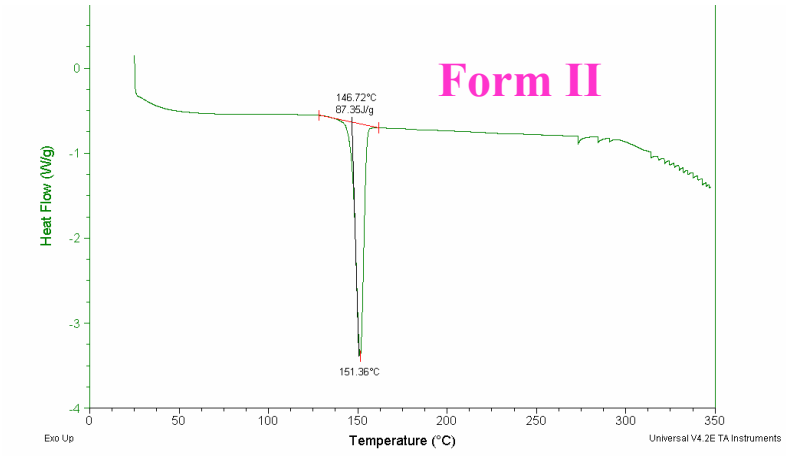


用DSC推测晶型的热力学稳定性





DSC results for three anhydrous forms



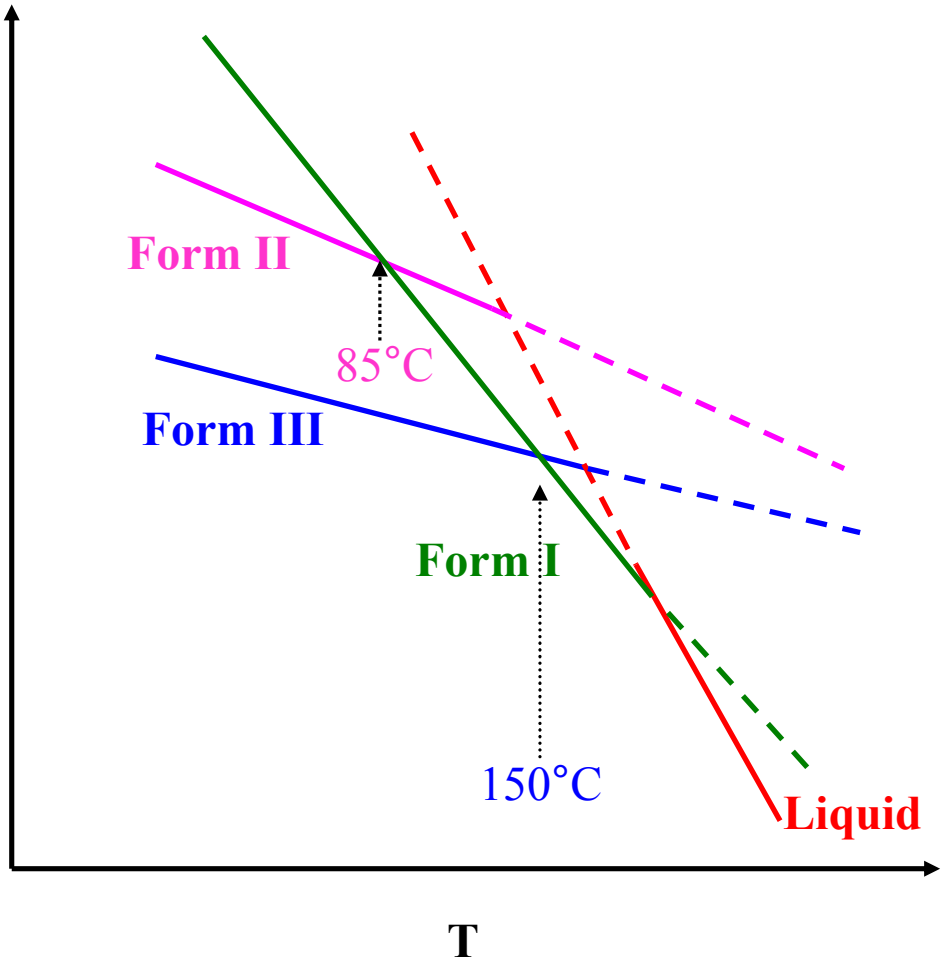
Form	tm (ºC)	Tm (K)	ΔH (J/g)
Form I	162.4	435.6	71.80
Form II	146.7	419.9	87.40
Form III	157.8	431.0	110.70

用DSC推测晶型的热力学稳定性

$$T_t \approx T_{m,A}\frac{\left(\Delta H_{m,A}/\Delta H_{m,B}-1\right)-yK}{\left(\Delta H_{m,A}/\Delta H_{m,B}-(1+y)\right)-yK}$$

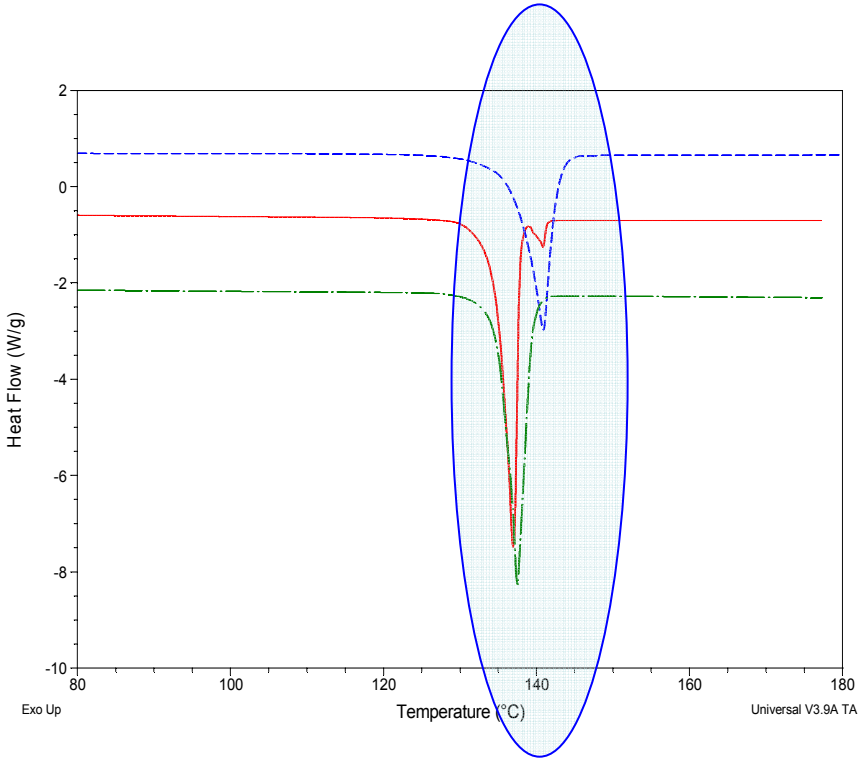
$$y \equiv \frac{T_{m,A}-T_{m,B}}{T_{m,B}} = \frac{T_{m,A}}{T_{m,B}}-1$$

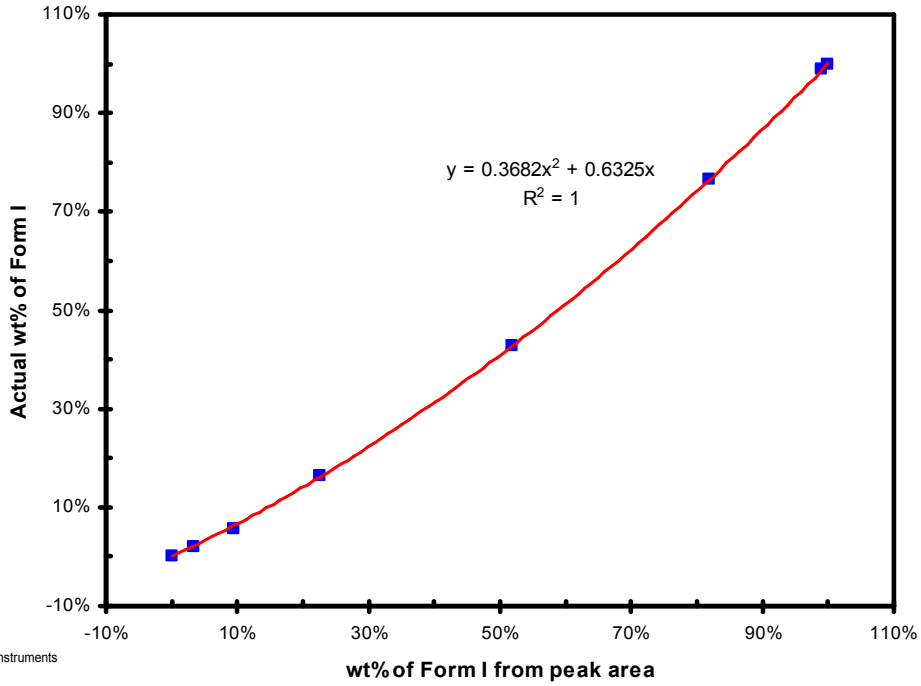
$$K \equiv \left(C_{p,L}-C_{p,B}\right)T_{m,B}/\Delta H_{m,B}$$



The relative thermodynamic stability between the three forms was confirmed by solubility measurement.

用DSC对晶型检测和定量分析

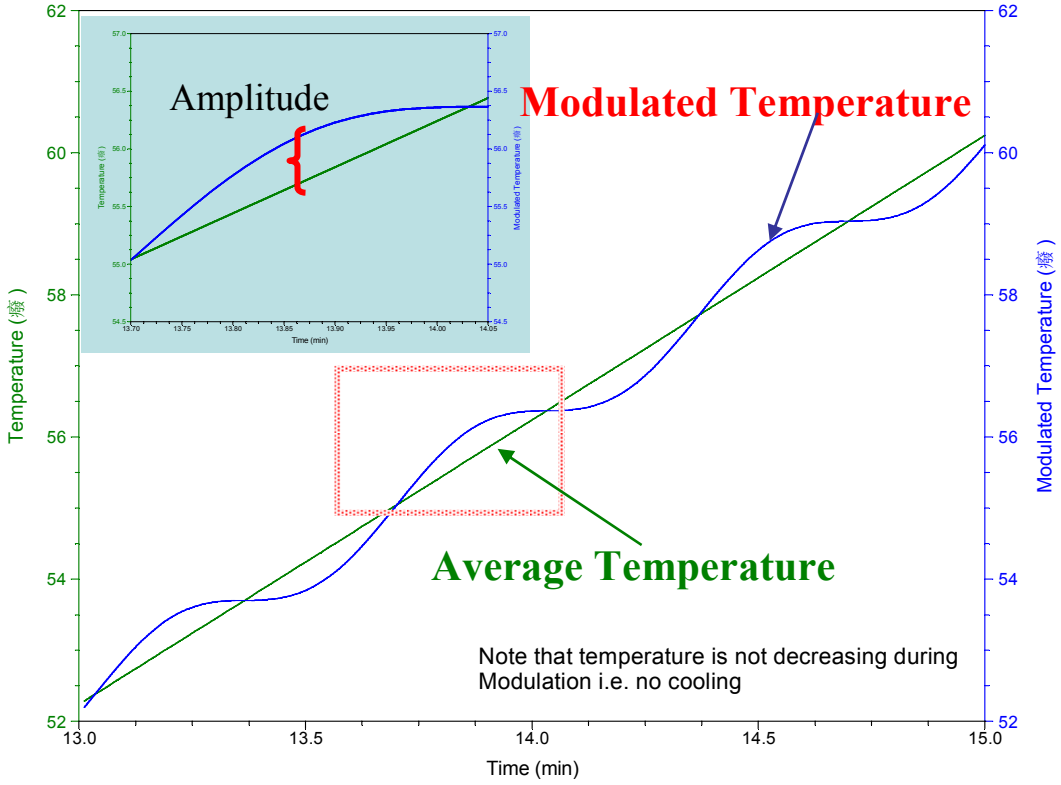




Limit of detection (LOD): < 1%

Limit of quantification (LOQ): < 1%

调制式差示扫描量热仪(mDSC)



- Heat the sample at a constant rate as in standard DSC
- Apply sinusoidal heating profile on top of underlying heating rate
- Separate “reversible” and “non-reversible” events

(“reversible” and “non-reversible” events refers to the timescale of material response, NOT thermodynamics)

mDSC的优缺点

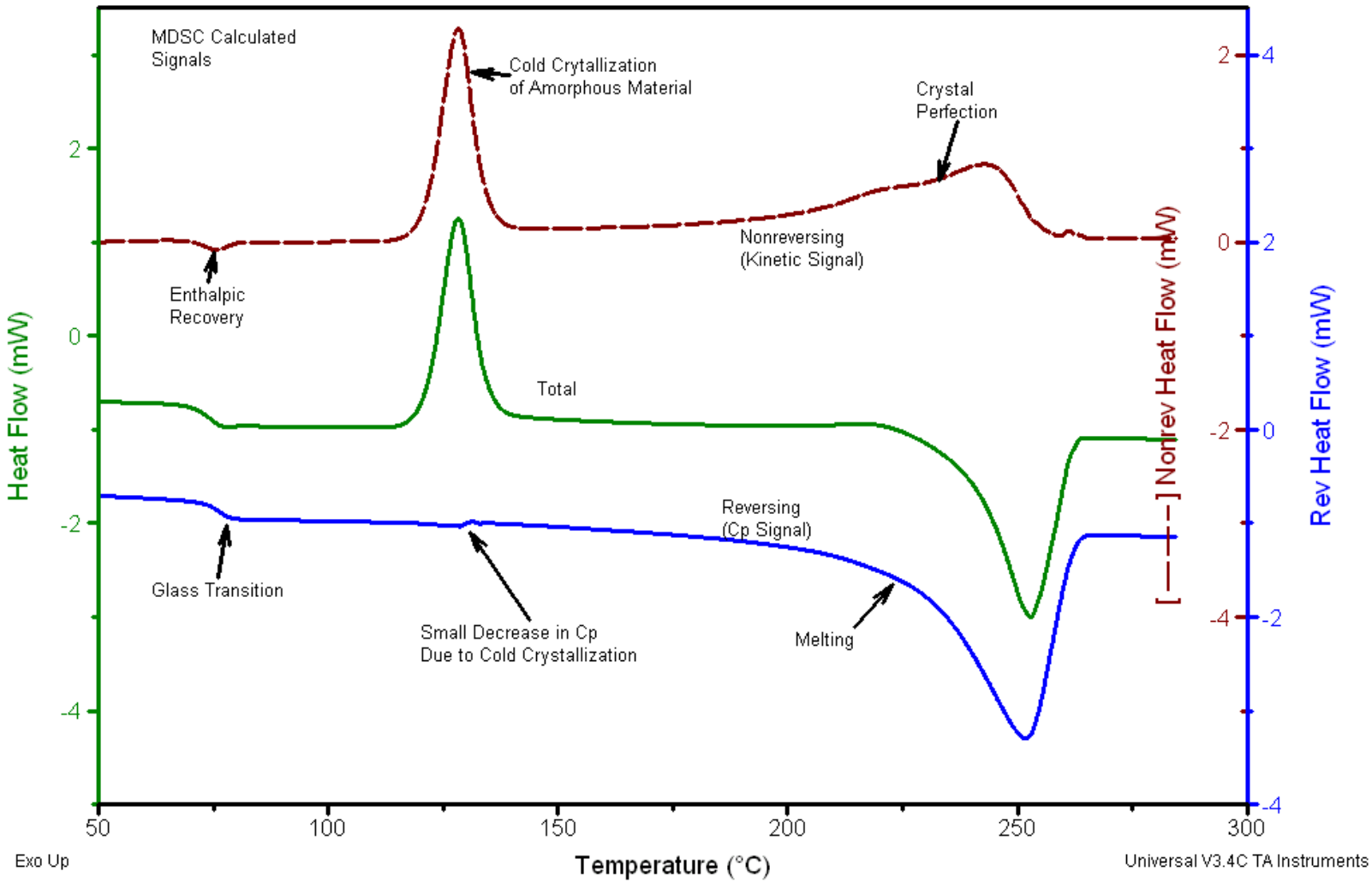
Benefits

- Increased sensitivity for detecting weak (glass) transitions
  - Eliminates baseline curvature and drift
- Increased resolution without loss of sensitivity
  - Two heating rates (average and instantaneous)
- Ability to separate complex thermal events and transitions into their heat capacity and kinetic components
- Ability to measure heat capacity (structure) changes during reactions and under isothermal conditions

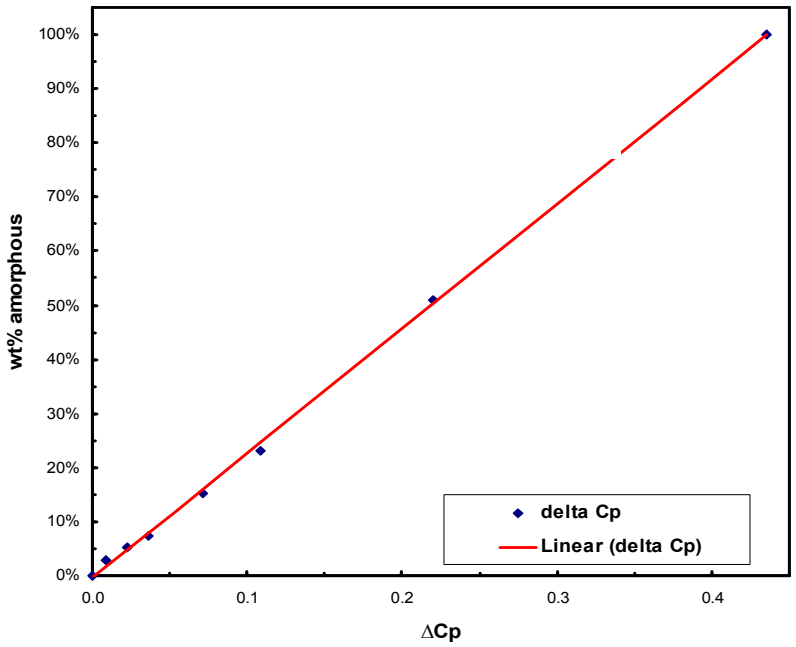
Downside

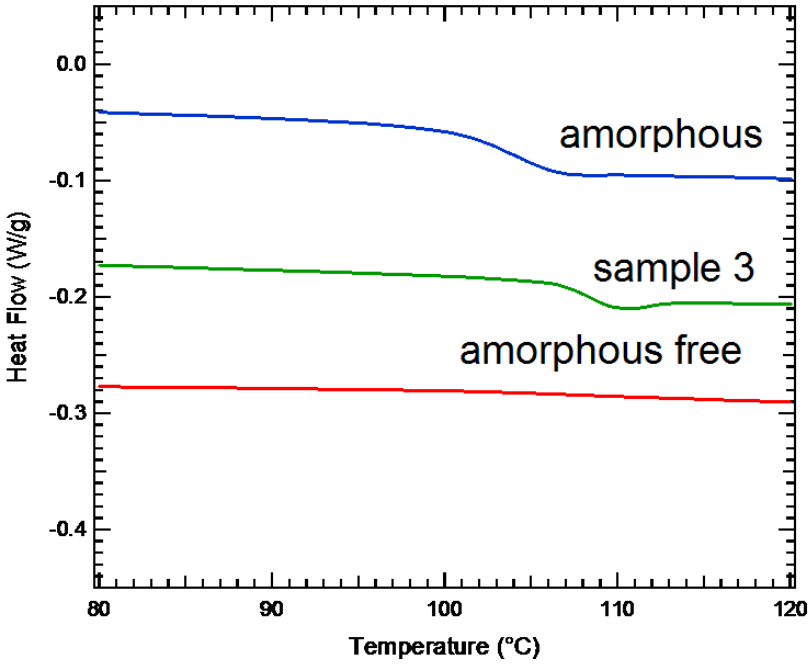
- Slow data collection

mDSC曲线：PET


MDSC Calculated
Signals
Cold Crytallization
of Amorphous Material
Crystal
Perfection
Nonreversing
(Kinetic Signal)
Enthalpic
Recovery
Total
Reversing
(Cp Signal)
Glass Transition
Small Decrease in Cp
Due to Cold Crystallization
Melting
Heat Flow (mW)
[— — —] Nonrev Heat Flow (mW)
Rev Heat Flow (mW)
Temperature (°C)
Exo Up
Universal V3.4C TA Instruments

用DSC/mDSC对无定形成分检测和定量分析

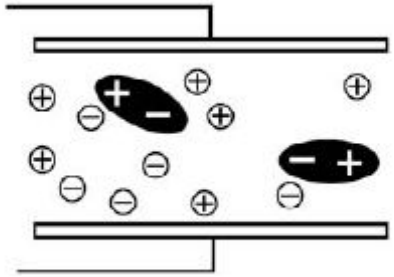




Sample	Amorphous content (wt%)	std (wt%)	# of measurements
Sample 1	**16.4**	2.0	3
Sample 2	**23.2**	2.9	3
Sample 3	**37.8**	2.0	3
Sample 3 stability study at 25°C/60%RH for 2 month	**39.6**	2.7	3

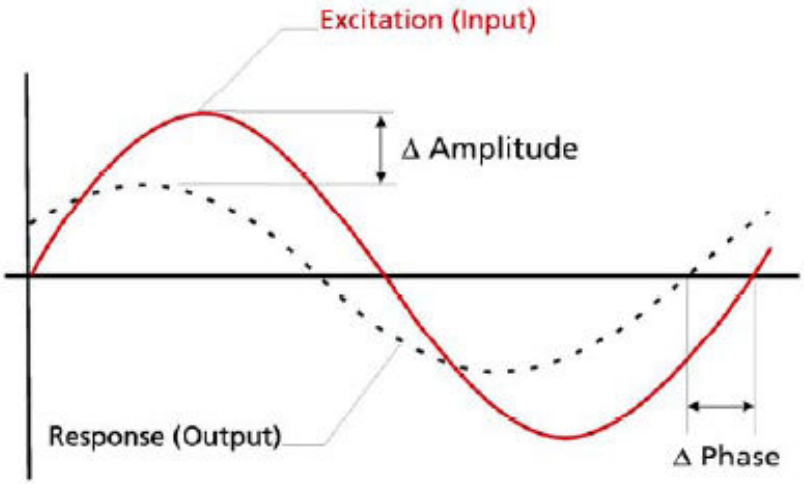
介电弛豫分析仪 (DEA)及应用

介电弛豫分析仪
(Dielectric relaxation analyzer)



A low voltage AC signal is applied at one electrode

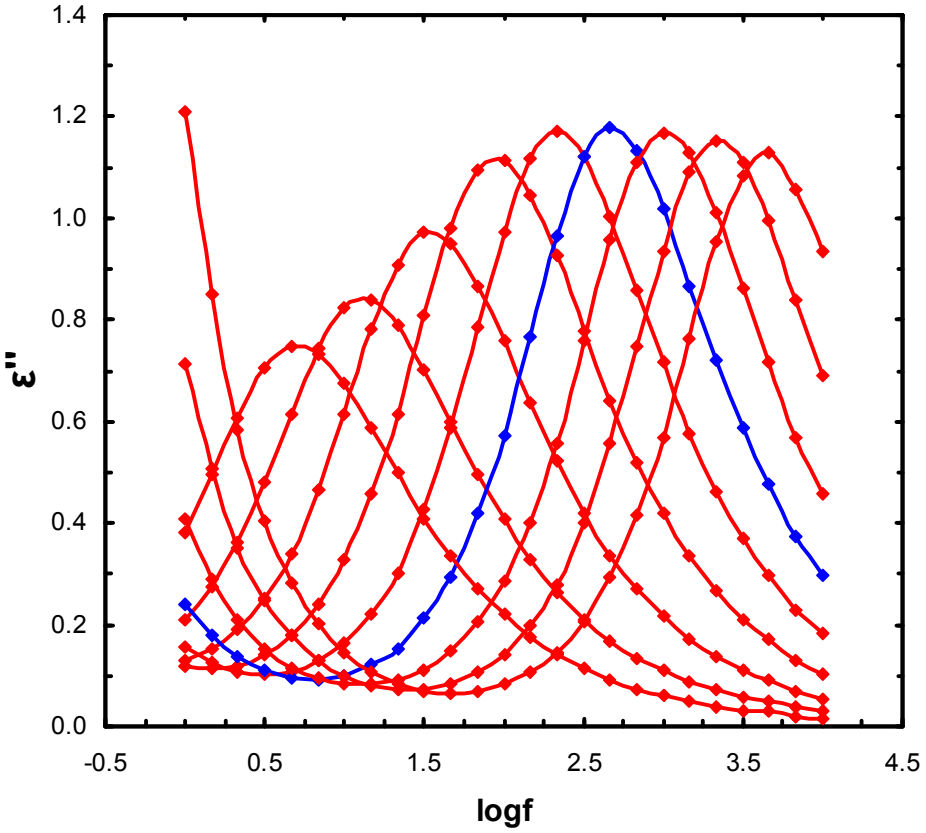
The response signal detected at the other electrode is **attenuated** and **phase** shifted

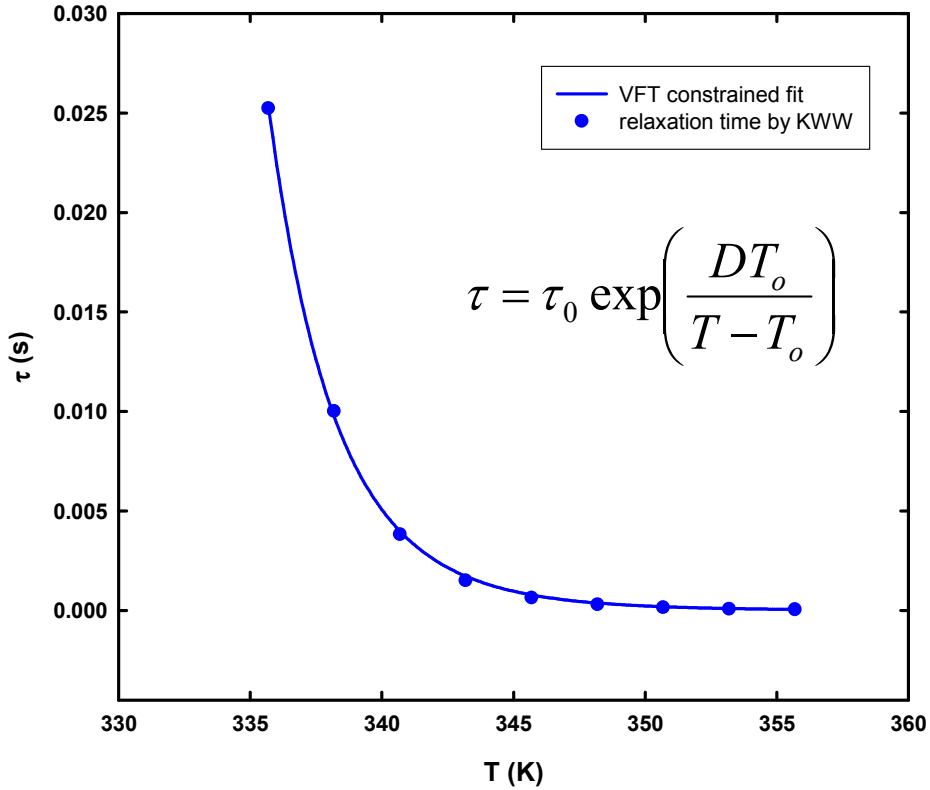


ε': permittivity, a measure of the alignment and number of dipolar groups

ε'': loss factor, a measure of total energy loss due to the work performed aligning dipoles and moving ions

介电弛豫分析仪：
研究无定形药物的弛豫现象



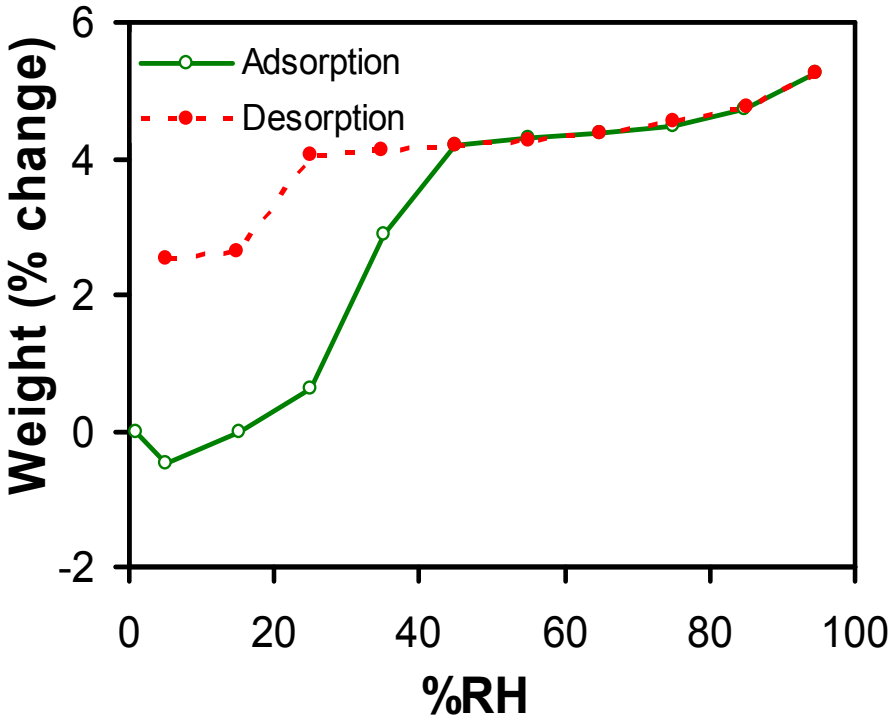


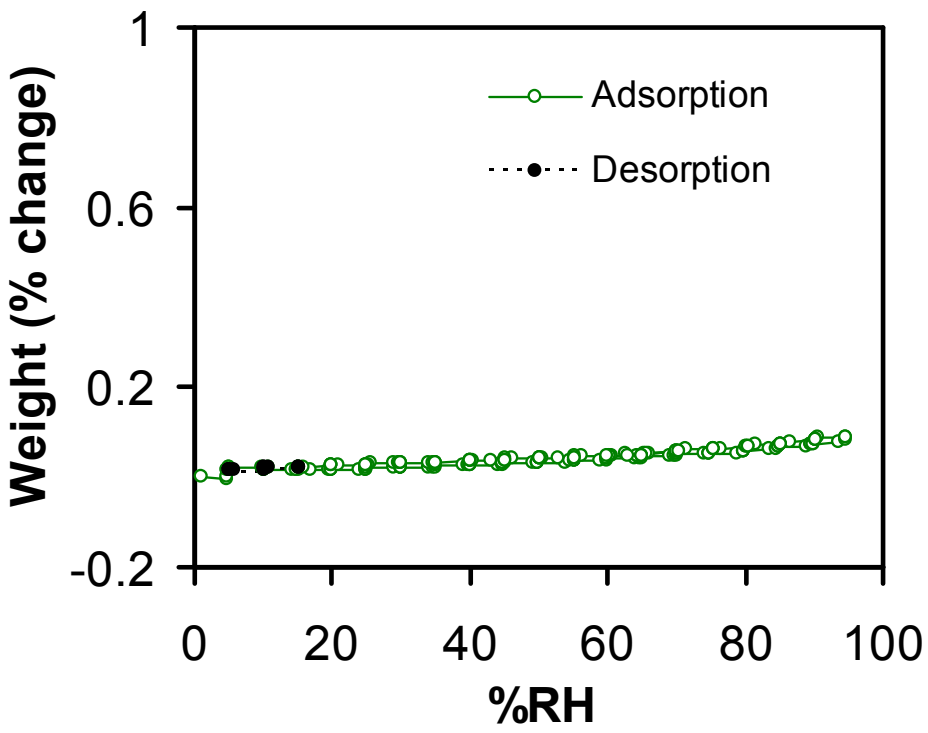
D = 7.4965, **T_0 = 267.3**

T_g = 321.7K (48.5 °C)

动态气相吸附仪
(Dynamic Vapor Sorption Analysis)

动态气相吸附仪：研究水分吸附性能

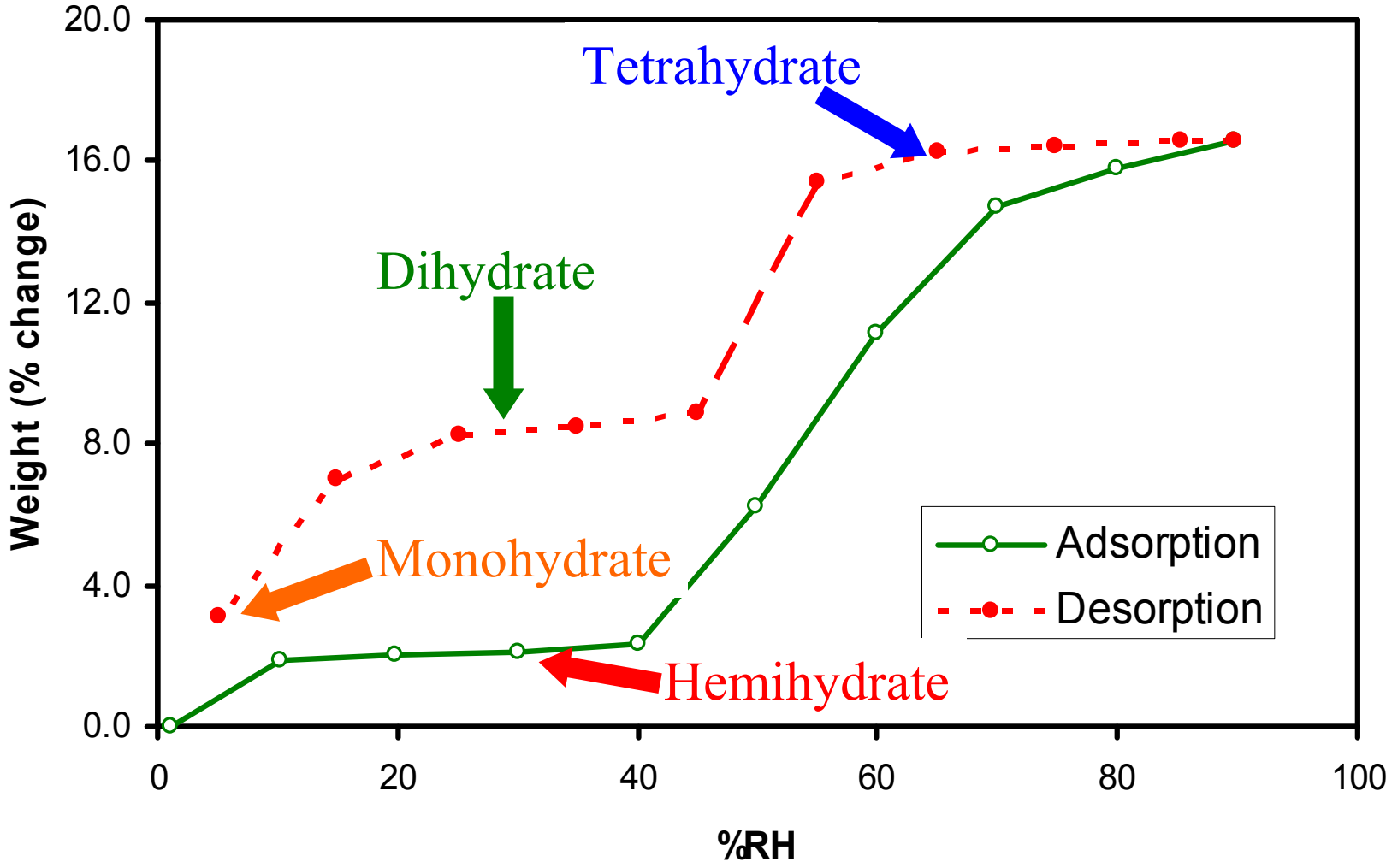




Information about

- storage conditions and drying conditions
- hydration-dehydration

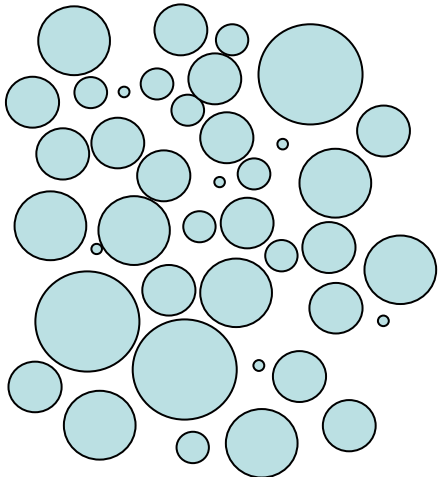
动态水分吸附仪：研究水合物的重要工具

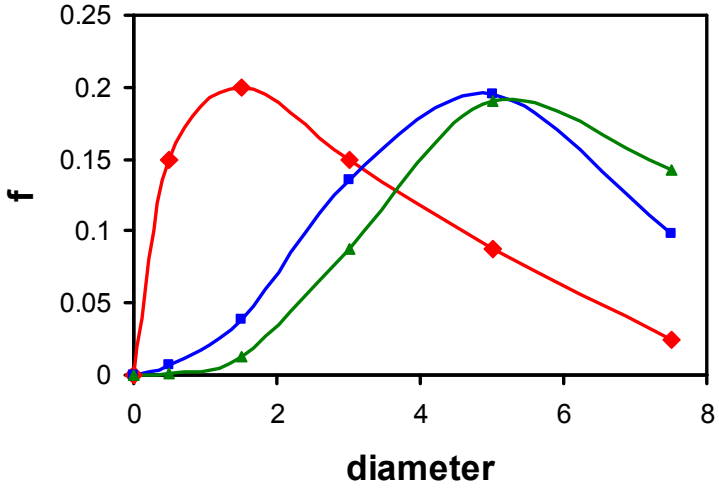


激光散射粒度分布分析仪
(Laser Light Scattering Particle Size Distribution Analyzer)

为什么要测药物颗粒大小分布

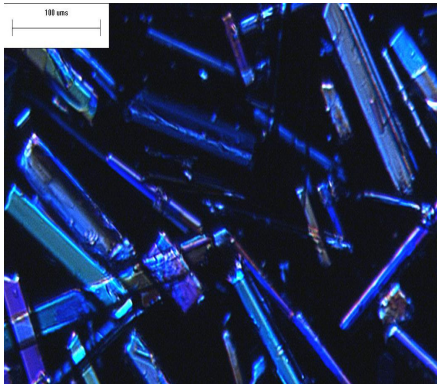
- Particle size can impact dissolution rate and bio-performance
- Particle size can impact formulation process: flow, compaction, sticking, bulk density, segregation
- Consistent product at full scale requires PSD control
- Particle size impacts API processing: equipment choice, cost, filtration rate

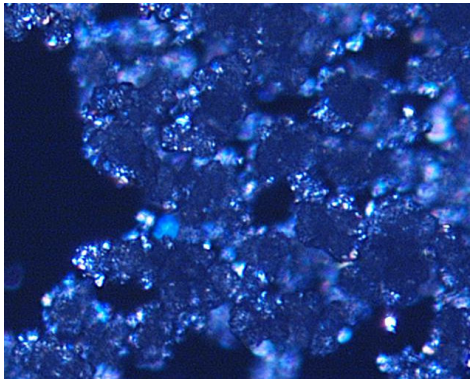




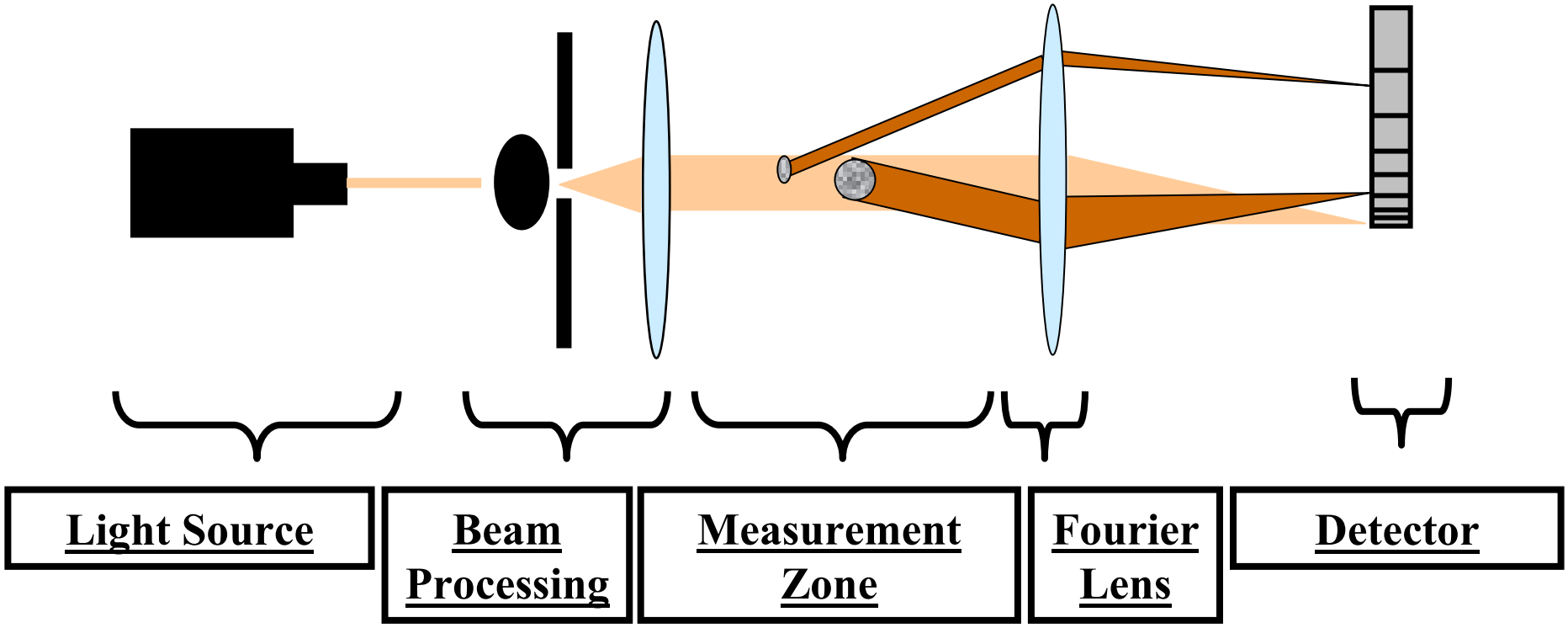
我们测量的是什么？

- Primary particles
- Mixture of primary particles and agglomerates
- Mixture of primary particles and aggregates
- Agglomerates
- Aggregates

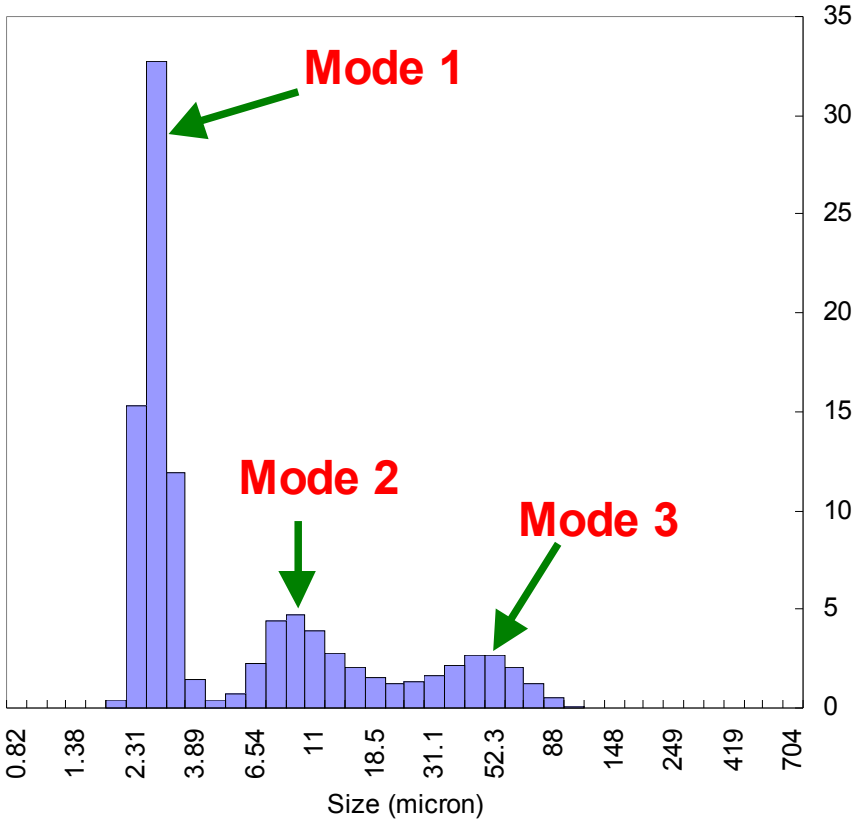


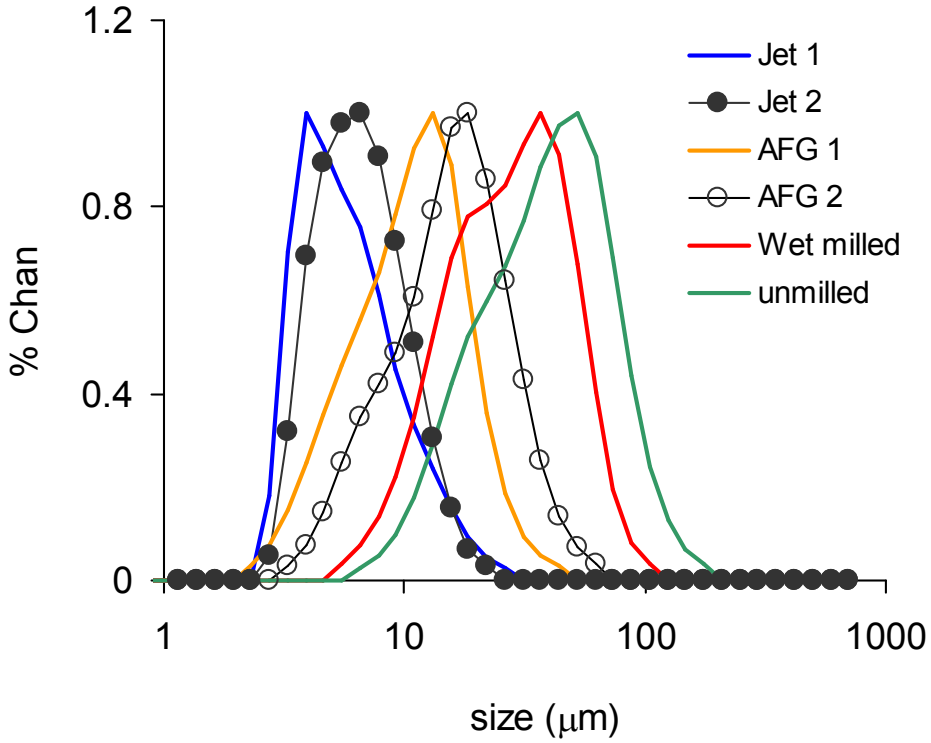


静态激光散射：颗粒大小测定



静态激光散射：颗粒大小分布研究



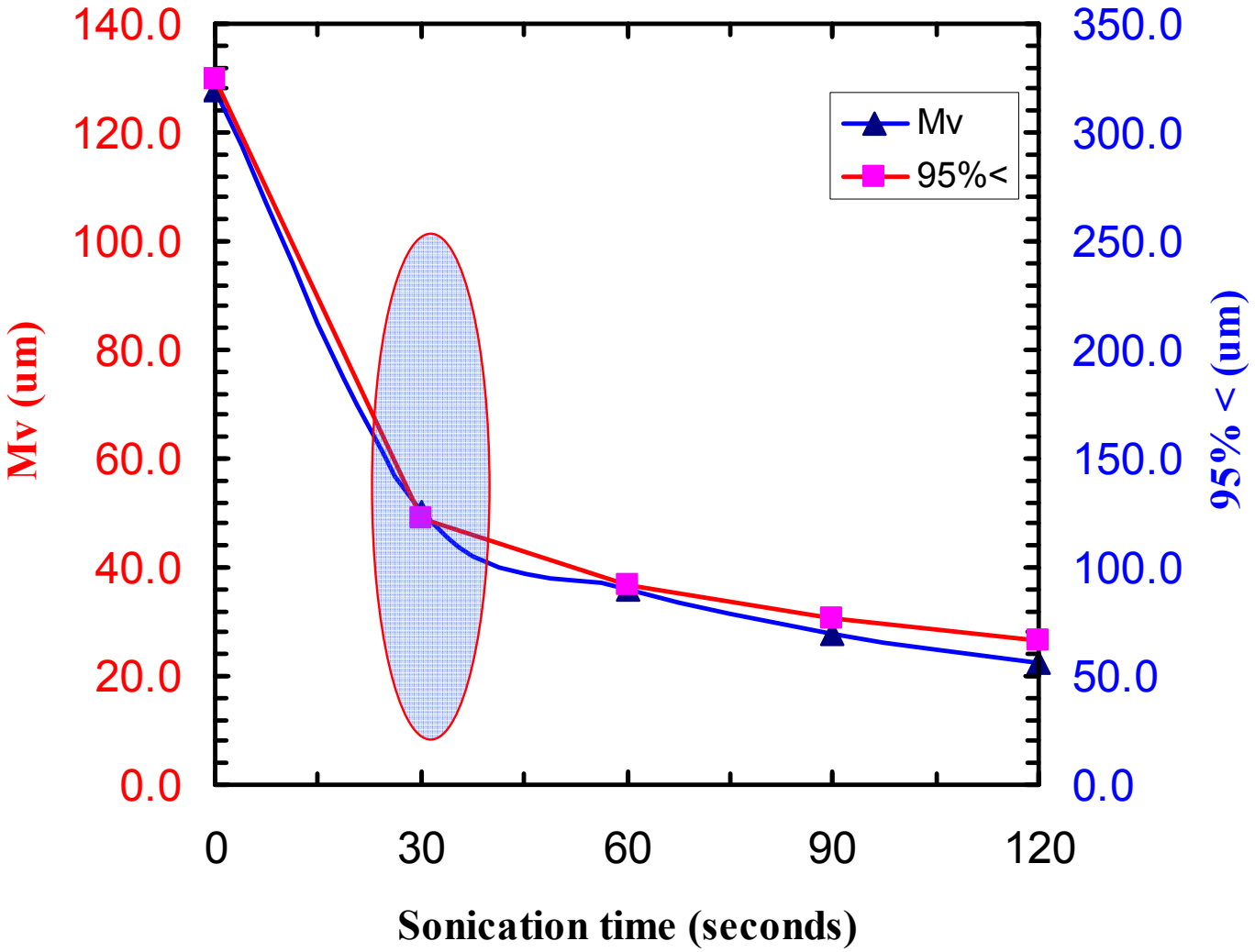


影响粒径分布结果的主要因素

- 是否使用超声，使用超声的时间和强度
- 使用的分散溶剂
- 颗粒的折射系数
- 不同厂家的仪器，同一厂家的不同型号的仪器，同一型号的仪器但是不同一个仪器
- 湿法分散 vs. 干法分散

没有注明测试条件所得的数据没有任何意义

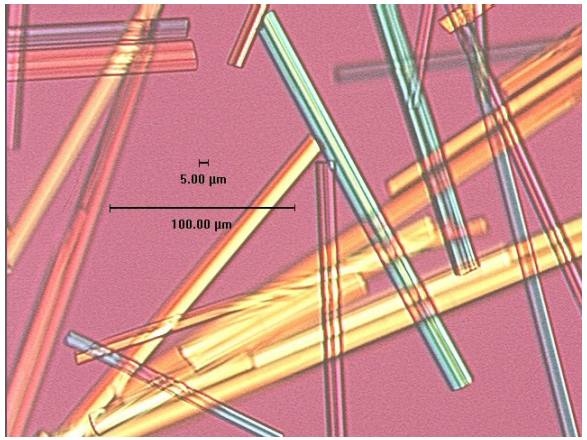
案例：超声时间对颗粒大小的影响



比表面积分析
(Surface Area Measurement)

比表面积测定的重要性

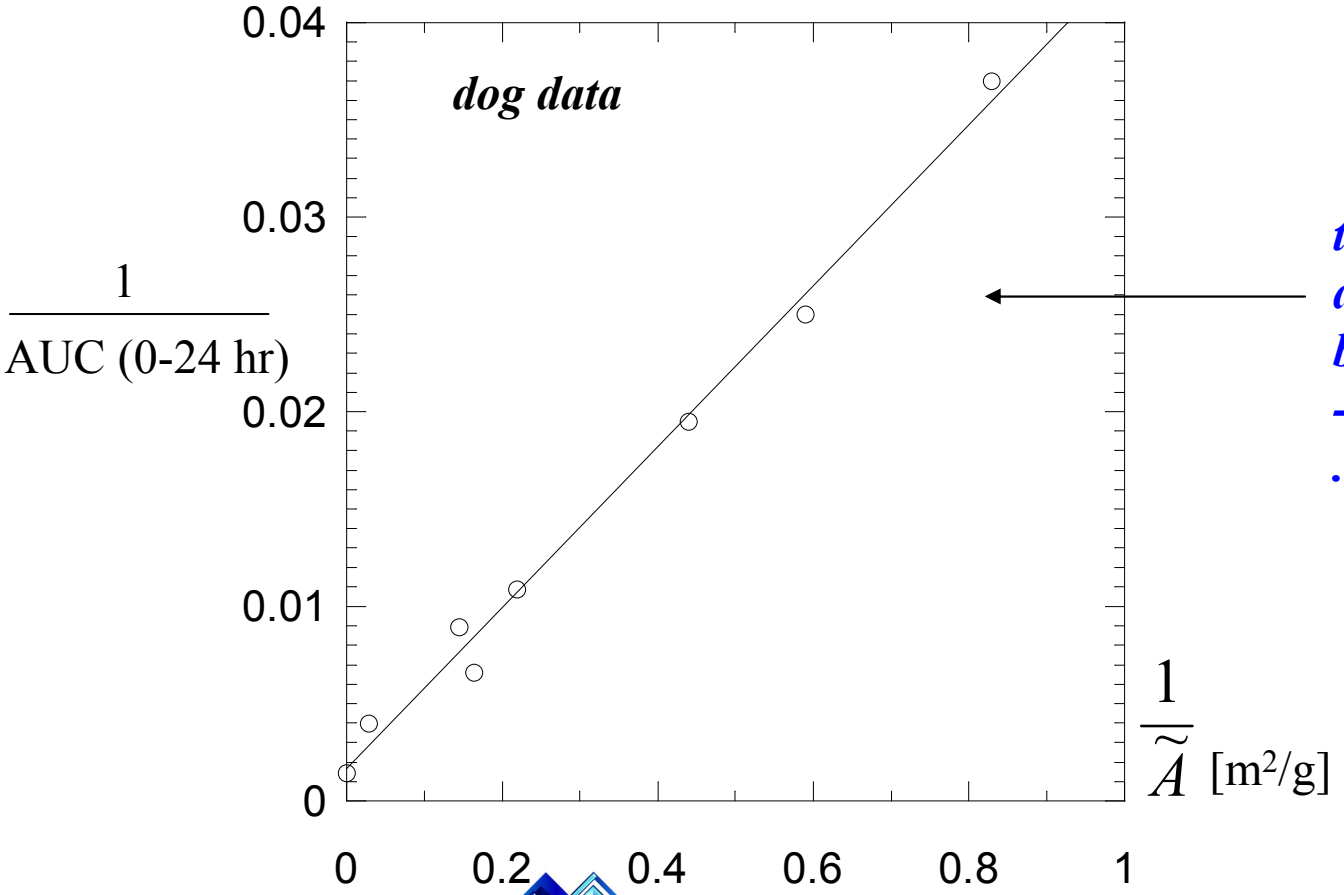
- Many sizing techniques yield distributions that are quite misleading for highly non-spherical shapes



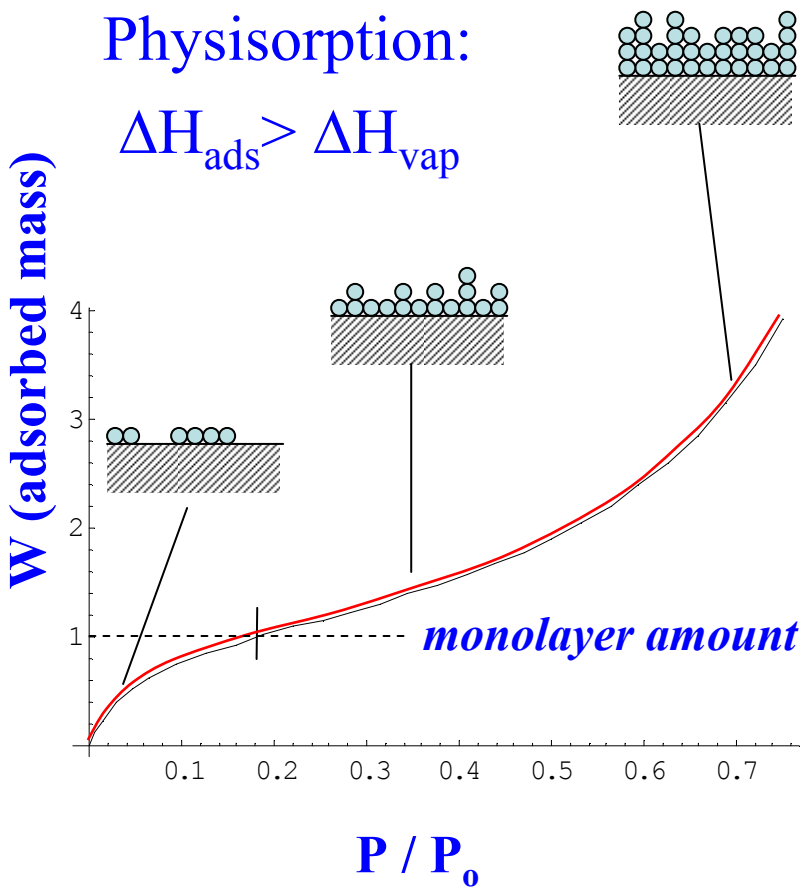
- Surface area is sensitive to surface roughness on a nm length scale (for gas adsorption)

比表面积测定的重要性

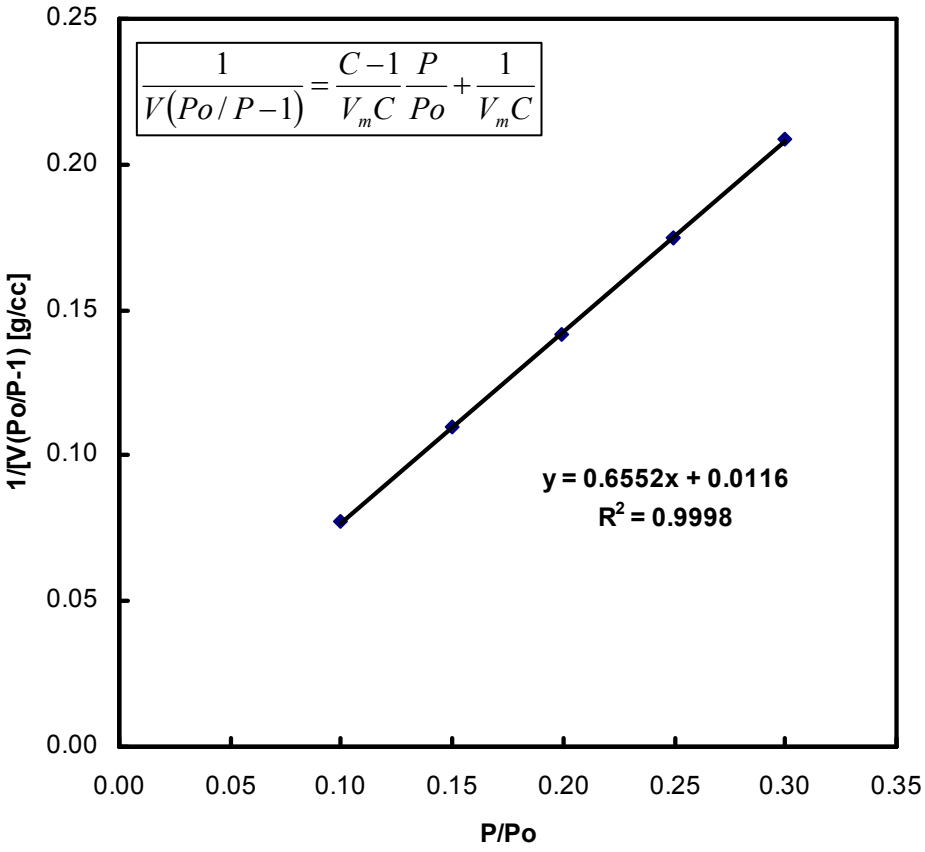
- Example: surface area can be a convenient quantity to correlate with coating, dissolution, etc.



比表面积测定：BET吸附



N_2 adsorption

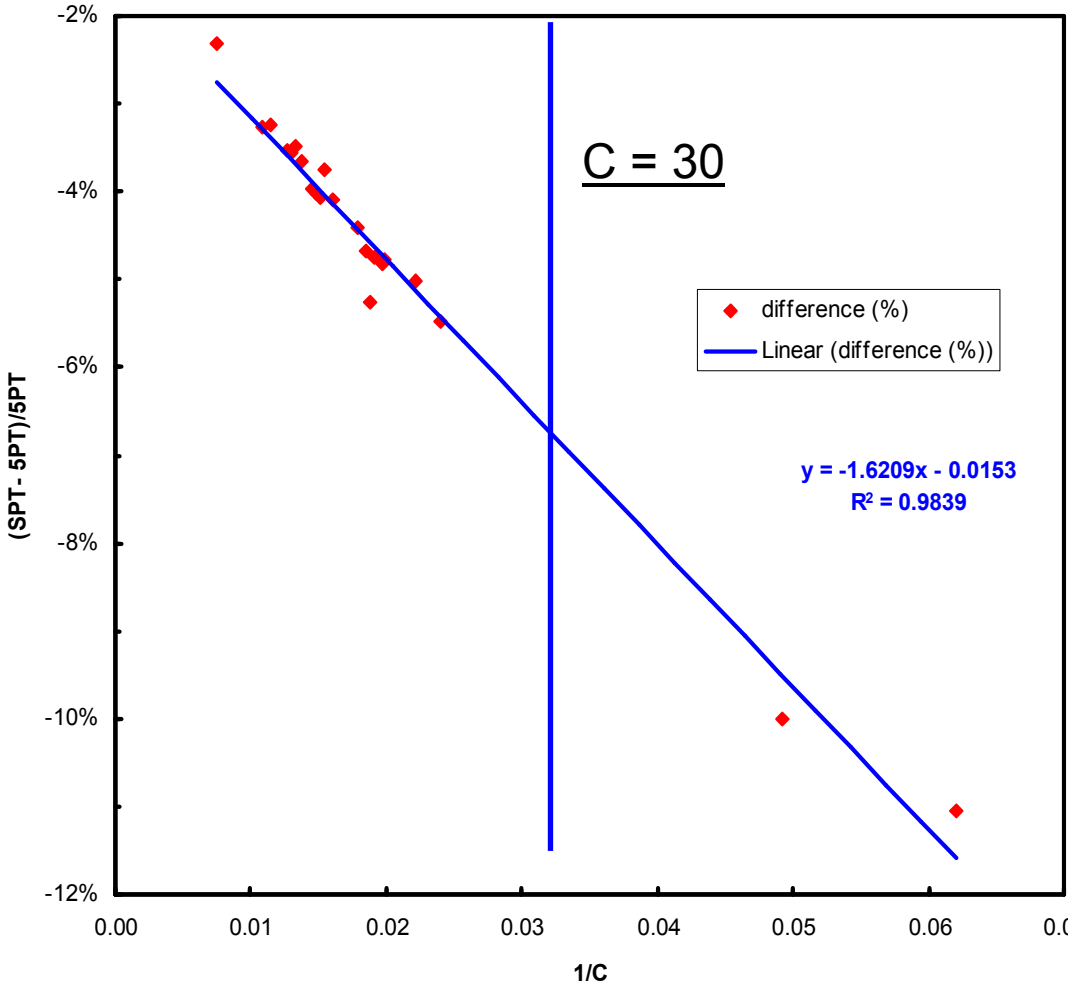


Surface area (m^2/g): 6.5

比表面积测量方法

- Multi-point measurement for gas adsorption ***isotherm***
  - ***slower*** (~1 hour / sample)
  - for special cases
  - absorbate = N_2 or Kr

- Single-point measurement for B.E.T. ***surface area*** [m^2/g]
  - ***quicker*** (as fast as 10 minutes)
  - absorbate = N_2
  - assumptions and pitfalls

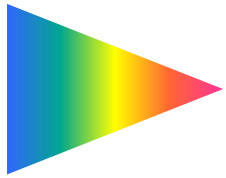


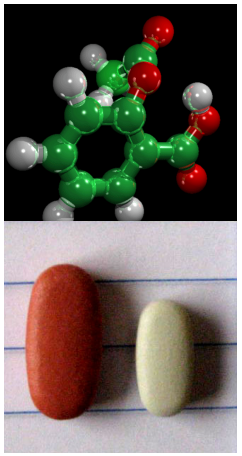
拉曼光谱
(Raman Spectroscopy)

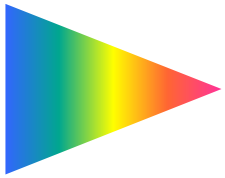
拉曼光谱简介

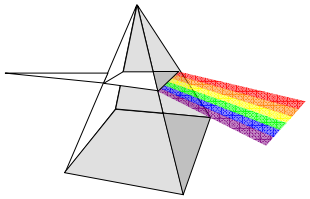
Light delivery via
Fiber optics
Process interface

Light Collection after
Absorption, emission, or
Scattering by sample



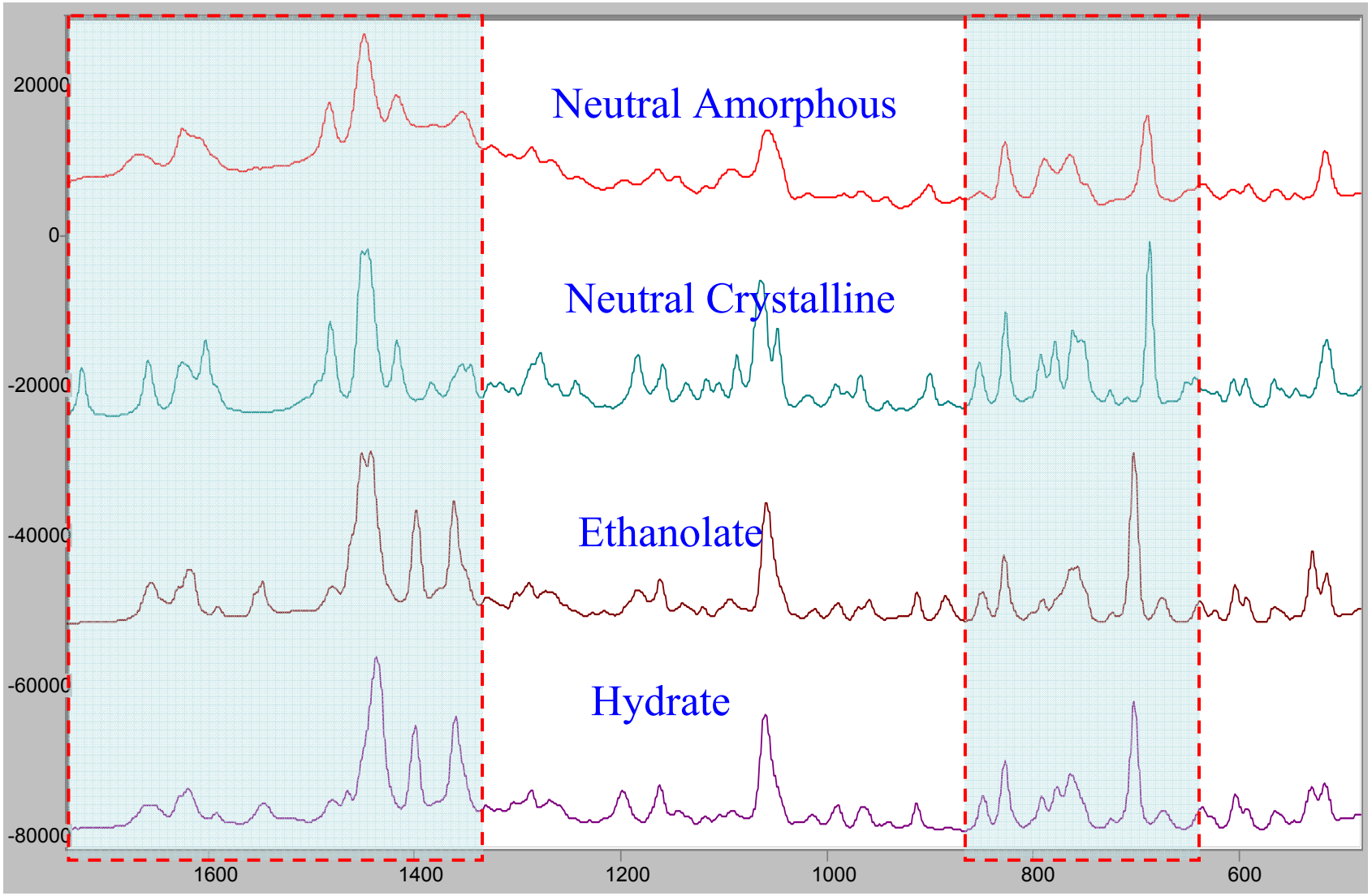




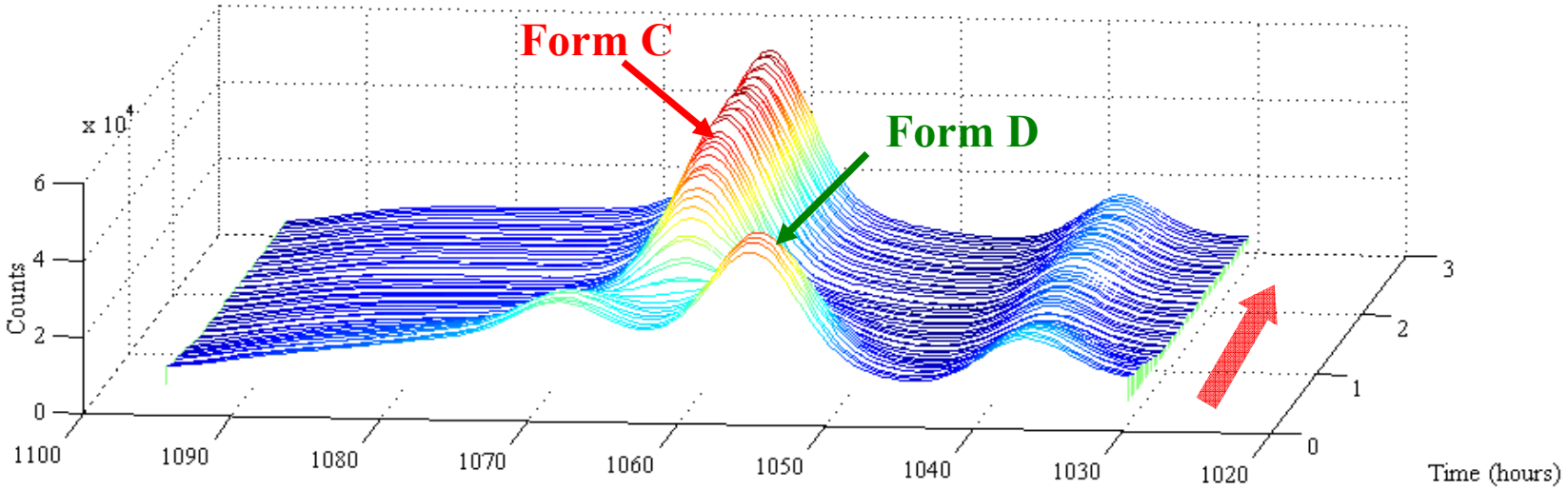


Source	Sample	Disperse	Detect
UV-Vis-NIR-IR (200-25,000 nm)	✓Tablets	Filter	PMT
D2, xenon	✓Powders	✓Grating	Photodiode
Tungsten	✓Liquids	FT Interferometer	PbS, InGaAs, TGS, MCT
Glowbar	✓Gases	AOTF	Pyrolelectric
✓Lasers	✓Drug		Thermopile
	✓Drug Product		✓CCD
	✓Biologics/Vaccines		

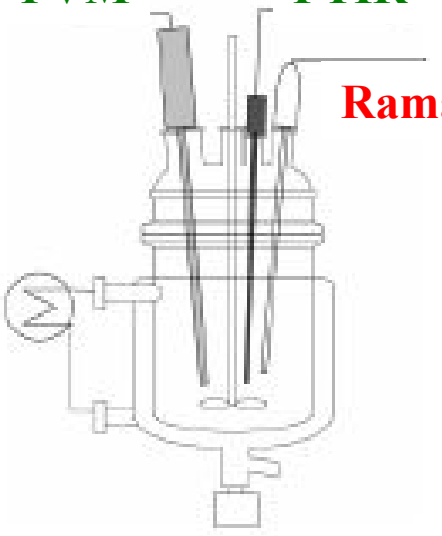
拉曼光谱用于药物晶型的检测和定量分析

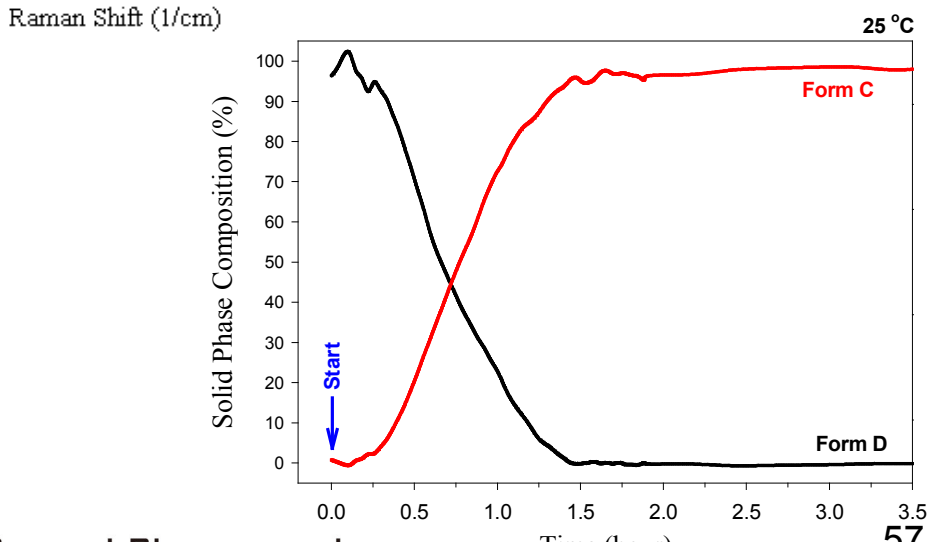


使用Raman在线检测晶型的转化



PVM FTIR





总结

- 各种固态表征方法是药物开发和生产中不可缺少的工具

- 每一种方法都有一定的适用领域，熟练掌握并灵活应用各种方法是药物固态研发中的关键，这需要理论知识和实战经验的长期积累

谢谢大家