药物晶型研究和固态研发中的无定形

主讲人：张炎锋博士，技术总裁
Crystal Pharmatech
苏州晶云药物科技有限公司
Email：sales@crystalpharmatech.com
电话：0512-69561921



Crystal Pharmatech
您的药物晶型研究和固态研发专家

提纲

- 为什么要研究无定形?
- 无定形基础知识
- 无定形固态分散物制剂
- 无定形固态分散物制剂的制备
- 无定形的检测和表征
- 无定形的稳定性问题

Crystal Pharmatech

为什么要研究无定形？

Crystal Pharmatech

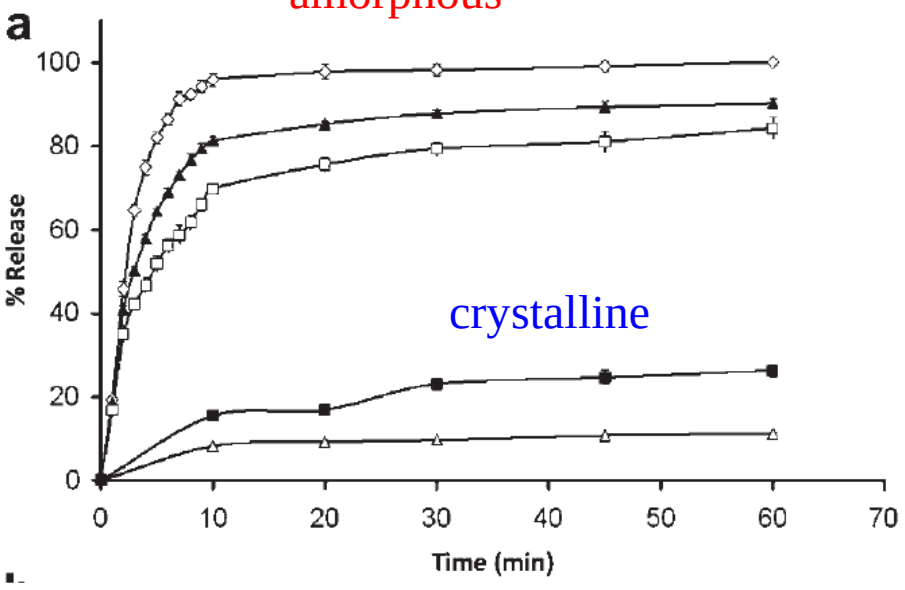
Crystal Pharmatech
您的药物晶型研究和固态研发专家

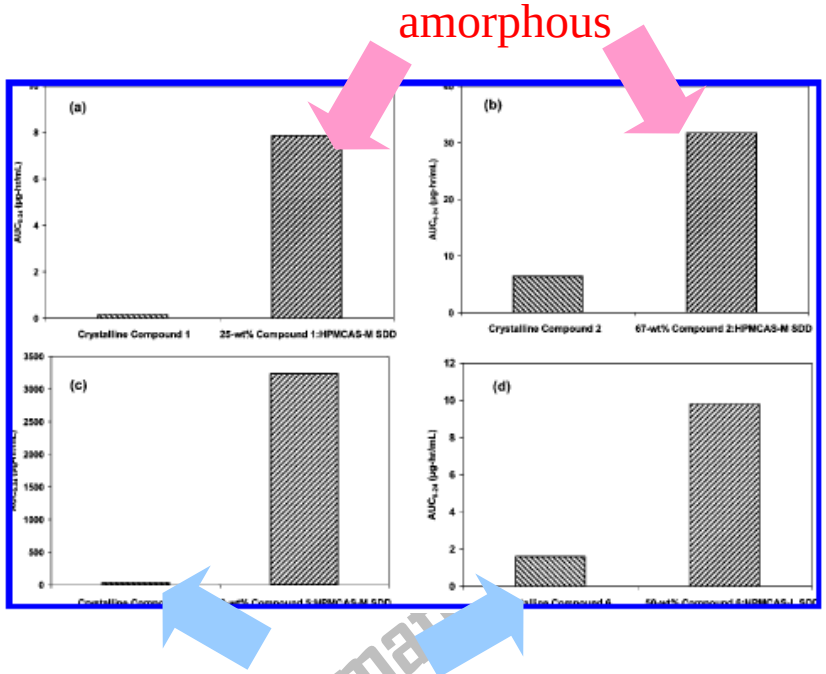
制药行业面临的挑战

- Revenues are under pressure
  - Change in target focus
  - Patents expiring
  - Increased regulatory standards
- Drug discovery shift starting in the 1990s:
  - In vitro biology screening approach change
  - Popularity of combinatorial chemistry increased
  - **New Chemical Entities (NCEs) are getting less soluble**
  - **Result: solubility and/or dissolution limited absorption in vivo**
- Significant candidate termination in clinical studies
  - PK/Bioavailability
  - Formulation
  - **Compounds are not achieving adequate exposure**

Crystal Pharmatech

无定形可以提高药物溶出和生物利用度





Dissolution Comparison: amorphous (in PVP SD) vs crystalline Bicalutamide.

ANDREWS, GP et al., Journal of Pharmaceutical Sciences, Vol. 99, 1322–1335 (2010)

Comparison of canine in vivo exposure for crystalline and amorphous drug (in HPMCAS SDDs)

Friesen, DT et al, MOLECULAR PHARMACEUTICS VOL. 5, NO. 6, 1003–1019 (2008)

Bioavailability: fraction of administered dose of a drug that reaches systemic circulation

Pharmatech
Crystal Pharmatech
Crystal Pharmatech
您的药物晶型研究和固态研发专家

无定形可以规避创新药对晶型专利的保护，提早将仿制药推向市场

缬更昔洛韦

RELATED KEYWORDS: Ranbaxy Laboratories

Ranbaxy settles patent dispute with Roche

Tweet

Submit

ET Bureau, Aug 26, 2010, 01.51am IST

Tags: Valcyte | Roche

NEW DELHI: Daiichi Sankyo-owned Ranbaxy Laboratories has settled its patent dispute with Swiss major Roche for the latter's drug valganciclovir sold under the brand Valcyte. The settlement was disclosed in a filing to a US appeals court in Washington so that it can be dismissed at the lower court. The request was granted on Tuesday, news agency Bloomberg said.

The terms of the settlement are not known. The Ranbaxy spokesman declined to comment while an email sent to the Roche spokeswoman in Basel, Switzerland remained unanswered. Ranbaxy is the first generic company to challenge valganciclovir's patent in the US. This means Ranbaxy can launch its generic version before valganciclovir's patent expires in 2015 with a 180-days marketing exclusivity if it succeeds in its patent dispute.

180-days marketing exclusivity

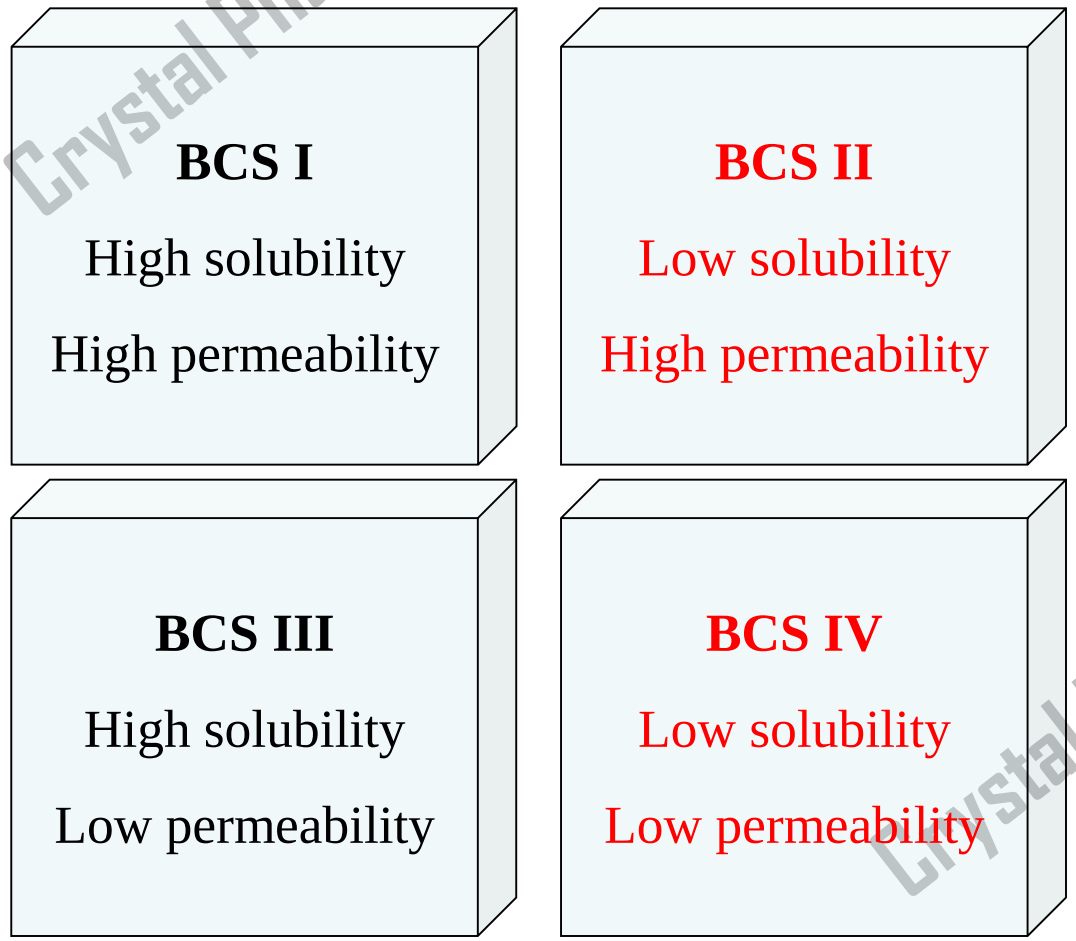
市场上的无定形药物

- Marketed Drug Products
  - Accolate (zafirlukast, 安可来， ASTRAZENECA)
  - Accupril (quinapril hydrochloride, 喹那普利)
  - Ceftin (cefuroxime axetil, 头孢呋辛酯， GSK)
  - Humulin* (insulin, 优泌林)
  - Rezulin (troglitazone, 曲格列酮)
  - Sporanox (itraconazole, 斯皮仁诺, J&J)

*Partially amorphous designed for rapid onset + extended release (crystalline fraction)

Crystal Pharmatech
您的药物晶型研究和固态研发专家

药物分子的BCS 分类



Dose number:

$$D_0 = (M_0/V_0)/C_s$$

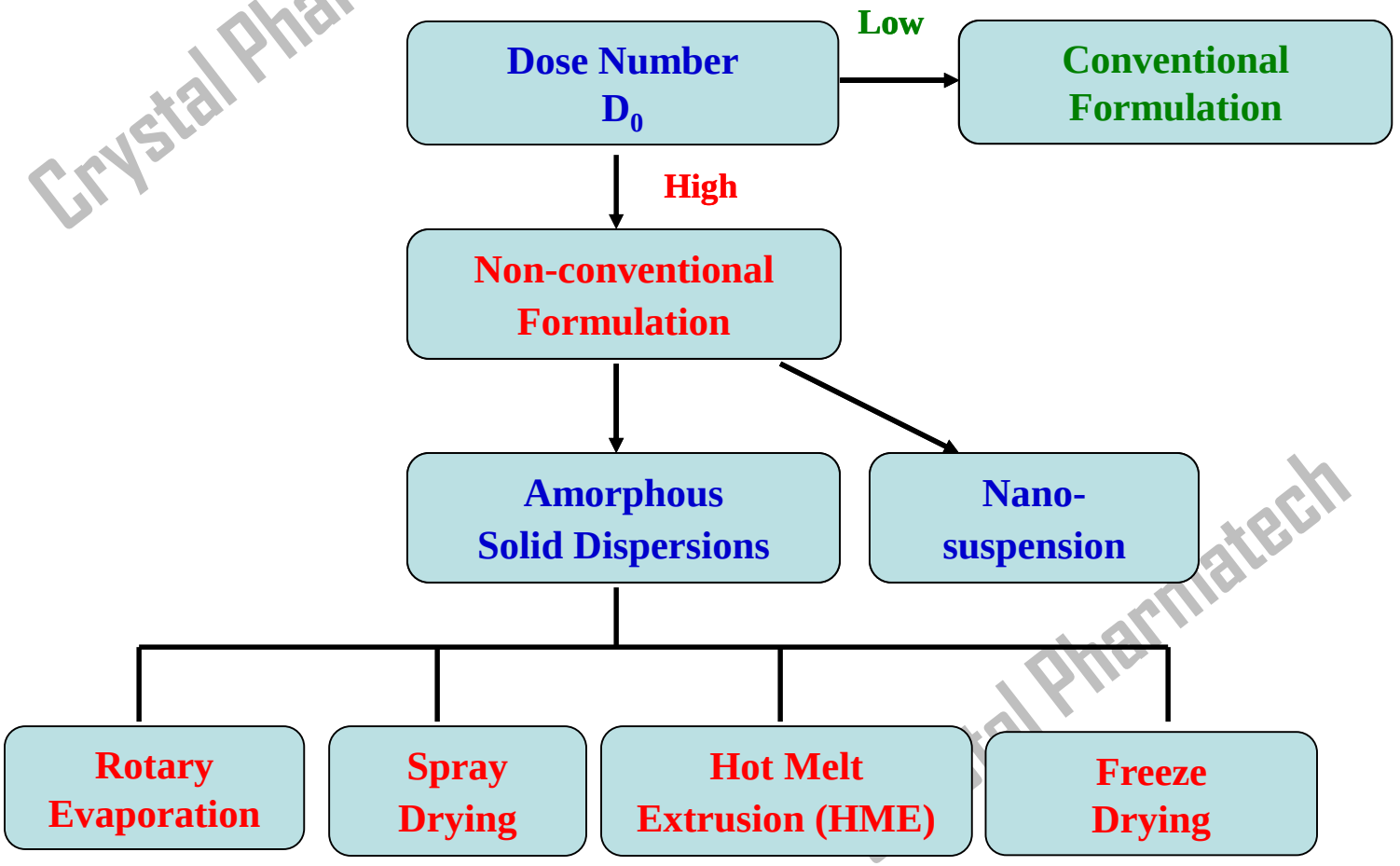
Dose volume:

$$V_d = M_0/C_s$$

Large D_0, More challenging

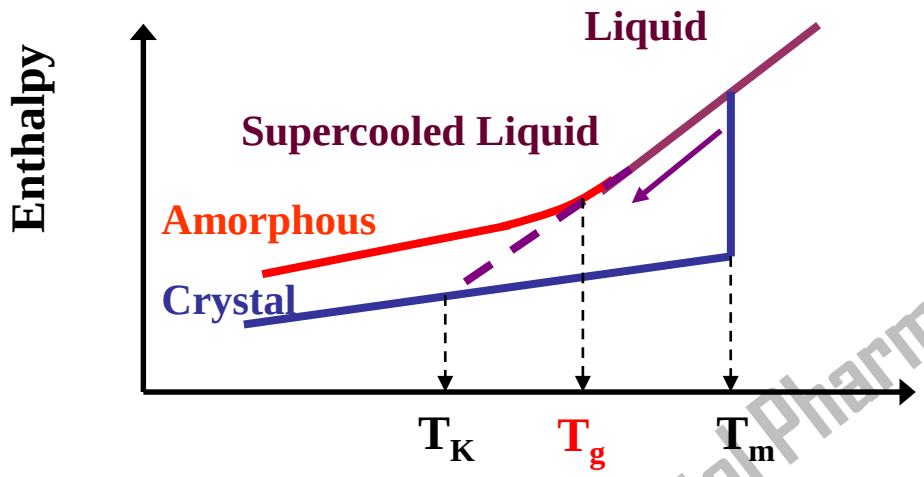
Crystal Pharmatech
Crystal Pharmatech
您的药物晶型研究和固态研发专家

药物研发中不同制剂方法的选择



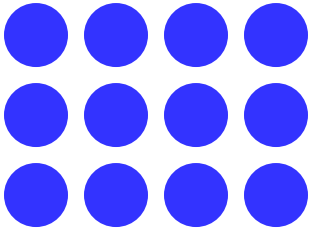
Crystal Pharmatech
您的药物晶型研究和固态研发专家

无定形的基础知识



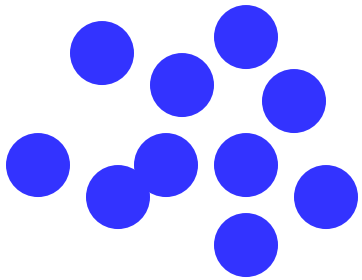
Crystal Pharmatech
Crystal Pharmatech
Crystal Pharmatech
您的药物晶型研究和固态研发专家

晶相和无定形



Molecules in a ordered, repeating pattern

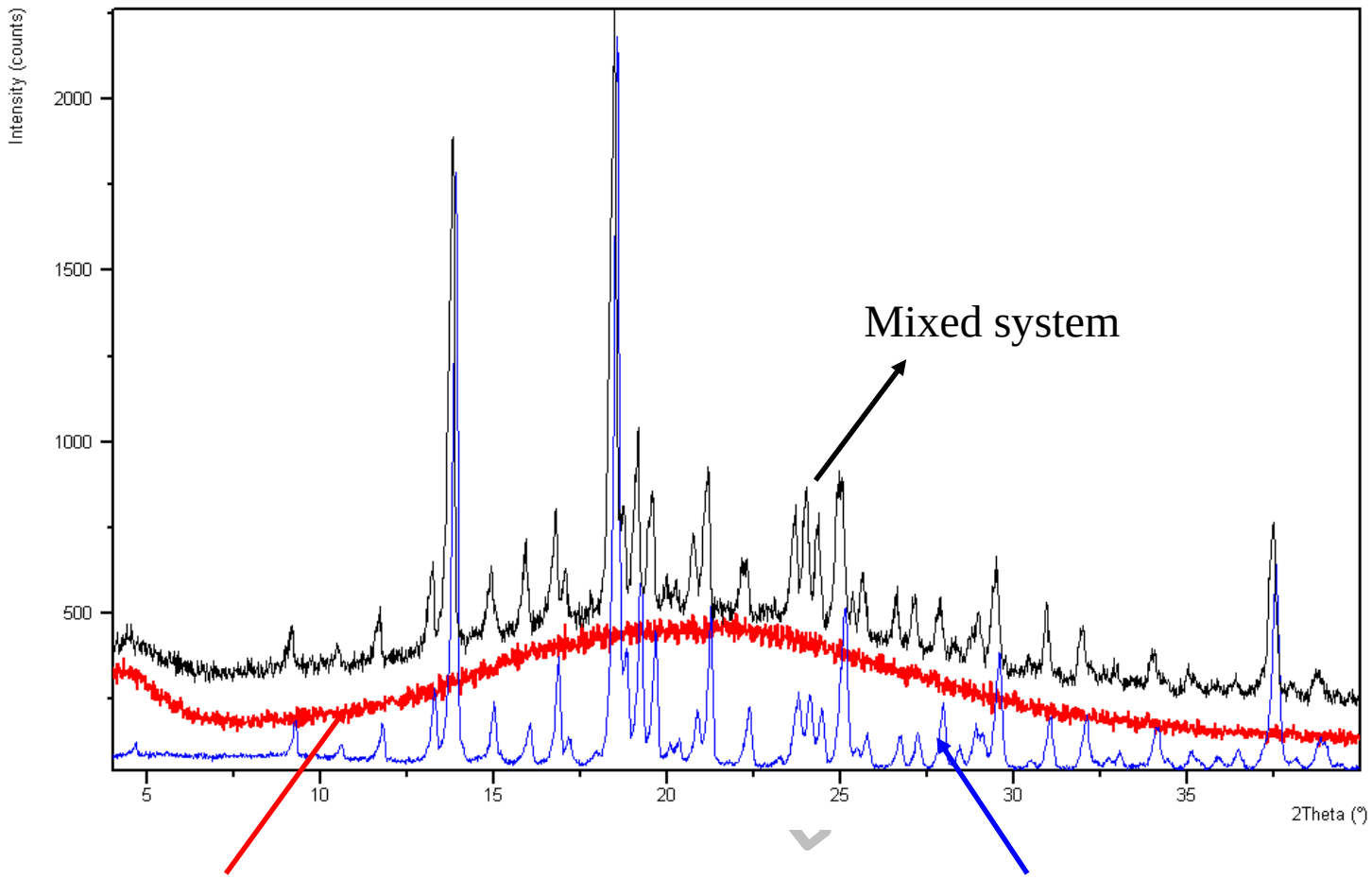
- Equilibrium state
- More stable
- Lower solubility
- Lower dissolution rate



Molecules in a random arrangement with some local order

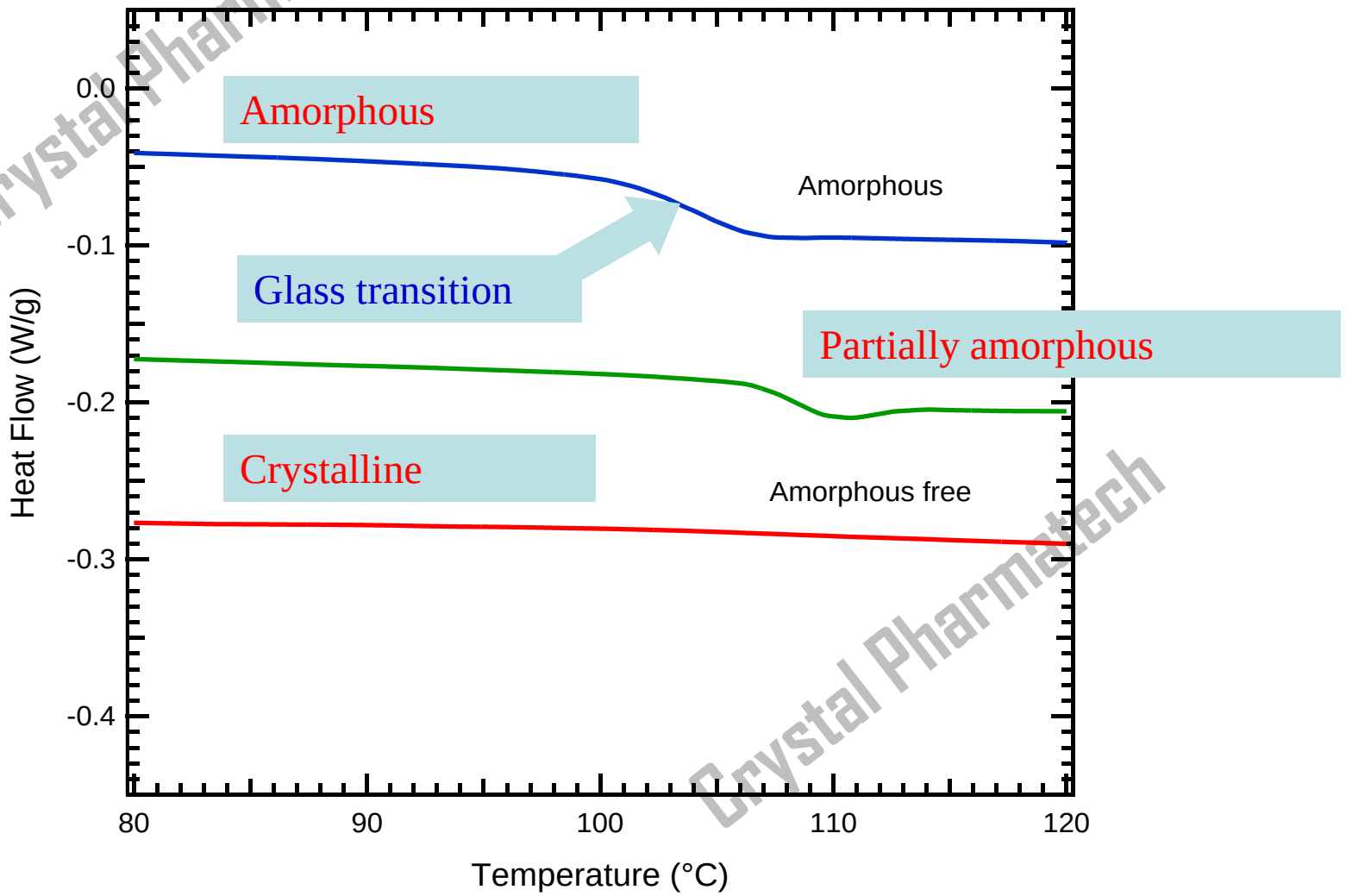
- Non-equilibrium state
- Typically less stable
- Higher apparent solubility
- Higher dissolution rate

晶型 vs. 无定形：XRPD



Crystal Pharmatech
您的药物晶型研究和固态研发专家

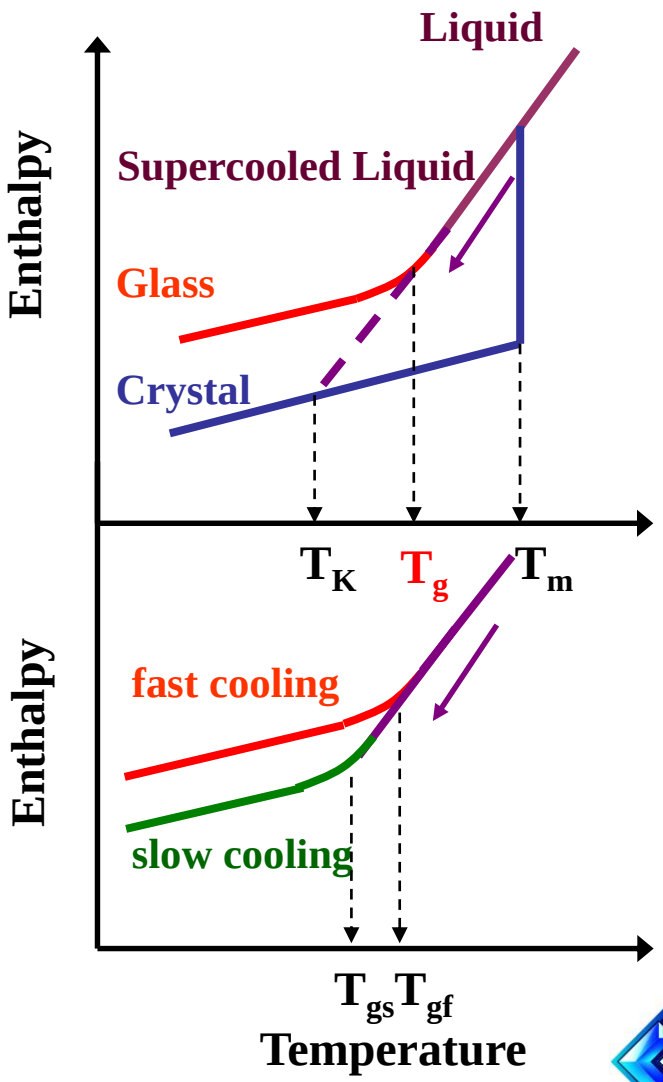
晶型 vs. 无定形:DSC/mDSC



Crystal Pharmatech

Crystal Pharmatech
您的药物晶型研究和固态研发专家

超冷却液体和无定形固体



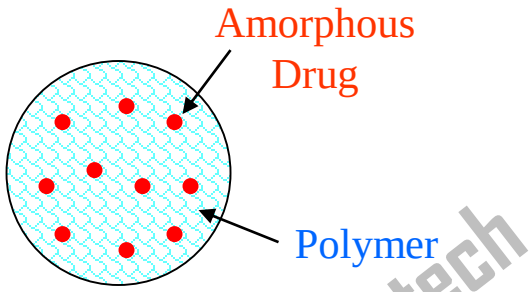
Upon cooling, molecular motions in liquids slow down. If crystallization is avoided below its freezing point, the liquid will exist in a supercooled state. Upon further cooling, the molecules in the supercooled liquid will rearrange so slowly that they appear 'frozen' on the laboratory timescale. This falling out of equilibrium occurs across a narrow transformation range where the characteristic relaxation time is of the order of 100 seconds. This transformation is normally referred as the glass transition. The slower a liquid is cooled, the colder it can become before falling out of equilbirrium.

T_g: glass transition temperature
T_k: Kauzmann temperature
T_m: melting point

Crystal Pharmatech
您的药物晶型研究和固态研发专家

Debenedetti, P. G.; Stillinger, F. H. Nature, 2001, 410, 259-267

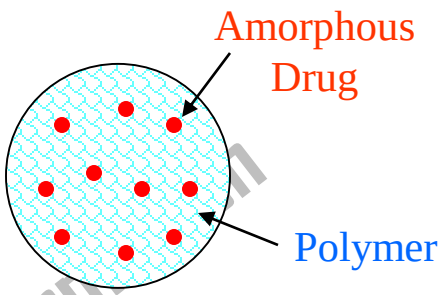
无定形固态分散物制剂



Crystal Pharmatech

什么是无定形固态分散物?

- A single phase amorphous solid solution of drug, polymer, optional surfactants, etc. as determined by common analytical techniques such as XRPD, DSC, ssNMR.

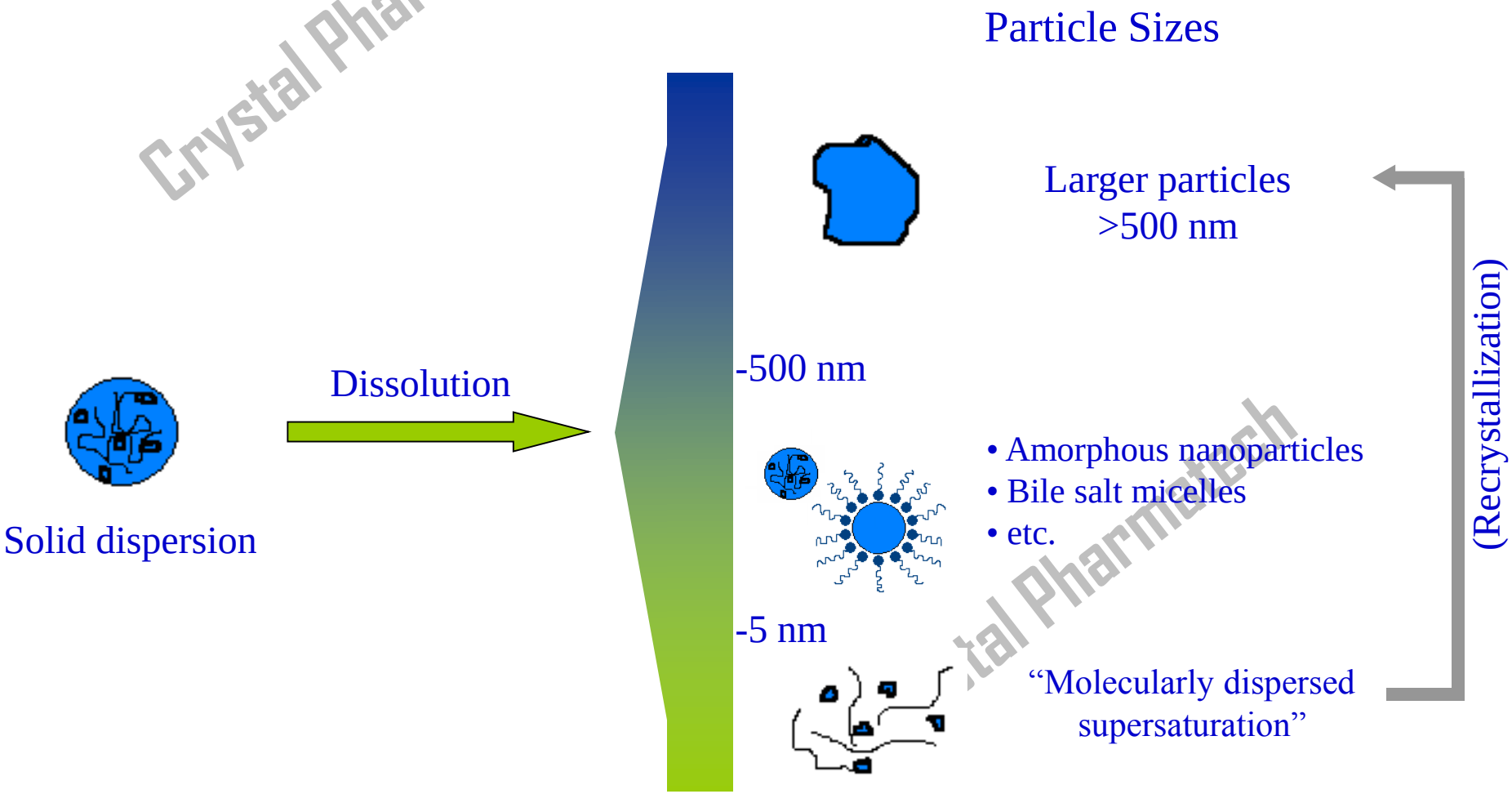


- Methods to obtain solid dispersions include: spray drying, hot melt extrusion and freeze drying, etc.

Crystal Pharmatech

无定形固态分散物：药物释放

Crystal Pharmatech



Crystal Pharmatech
您的药物晶型研究和固态研发专家

无定形分散物中辅料的选择

- Polymers
  - Carriers for the drug
  - Inhibit crystallization both in dosage form and in-vivo
- Surfactants
  - Solubilizers or emulsifying agents
- Organic solvents
  - Needed to dissolve all components

Crystal Pharmatech

Crystal Pharmatech
您的药物晶型研究和固态研发专家

无定形分散物中高分子的选择

- Increase aqueous solubility
  - Use water soluble macromolecules
  - Use amorphous polymers

- Improve physical stability (inhibit crystallization)
  - Use macromolecules
    - Reduced mobility (long relaxation times)
    - Produce single phase solid solutions with drugs
    - Use polymers with high Tg
    - Frustration against crystallization

Crystal Pharmatech

Crystal Pharmatech
您的药物晶型研究和固态研发专家

无定形分散物中高分子的选择

Table 1: Properties of Polymers Commonly Used in ASDs [7]

Polymer	Tg (°C)	Solvent Solubility	Hygroscopicity	Amenable Methods of Manufacture
Copovidone	106	Dichloromethane Ethanol Methanol Water Acetone	<10% @ 50% RH	Rotary Evaporation Spray Drying Hot Melt Extrusion
Polyvinyl caprolactam-polyvinyl acetate-polyethyleneglycol copolymer	70	Water Ethanol Methanol Acetone	~5% @ 50% RH	Rotary Evaporation Spray Drying Hot Melt Extrusion
PVP	130 (K17) 168 (K30)	Chloroform Ethanol Methanol Water Acetone	~15% @ 50%RH	Rotary Evaporation Spray Drying Hot Melt Extrusion
HPMC	170	Cold Water Dichloromethane: Ethanol Dichloromethane: Methanol Water: Alcohol	<10% @ 50% RH	Spray Drying
HPMC P	133 - 137	Acetone: Methanol Acetone: Ethanol Methanol: Dichloromethane	2 – 5% @ 50%RH	Spray Drying
HPMC AS	110 - 130	Acetone* Ethanol:Dichloromethane* *clear or turbid viscous solution	~3% @ 50%RH	Spray Drying
Methacrylate/ methacrylic acid copolymer	110 - 150	Ethanol, Methanol, Acetone, Acetone with 3% water	<5% @ 50% RH	Rotary Evaporation, Spray Drying, Hot Melt Extrusion

Reference: Amorphous solid dispersions as enabling formulations for discovery and early development, American Pharmaceutical Review, Jan/Feb 2011

无定形分散物中表面活性剂的选择

Table 2. Properties of Surfactants Commonly Used in ASDs [7]

Surfactant	HLB	T_m (°C)	Solvent Solubility
Vitamin E Polyethylene Glycol Succinate	13.2	37 - 41	Water Acetone
Sorbitan Monostearate – 60/80	4.3	53 - 57	Most organic solvents
Polysorbate 20	16.7	n/a	Ethanol Water
Polysorbate 80	15.0	n/a	Ethanol Water
Polyoxyl 40 Hydrogenated Castor Oil	14 - 16	30	Chloroform Ethanol Acetone Water

Reference: Amorphous solid dispersions as enabling formulations for discovery and early development, American Pharmaceutical Review, Jan/Feb 2011

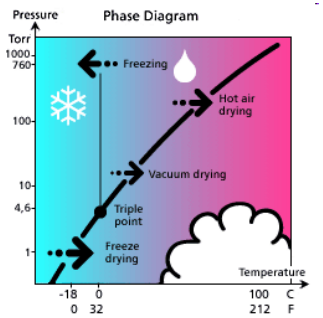
无定形分散物工艺中溶剂的选择

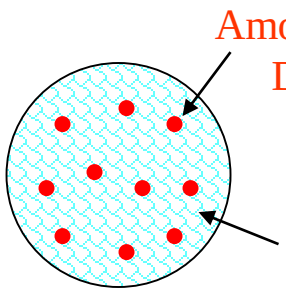
Table 3. Properties of Organic Solvents Commonly Used for Preparation of ASDs [8]

Solvent	Boiling Point (°C)	Flash Point (°C)	ICH Class
Ethanol	78	13	II
Methanol	65	12	III
Acetone	57	17	III
IPA	83	12	III
Tetrahydrafuran	66	-14	III
Dichloromethane	40	None	II

Reference: Amorphous solid dispersions as enabling formulations for discovery and early development, American Pharmaceutical Review, Jan/Feb 2011

无定形固态分散物制剂的制备

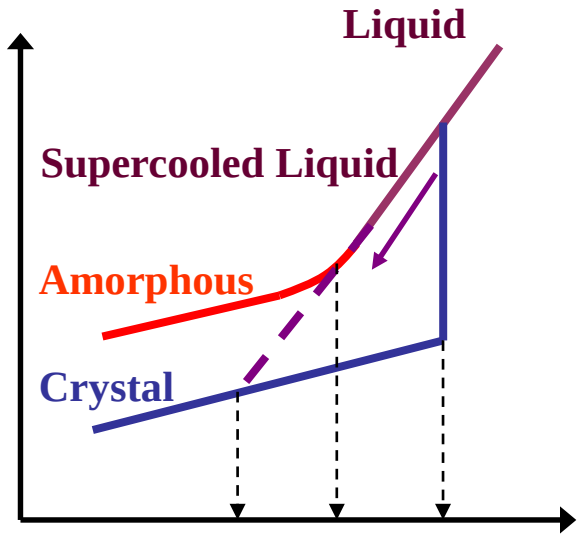


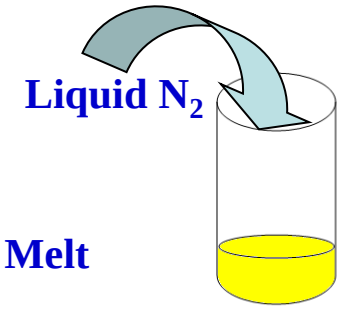


Crystal Pharmatech

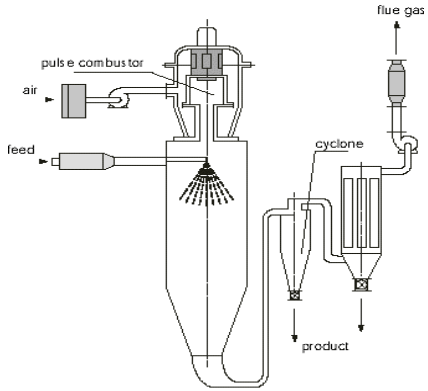
Crystal Pharmatech
您的药物晶型研究和固态研发专家

怎样得到无定形？

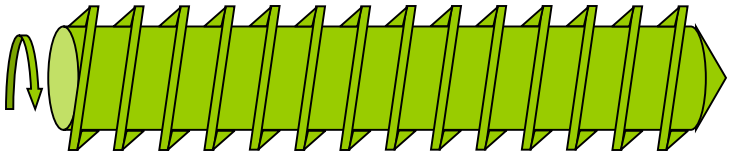




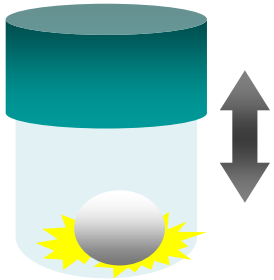
Melt Quenching



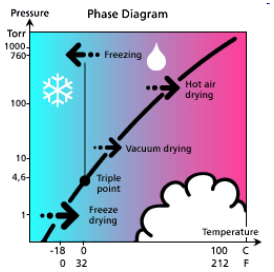
Spray Drying



Hot Melt Extrusion

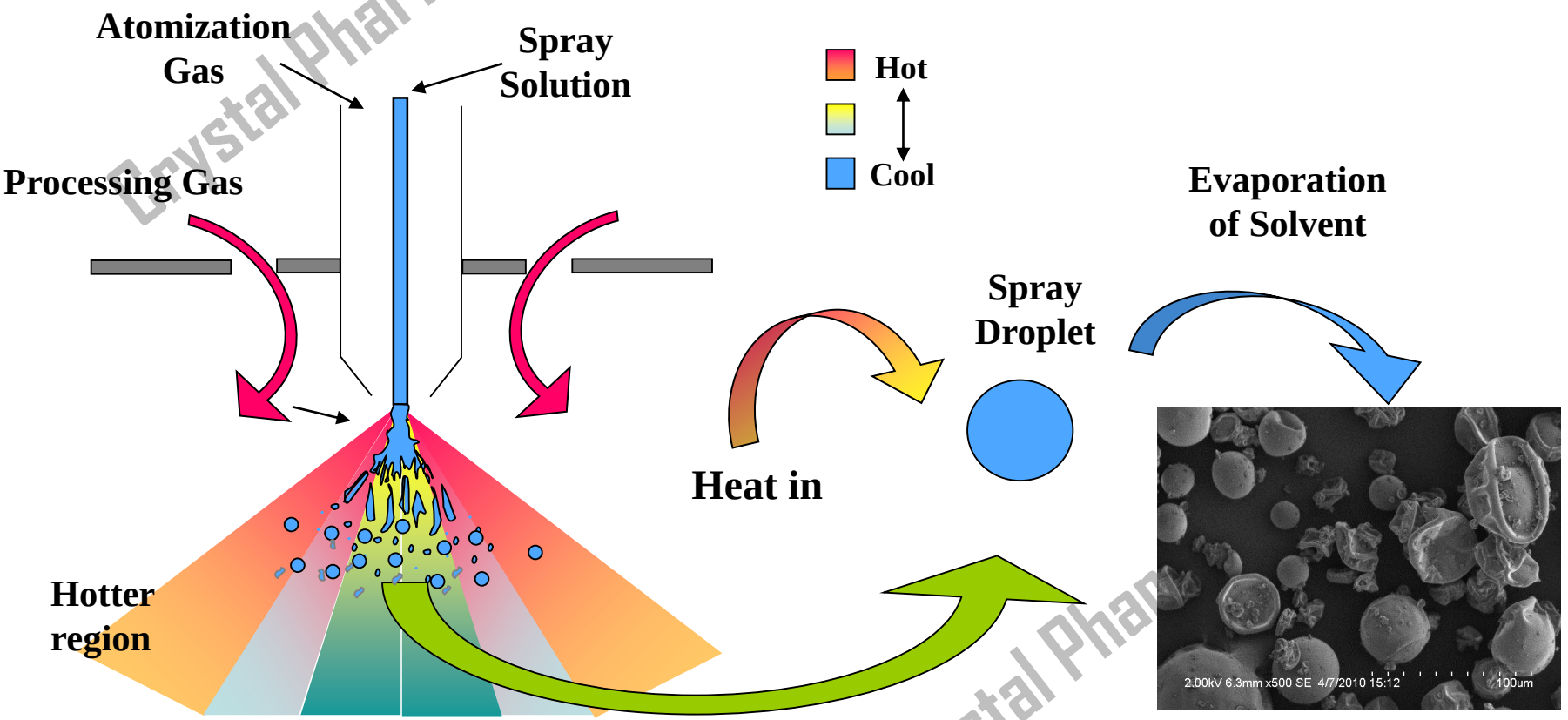


Ball Milling



Freeze Drying

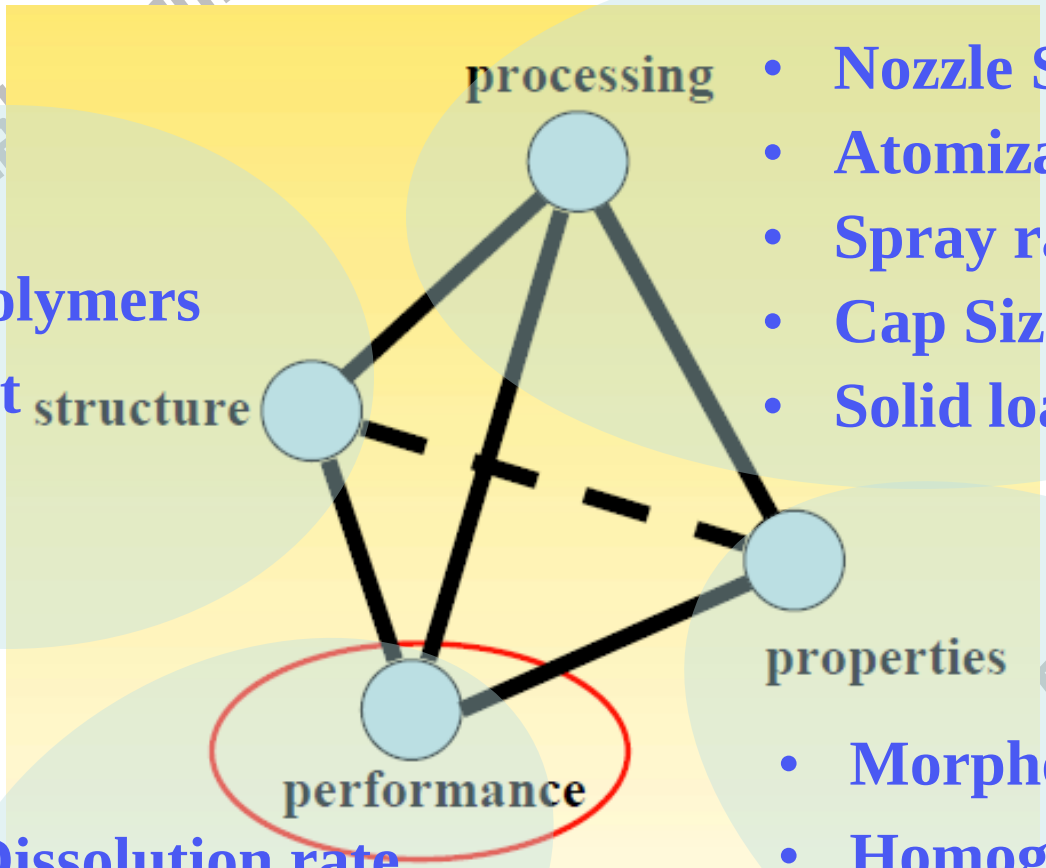
喷雾干燥法



Spray Dried drug/PVP-PVA

Crystal Pharmatech
Crystal Pharmatech
您的药物晶型研究和固态研发专家

喷雾干燥工艺参数对产品质量的影响



- Type of polymers
- Surfactant
- Solvents

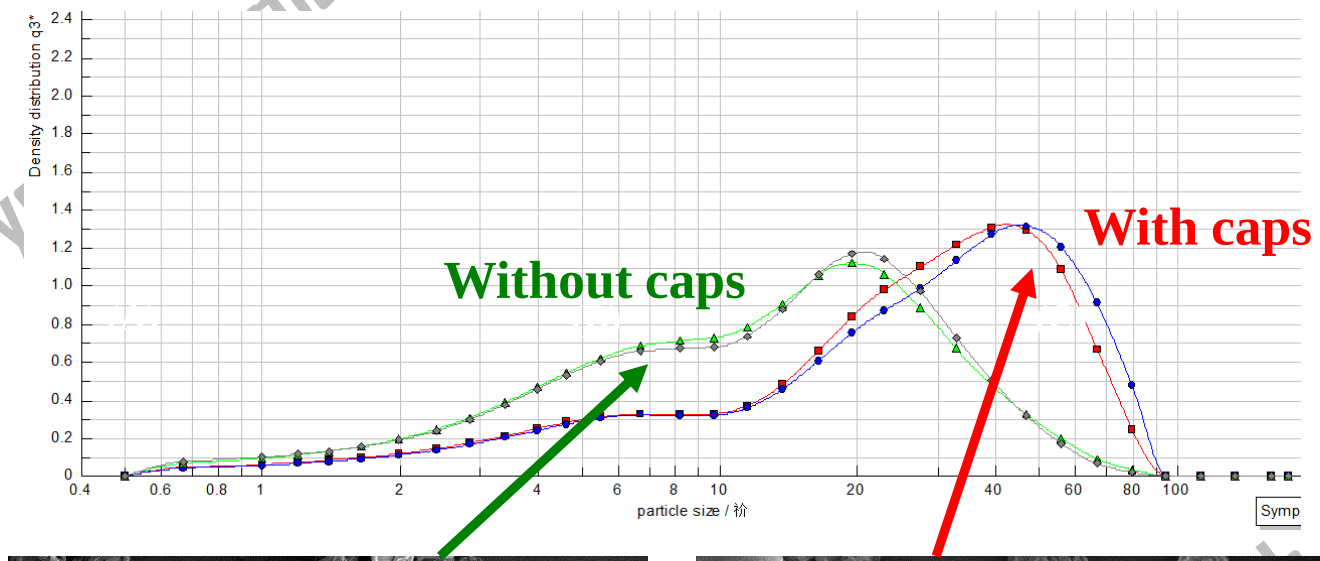
- Nozzle Size
- Atomization Gas Rate
- Spray rate
- Cap Size
- Solid loading

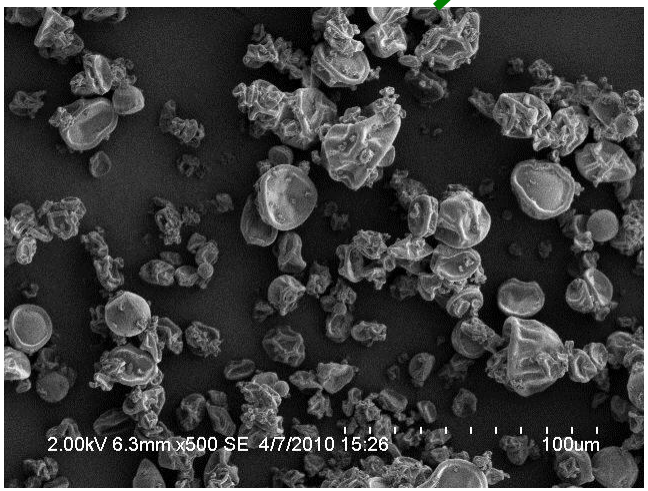
- Morphology
- Homogeneity
- Particle size distribution

- Dissolution rate
- Bioavailability
- Processability

Crystal Pharmatech
您的药物晶型研究和固态研发专家

喷雾干燥工艺参数对产品质量的影响

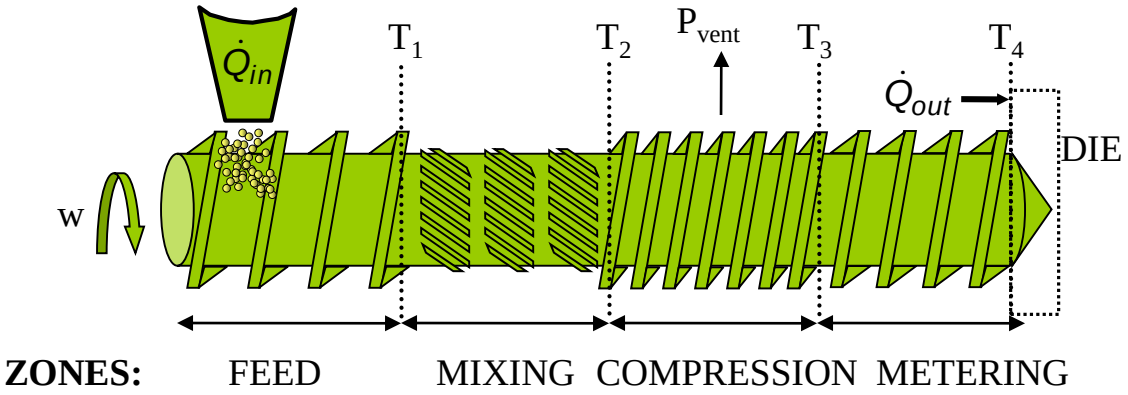




Crystal Pharmatech
您的药物晶型研究和固态研发专家

熔融挤出法

Modern Engineering Polymer Extrusion

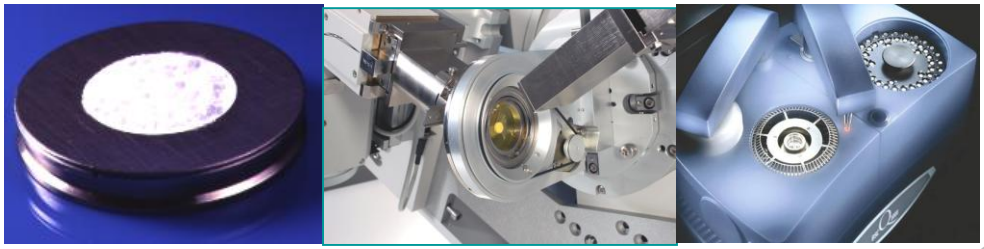


robust platform

- Zone Temp control
- Deliberate Mixing
- Compression
- Venting
- Addition of liquid to granulate via side ports

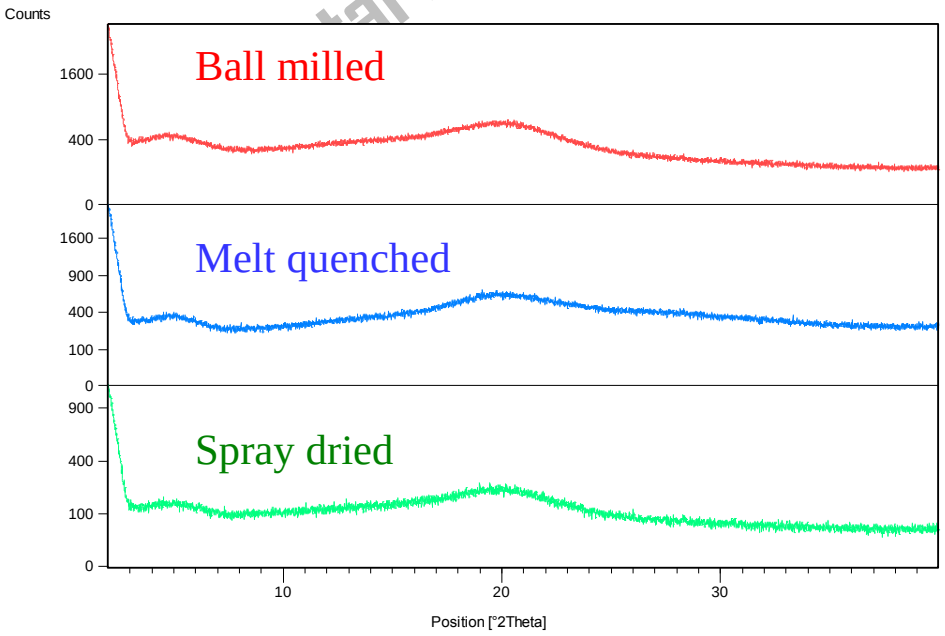
⇒

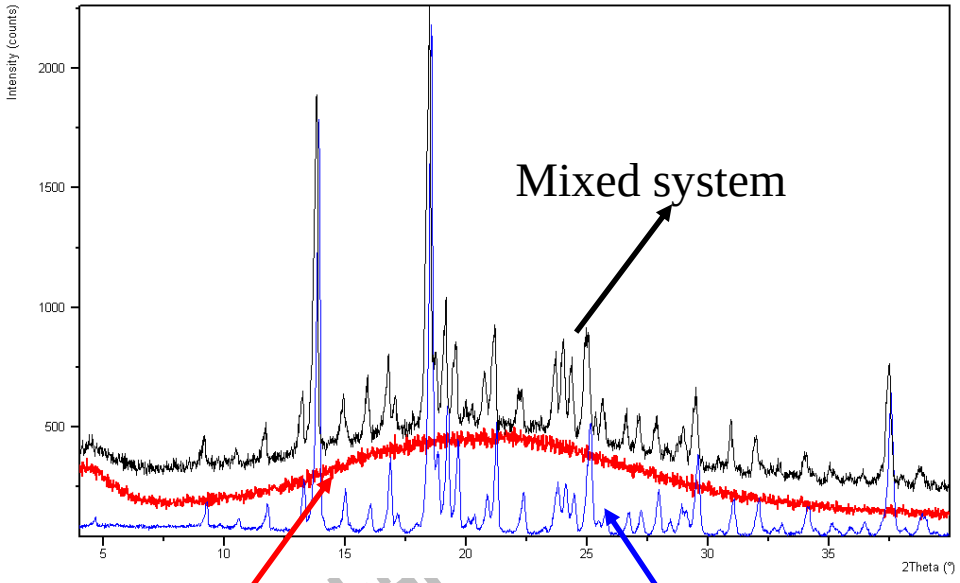
无定形的检测和表征



Crystal Pharmatech

无定形的检测和表征：XRPD

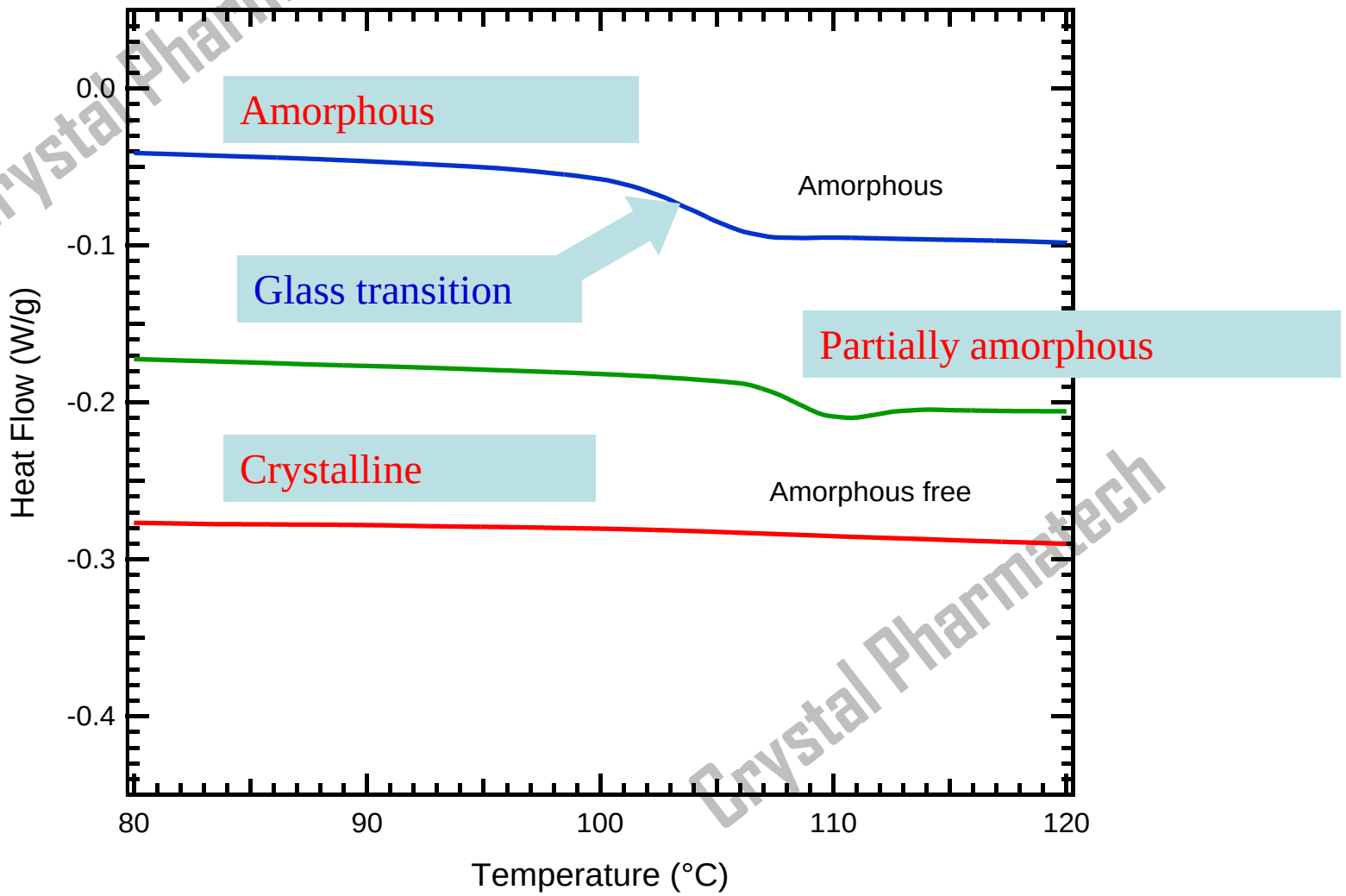




Amorphous halo by XRPD: characteristic

Crystal Pharmatech
Crystal Pharmatech
您的药物晶型研究和固态研发专家

无定形的检测和表征:DSC/mDSC



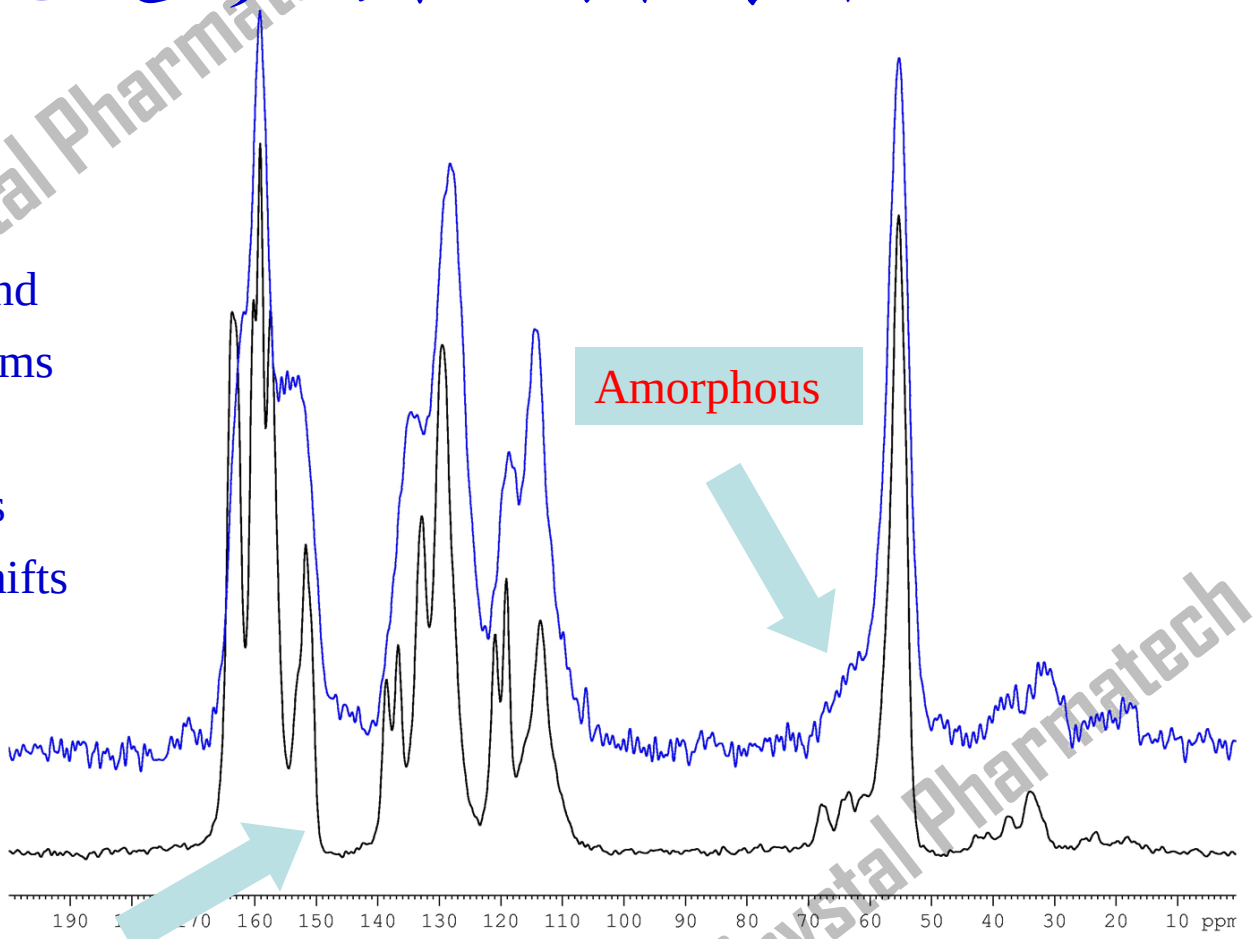
Crystal Pharmatech
Crystal Pharmatech
Crystal Pharmatech
您的药物晶型研究和固态研发专家

无定形的检测和表征：ssNMR

Amorphous and crystalline forms identifiable:

→ Linewidths

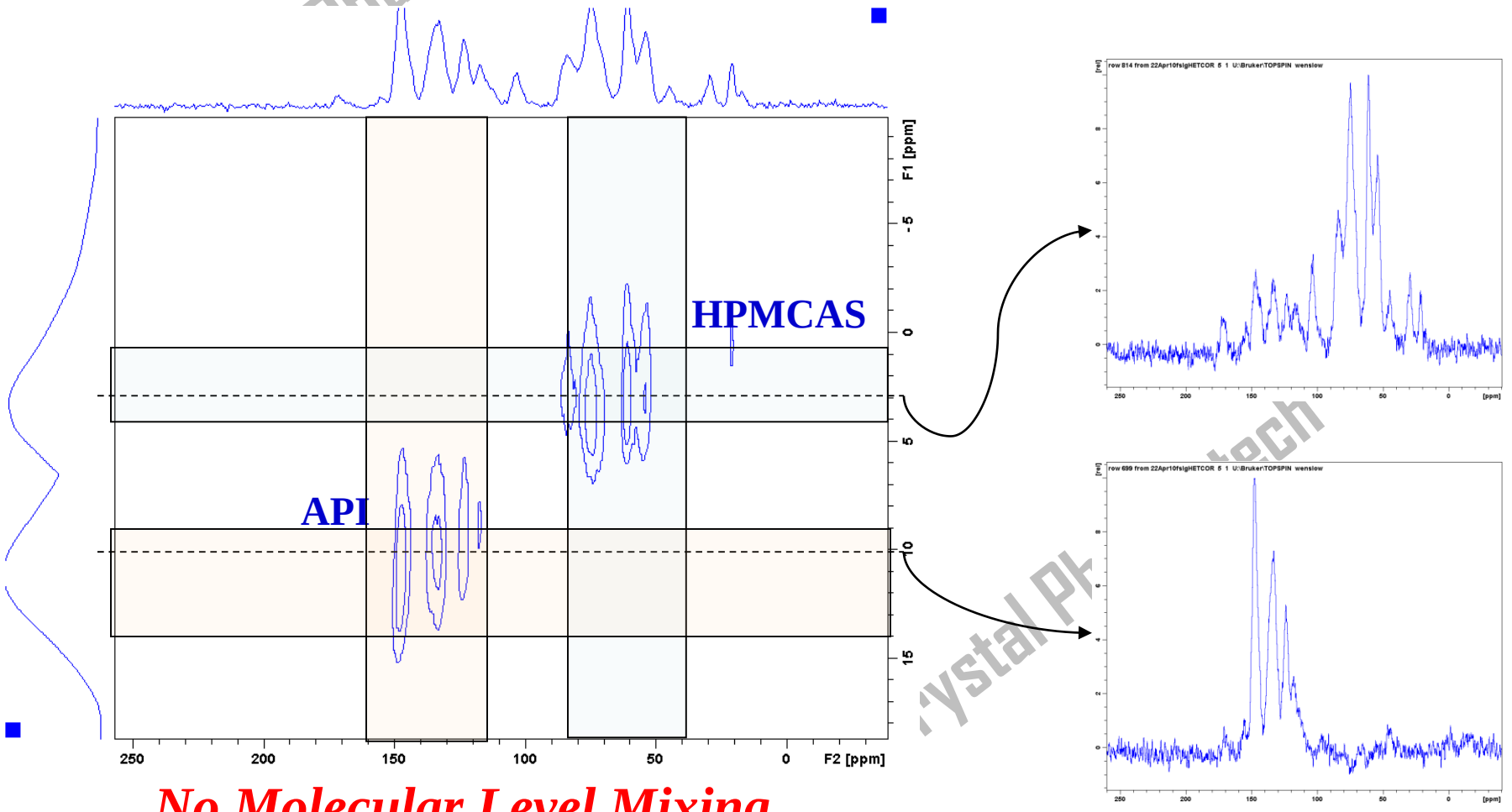
→ Solution shifts



Crystal Pharmatech
Crystal Pharmatech
Crystal Pharmatech
您的药物晶型研究和固态研发专家

固态核磁共振应用

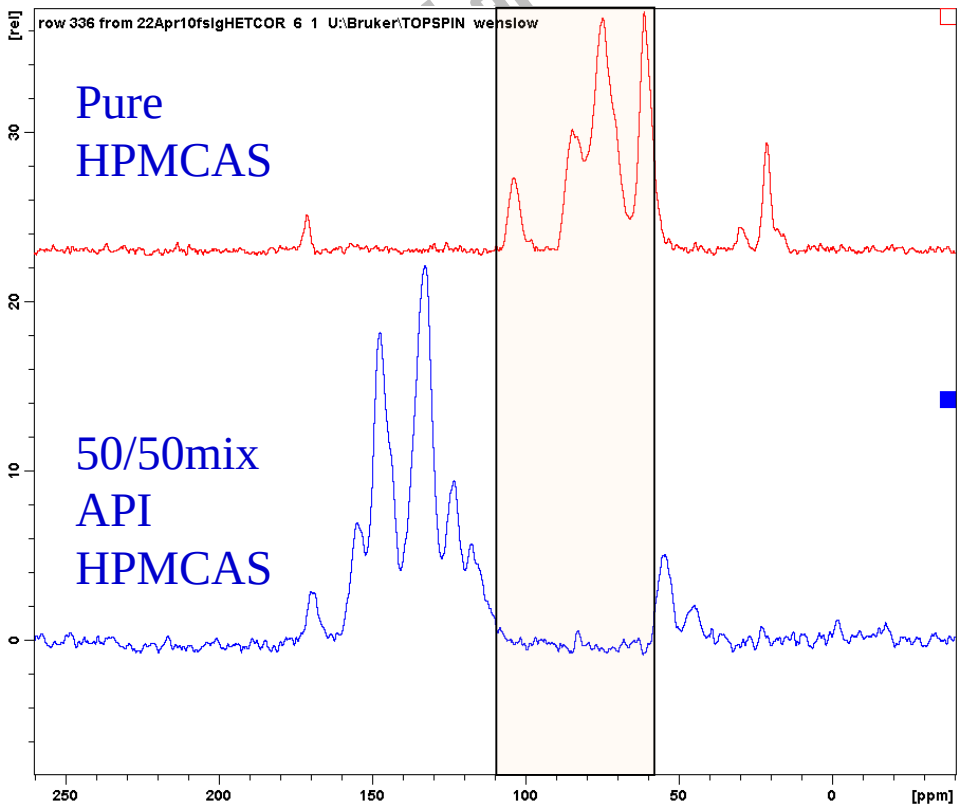
HETCOR– ^{13}C projections

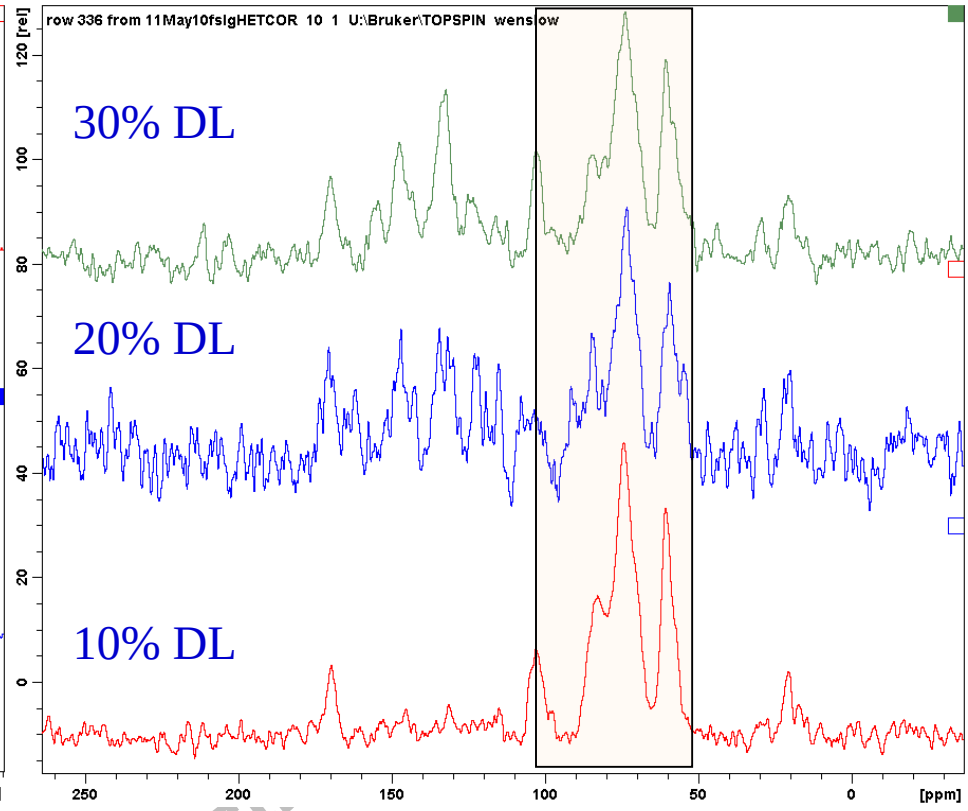


No Molecular Level Mixing

Crystal Pharmatech
您的药物晶型研究和固态研发专家

固态核磁共振应用: 无定形固态分散物



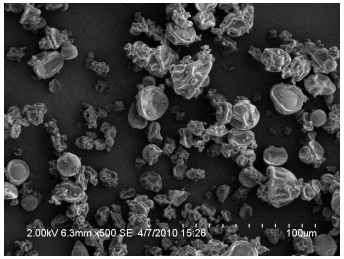


No Molecular Level Mixing

Significant Molecular Level Mixing

Crystal Pharmatech
您的药物晶型研究和固态研发专家

无定形的稳定性研究

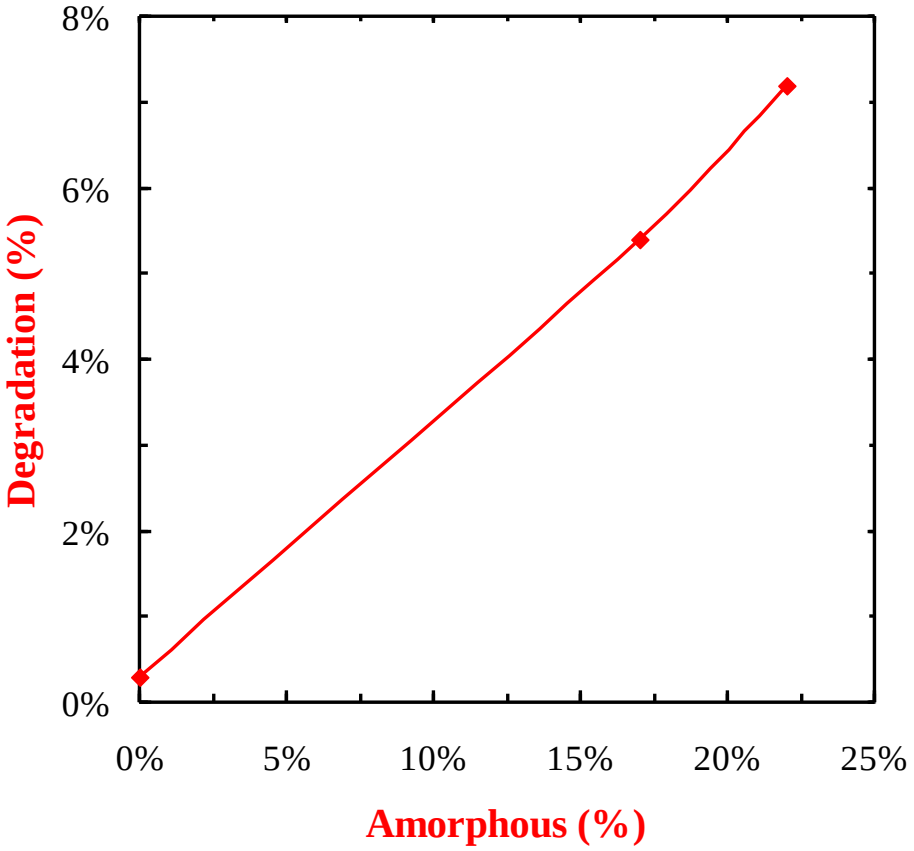


?

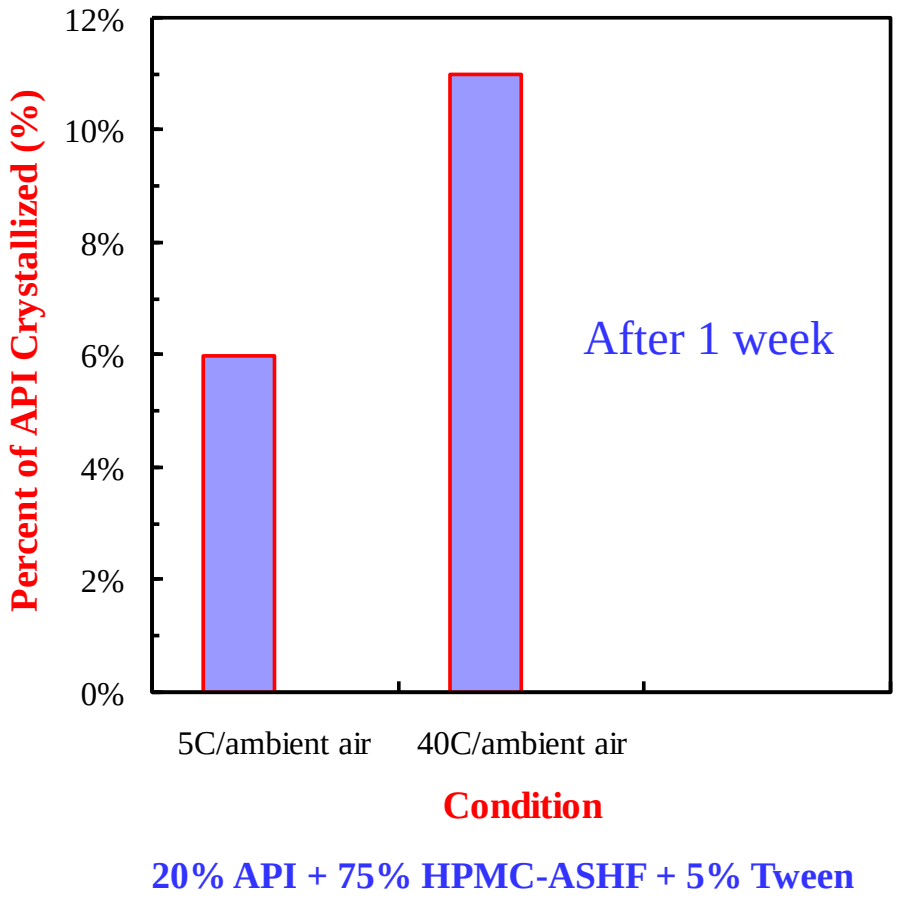
Crystal Pharmatech

无定形原料药和制剂的稳定性

Effect on chemical stability: 40C/75%/2wk



physical stability: 40C/75%/2wk



20% API + 75% HPMC-ASHF + 5% Tween

无定形体系稳定性的影响因素

The stability of an amorphous phase depends on

(a) Thermodynamic properties of the amorphous phase, such as

- Configurational entropy (Sc)
- Excess enthalpy relative to a crystalline phase (ΔH_{ex})

(b) Dynamic properties of the amorphous phase, such as

- Structure relaxation (alpha-relaxation)
- Beta-relaxation process
- Activation energy barrier

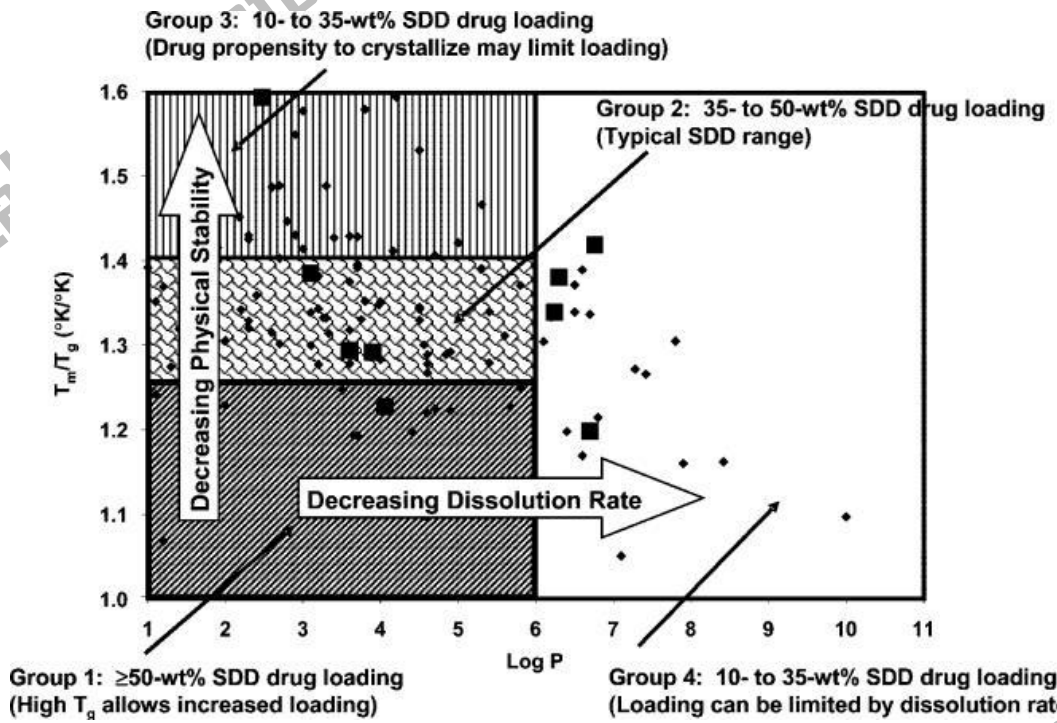
(c) Other factors such as the presence of nuclei, additives, and thermal history (sample preparation)

无定形体系稳定性的重要物理参数

- Chemical/supramolecular structure
- $T_g/T_k/T_0$
- Structure relaxation
- Energy landscape perspective
- Configurational entropy
- Interfacial energy
- Beta-relaxation process
- Activation energy barrier to nucleation

Crystal Pharmatech
Crystal Pharmatech
Crystal Pharmatech
您的药物晶型研究和固态研发专家

无定形体系的稳定性

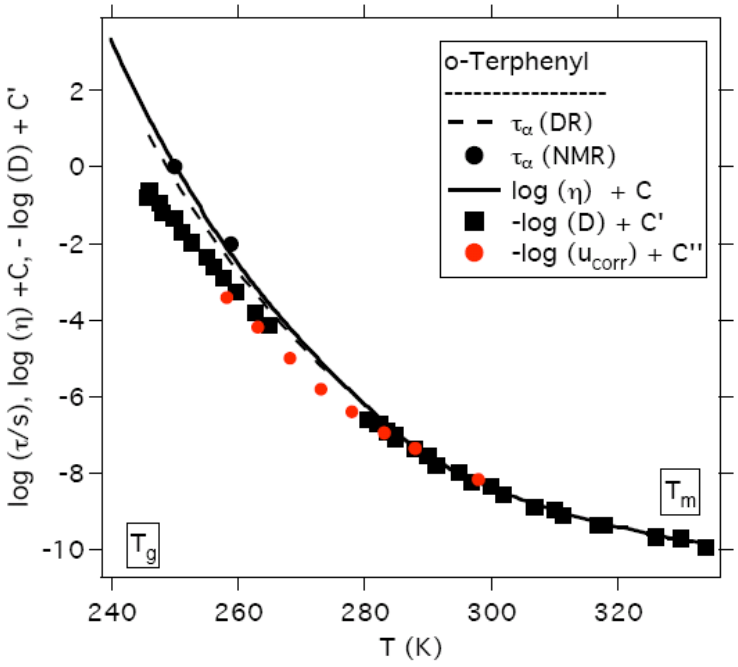


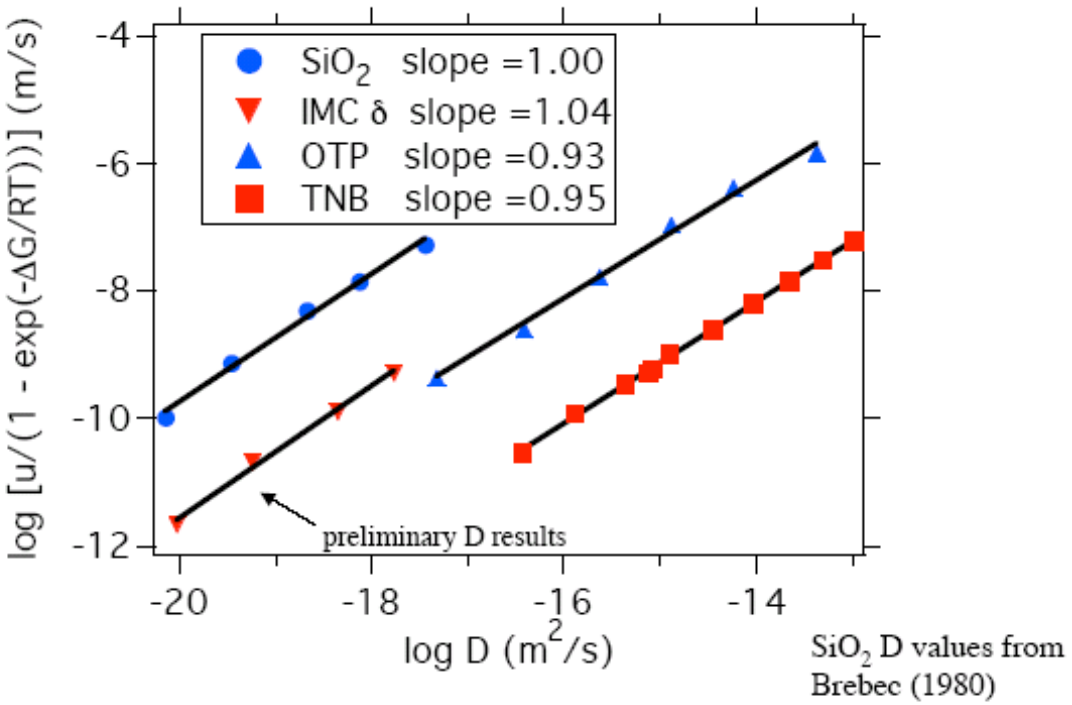
- Compounds with high T_m have high tendency to crystallize
- Compounds with high T_g have high kinetic barrier for mobility
- Compounds with high logP (>4) could have wetting problems in aqueous media

Crystal Pharmatech
您的药物晶型研究和固态研发专家

案例：无定形体系中晶体生长速率

Crystal growth rates could depend on D, η





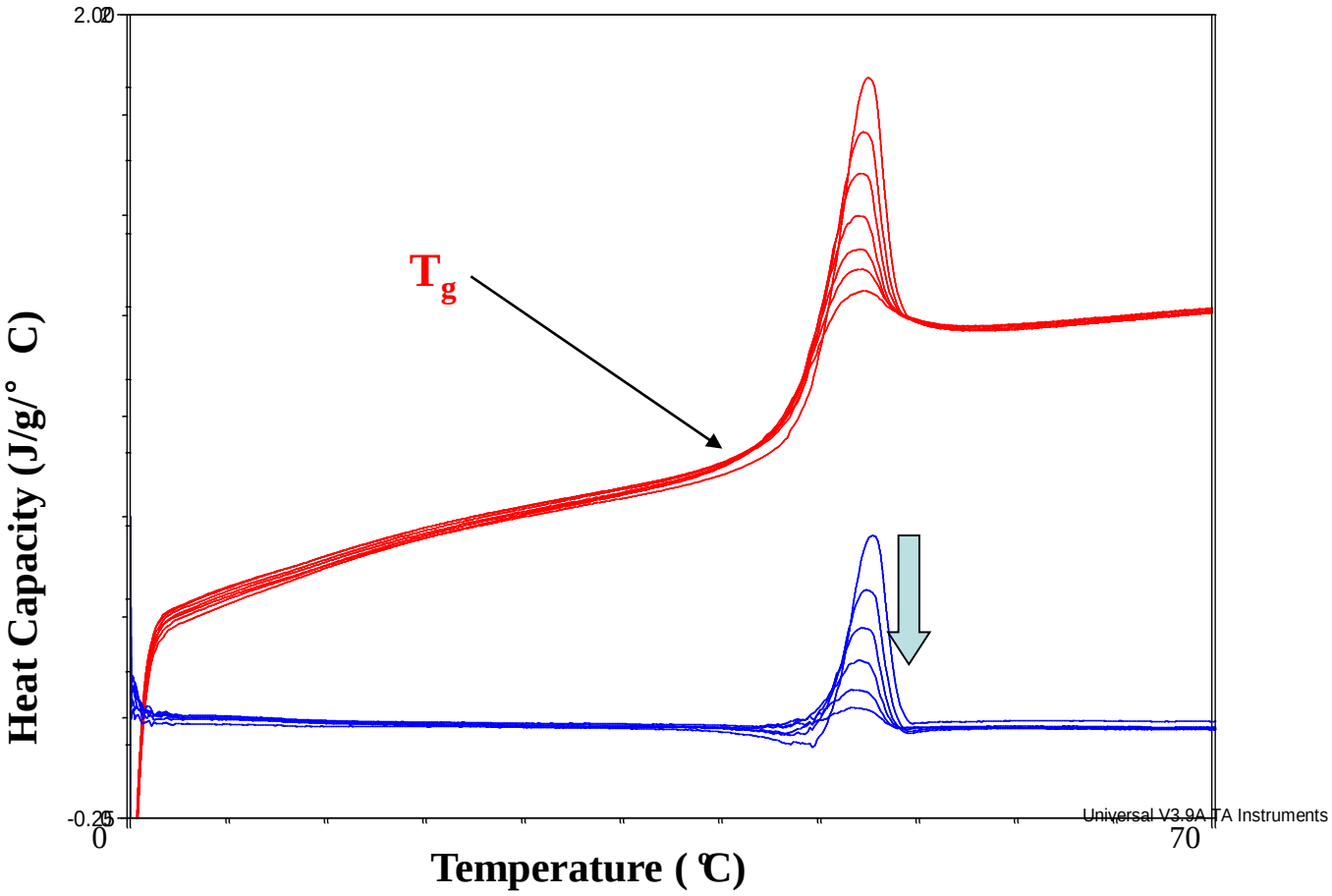
u follows D better than η

D reasonably predicts u for many systems

Ediger, 2006

Crystal Pharmatech
您的药物晶型研究和固态研发专家

无定形结构驰豫研究：DSC



Crystal Pharmatech
您的药物晶型研究和固态研发专家

无定形结构驰豫研究：DEA

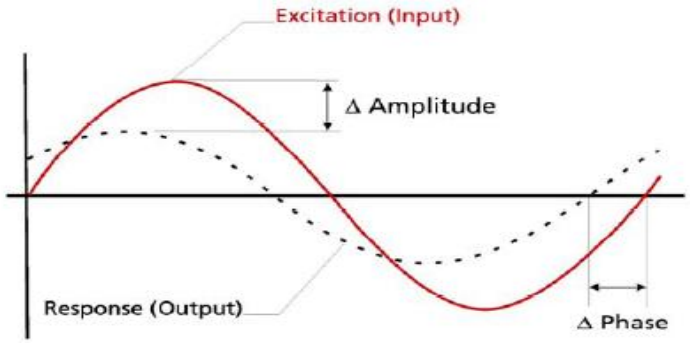
Relative dielectric constant

$$\varepsilon^* = \varepsilon' - i\varepsilon''$$

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

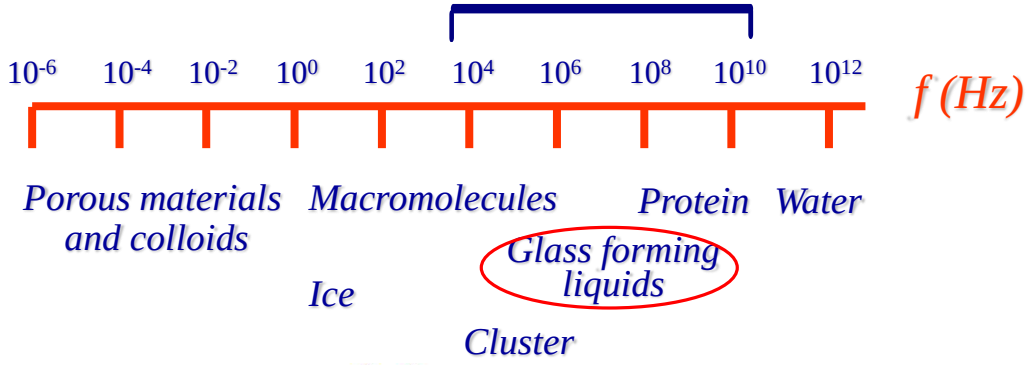
ε": loss factor, a measure of total energy loss due to the work performed aligning dipoles and moving ions

Dielectric Relaxation



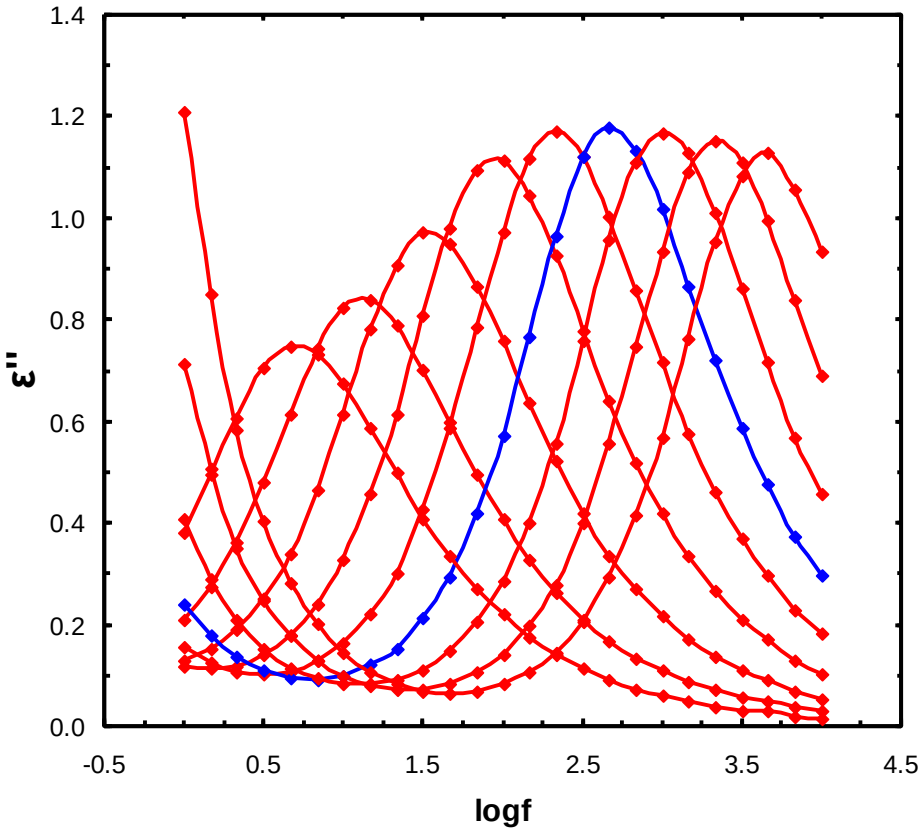
Dielectric Spectroscopy

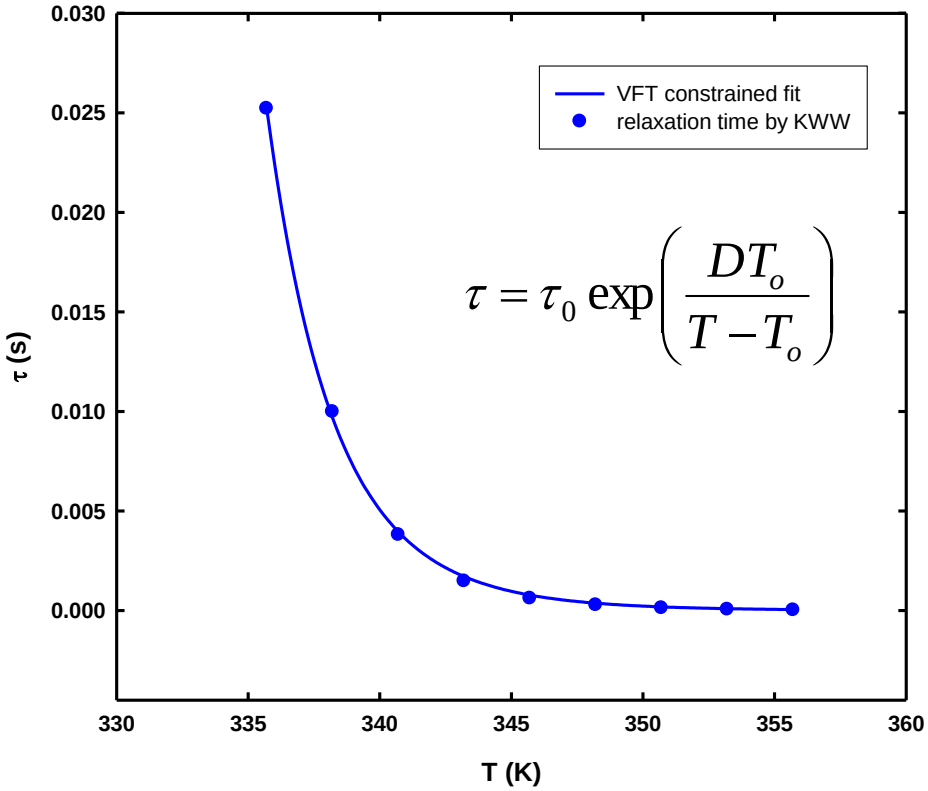
Time Domain Dielectric Spectroscopy



Crystal Pharmatech
您的药物晶型研究和固态研发专家

无定形药物的弛豫现象研究:DEA



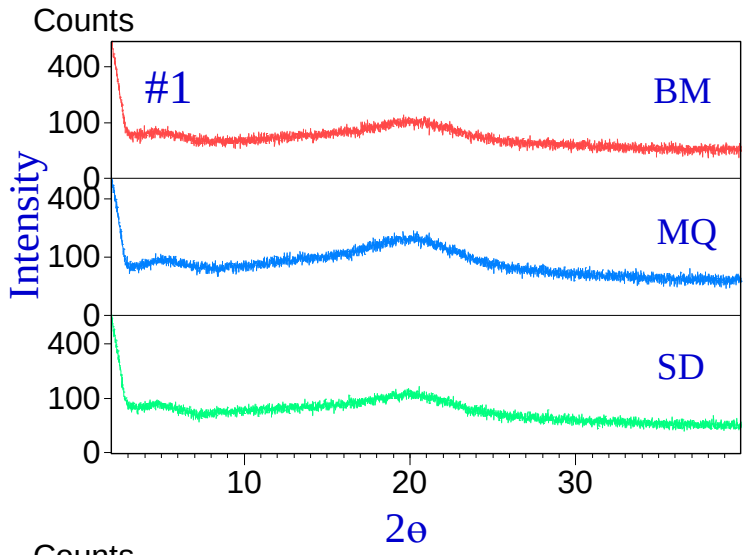


D = 7.4965, **T_0 = 267.3**

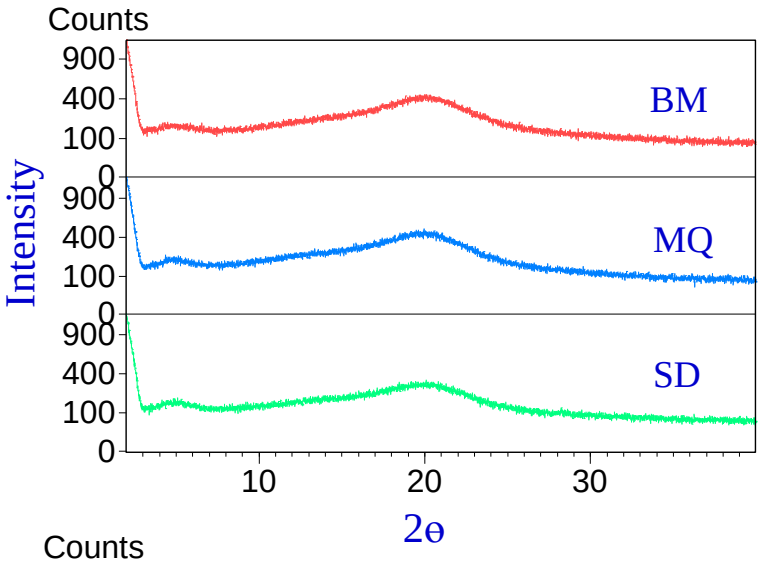
T_g = 321.7K (48.5 ° C)

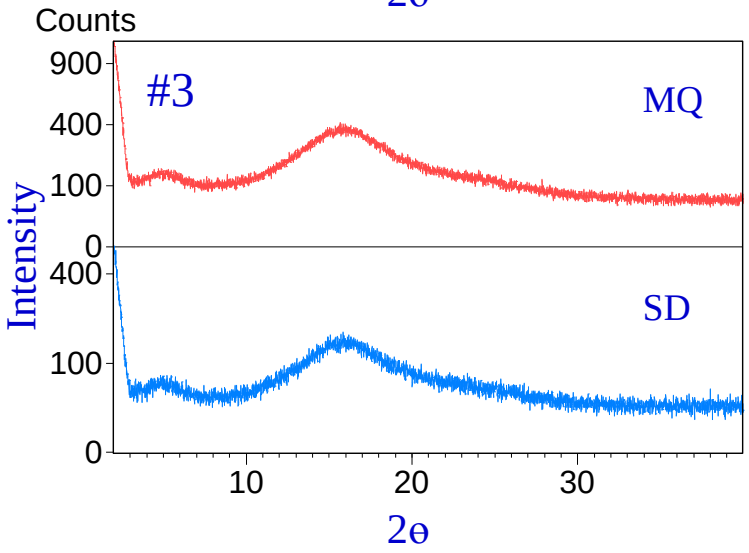
Crystal Pharmatech
您的药物晶型研究和固态研发专家

无定形药物物理稳定性：分子结构影响

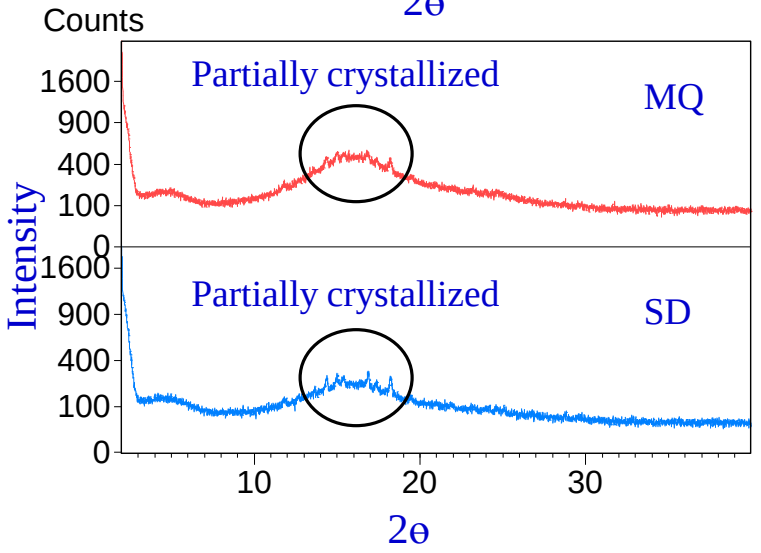


Vacuum chamber 40 C 24 days



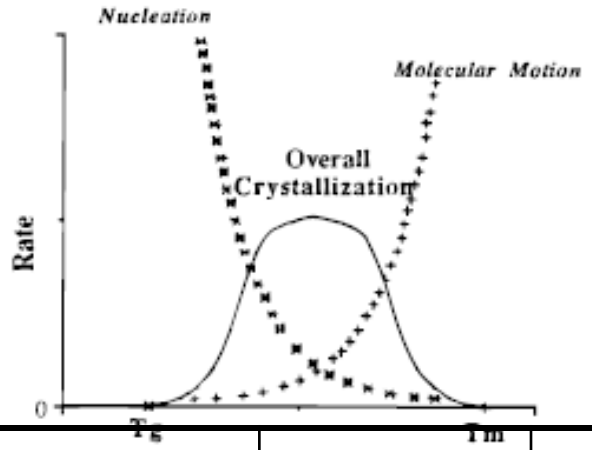


Vacuum chamber 40 C 4 days



结构驰豫是无定形稳定性的唯一参数？

Structure relaxation time is inversely proportional to the molecular mobility - A key determinant of the physical and/or chemical stability of amorphous phase

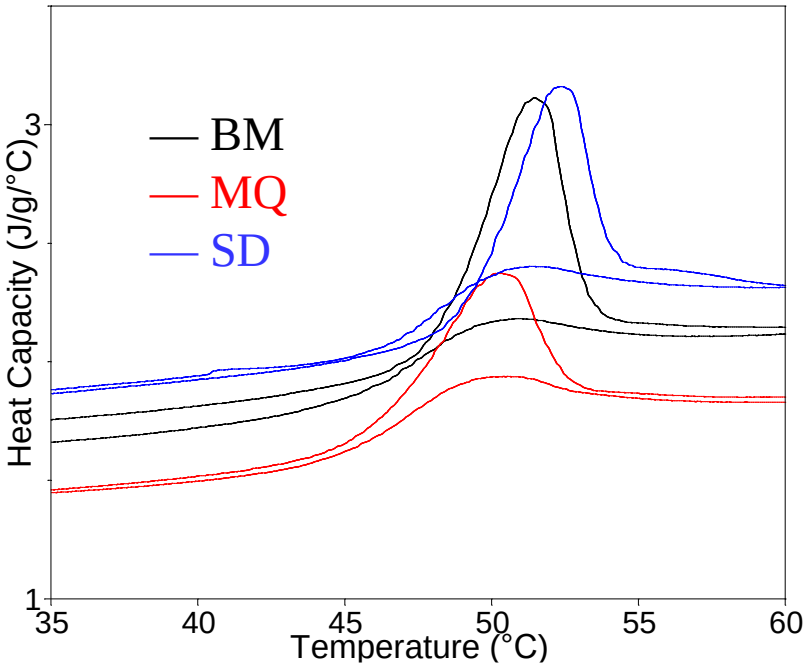


- Molecular mobility partially involved in the rate-limiting step for crystallization
- Extent of correlation between the rate of crystallization and molecular mobility could be different above and below T_g

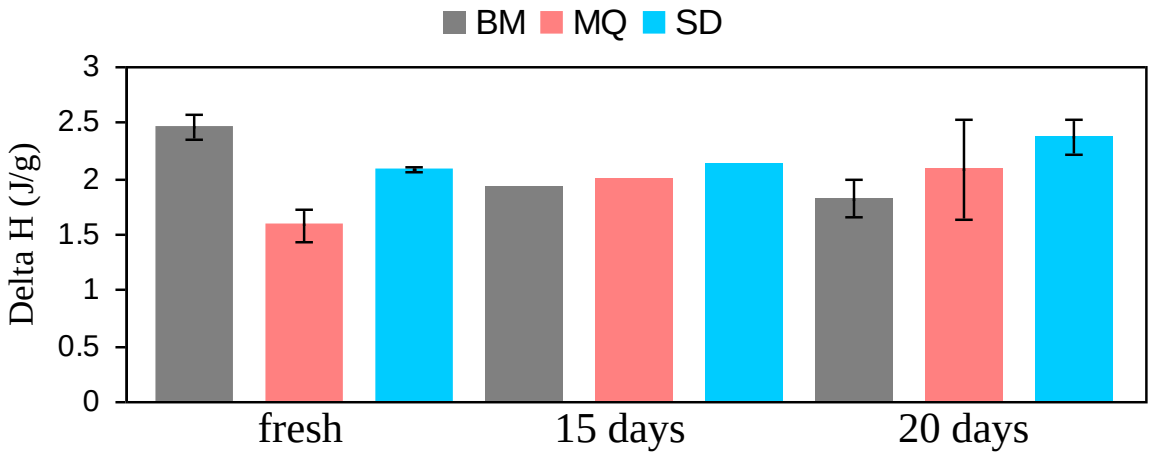
	T_g (C)	T_0 (C)	m	D	τ_{40C} (s)	τ_{40C} (day)
Compound#1	44.5	-5	98	7.21	$5x10^4$	0.5
Compound#3	78.5	24	104	6.69	$9x10^{39}$	10^{35}

- Compound #1 with lower T_g, greater molecular mobility and faster dynamic shows much slower crystallization rate
- There are other important factors affect the crystallization process as well

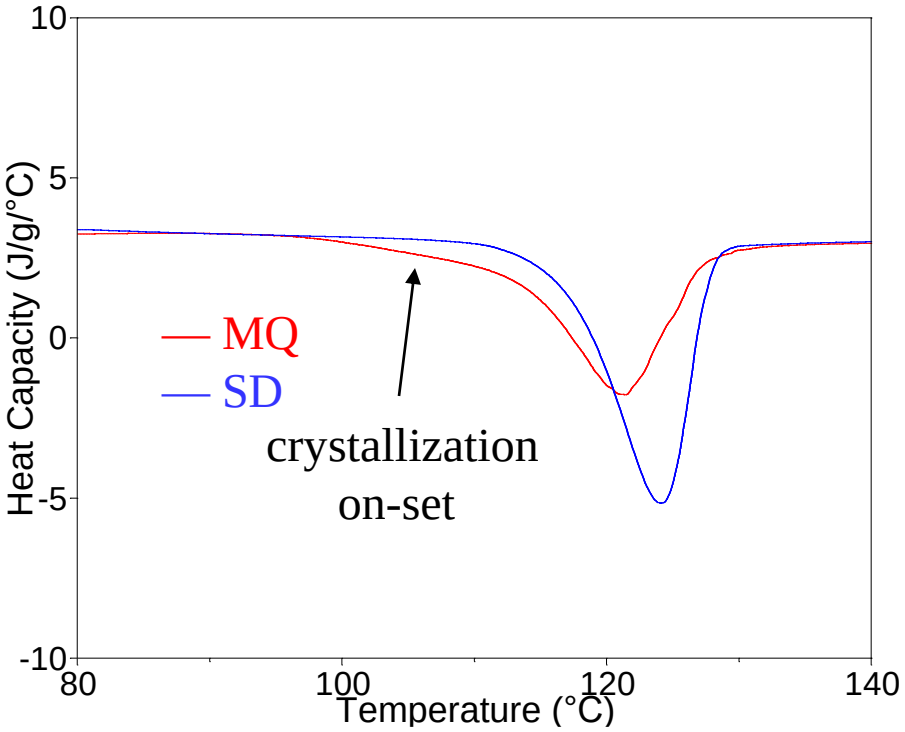
无定形制备方法对稳定性影响



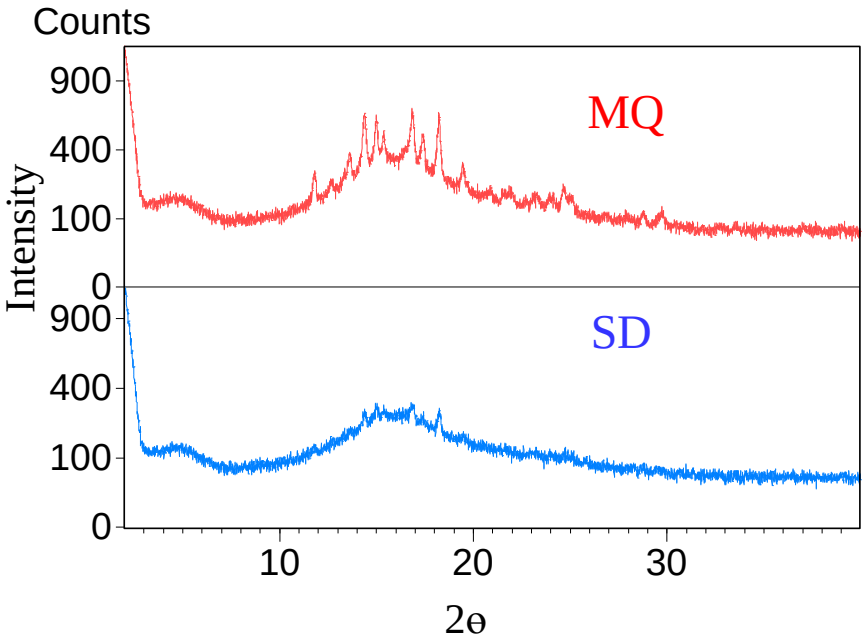
- Different preparation methods result in varied excess enthalpy value (corresponding to different energy level in energy landscape)
- Enthalpy relaxes as a function of time



无定形制备方法对稳定性影响



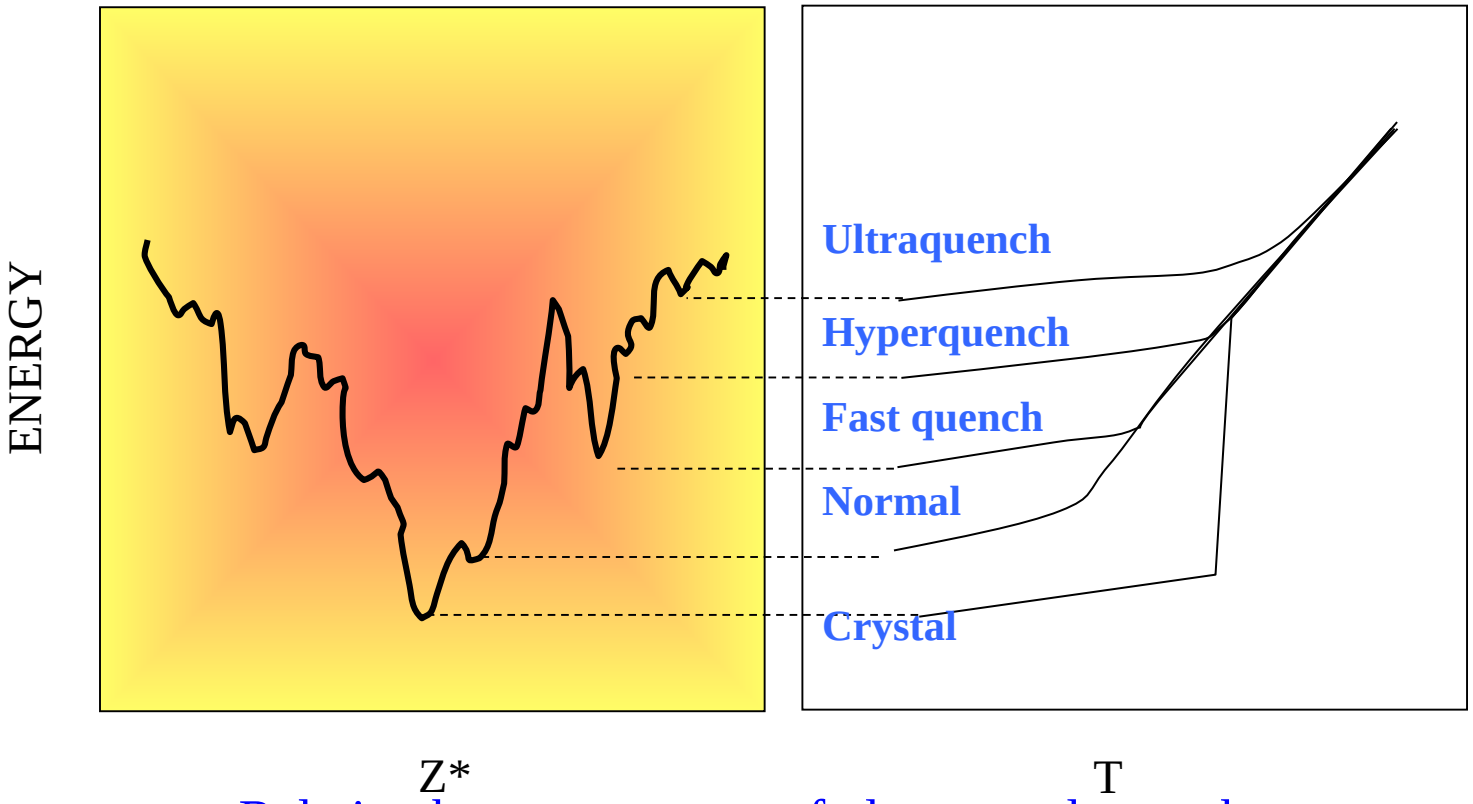
#3 at 40C/75%RH for 10h



- Spray dried (SD) #3 is more stable than melt quenched (MQ) #3.
- It is consistent with the result that SD freeze the system at a lower energy state (larger excess enthalpy).

Crystal Pharmatech
您的药物晶型研究和固态研发专家

用能量谱图对无定形稳定性的解释

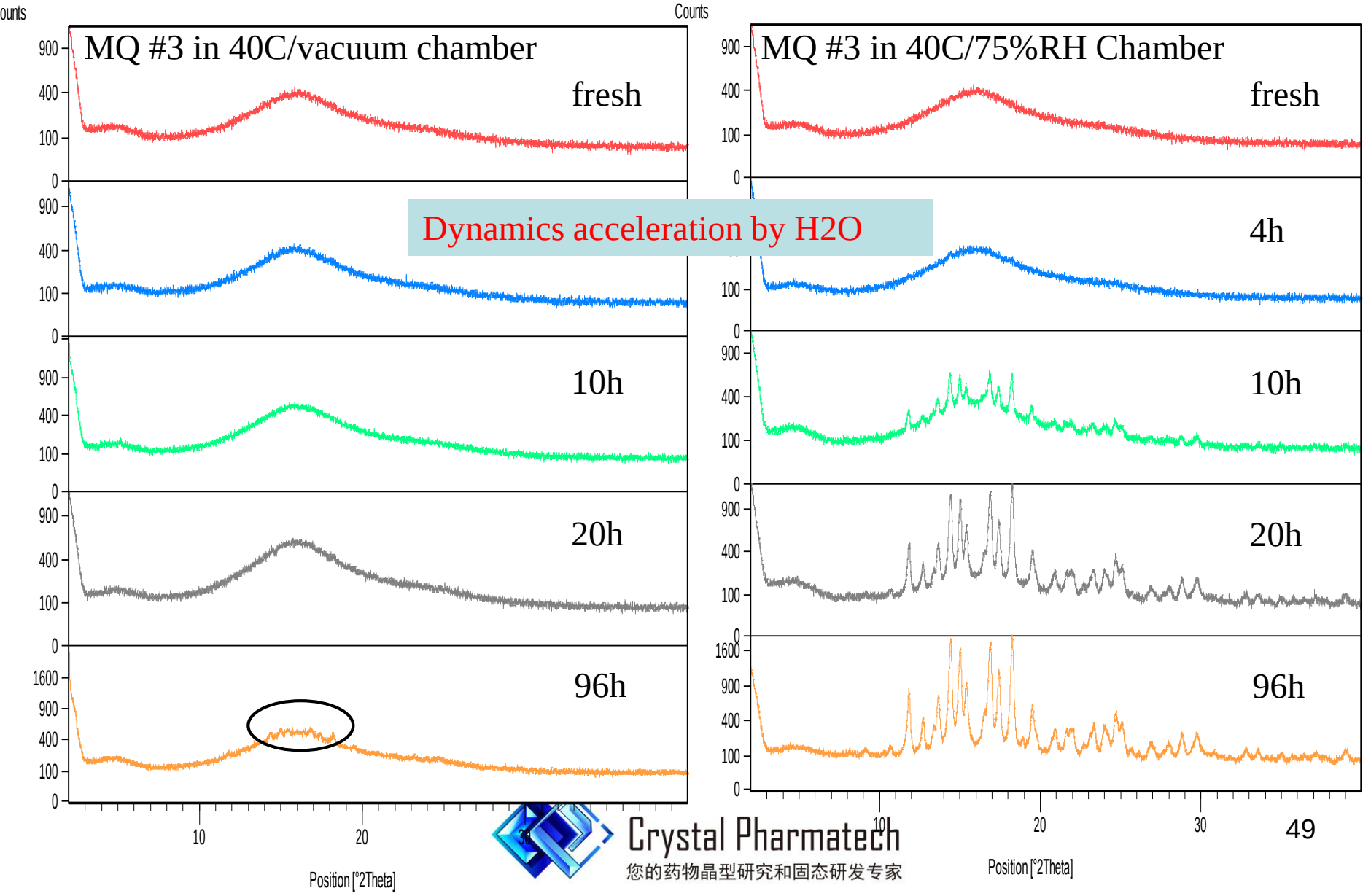


Relation between energy of glasses and quench rate

$$m \propto \frac{\text{Density of energy minima}}{\text{Energy barrier heights}}$$

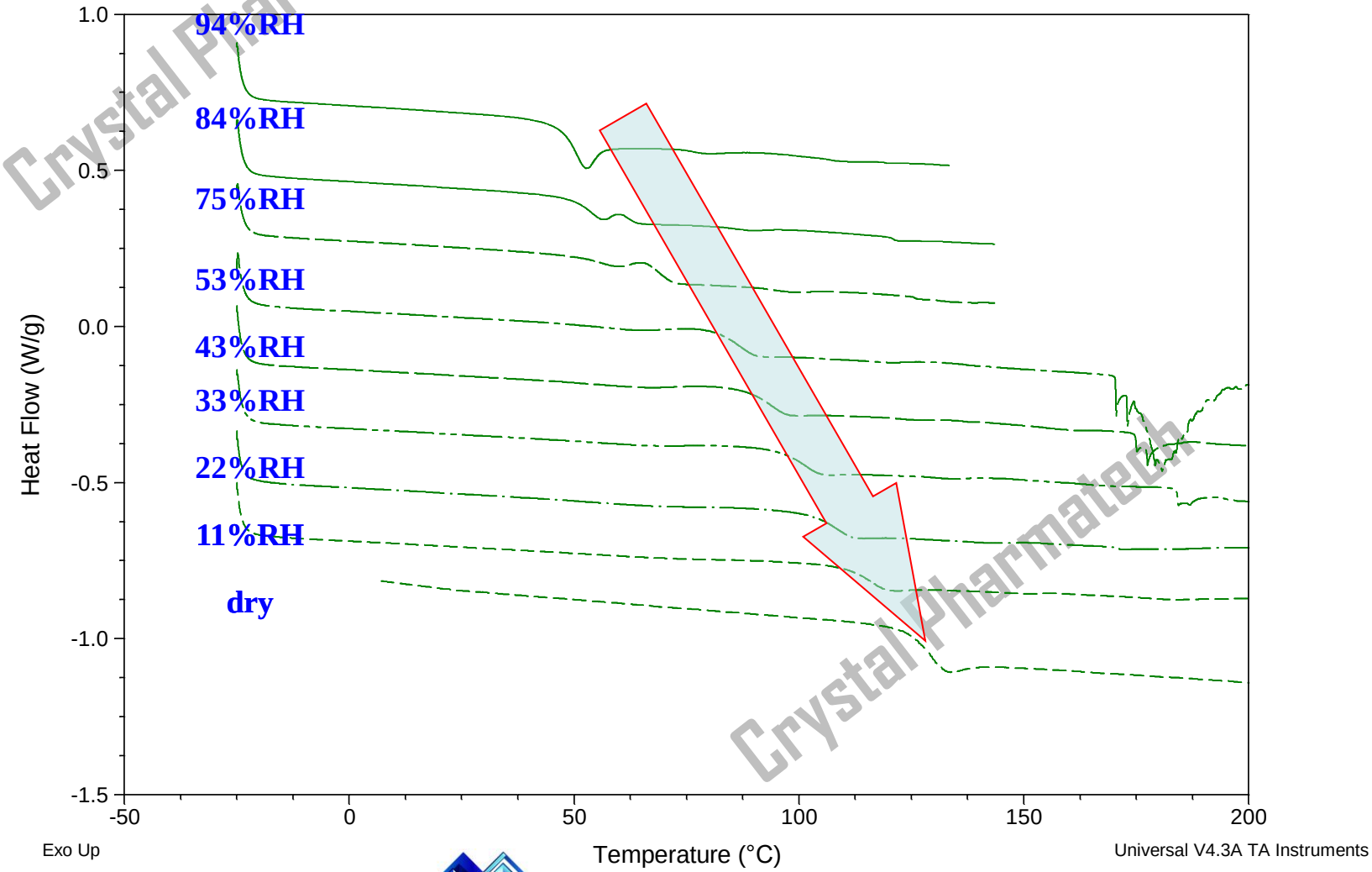
Crystal Pharmatech
您的药物晶型研究和固态研发专家

水分对无定形稳定性影响



Crystal Pharmatech
您的药物晶型研究和固态研发专家

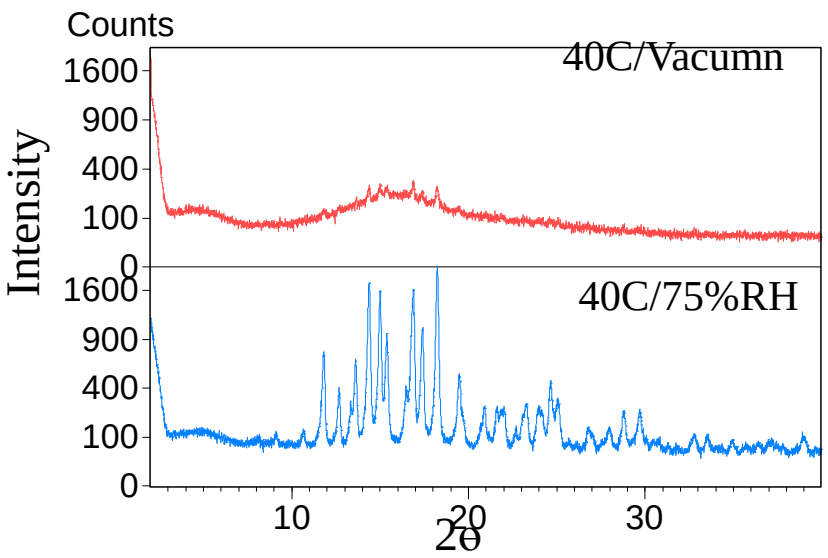
水分对玻璃化温度的影响



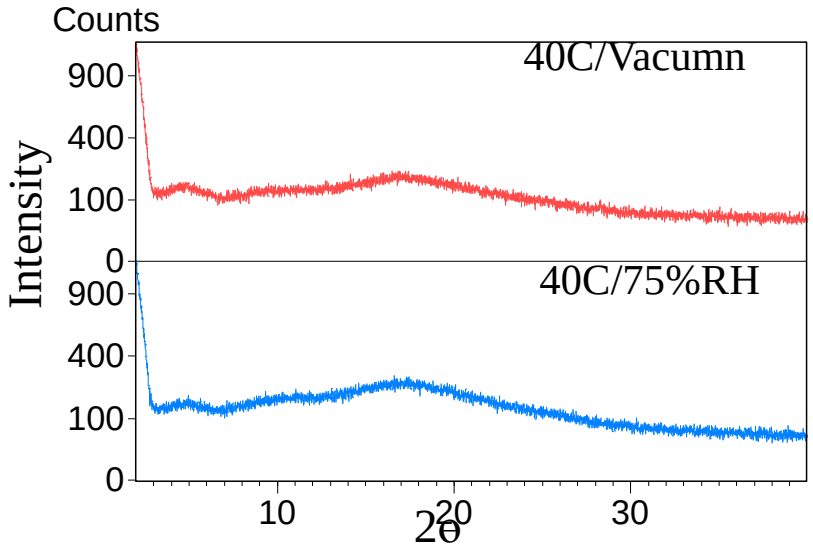
Crystal Pharmatech
Crystal Pharmatech
Crystal Pharmatech
您的药物晶型研究和固态研发专家

高分子添加剂对无定形稳定性影响

Compound#3 (SD) 4 days



#3 + HPMCASHF (SD, 1:2) 10 days



Polymer stabilized API

- Slower molecular mobility?
- Changed nucleation process?

总结

- 无定形制剂研发越来越受重视，对溶解度较低(D_o高)或者晶型专利受保护的药物分子尤为重要
- 无定形的稳定性和许多物理性质密切相关，对无定形的深刻理解是开发稳定无定形制剂的关键
- 多种固态分析手段是无定形研发中必不可少的工具

Crystal Pharmatech

Crystal Pharmatech

谢谢大家！

Crystal Pharmatech