Real Time "*in-situ*" Reaction Chemistry

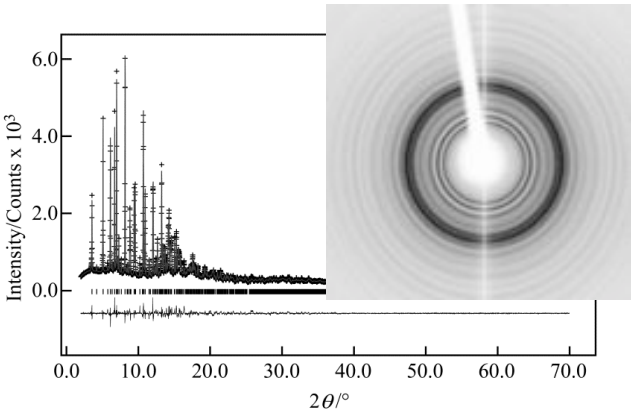
May 23, Beijing

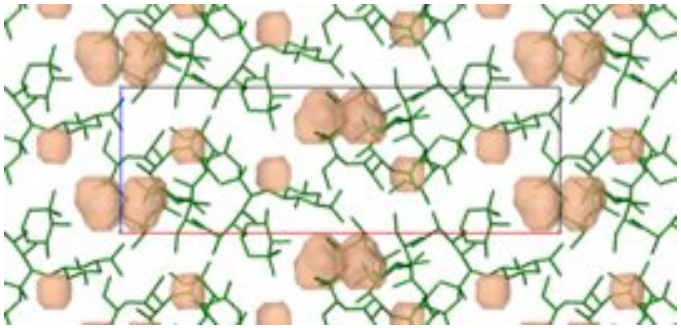
PPXRD-12
20-24 May 2013
The 12th Pharmaceutical Powder X-ray Diffraction Symposium
at the Institute of Physics, Chinese Academy of Sciences, Beijing, China

Tokyo Institute of Technology
Department of Chemistry
Uekusa Group

XRPD Techniques/Rietveld Refinement

Hydration / dehydration transformation mechanism of pharmaceutical crystals revealed by SDPD method





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This document was presented at PPXRD - Pharmaceutical Powder X-ray Diffraction Symposium

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PPXRD Website – www.icdd.com/ppxrd

ICDD Website - www.icdd.com

About this talk

1. Hydration / dehydration phenomena and powder structure analysis
   - Dehydration and Hydration phenomena
   - Structure Determination from Powder Diffraction data
   - Pharmaceutical application: Dehydration of Acrinol
2. Isomorphic desolvates (dehydrate, but same structure)
   - Cefalexin, Cefaclor
   - Erythromycin A

Collaboration with Pharmaceutical groups.
Prof. Katsuhide Terada (Toho univ.)
Prof. Etsuo Yonemochi (Hoshi univ.)

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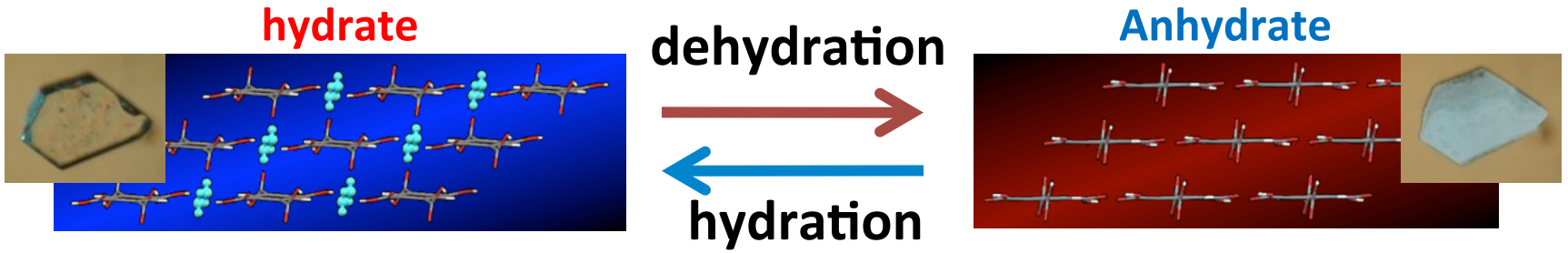
"CREST (Core Research for Evolutional Science & Technology) program."

In dehydration & hydration

- Crystal structure changes with solvent (water) molecular leaving out or coming in
- When we analyze the both crystal structures before and after phase transition, we can deduce the process of dehydration / hydration
- For example …

Pseudo polymorphic phase transition between hydrate and anhydrous phases



- For Pharmaceuticals, de/hydration is a big problem

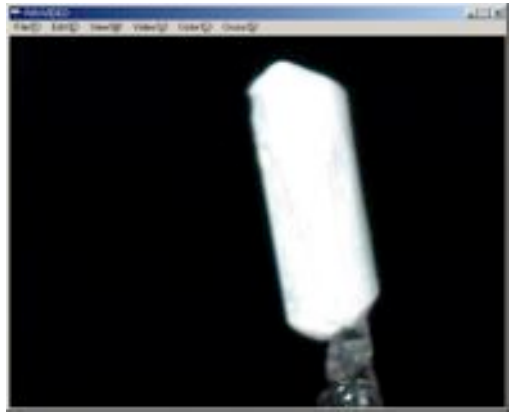
  Hydration/dehydration changes physicochemical property:
  Solubility, solution rate, stability, bioavailability…

- It may occur in manufacturing, processing, and storage
- Structural study is essential to understand and control such *dynamic aspects of molecular crystals.*

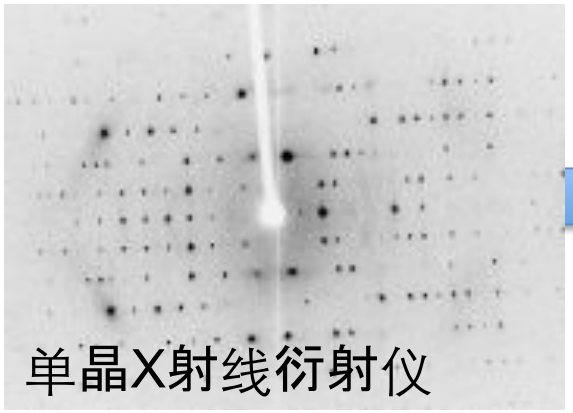
However,

Structural change makes powder crystals!

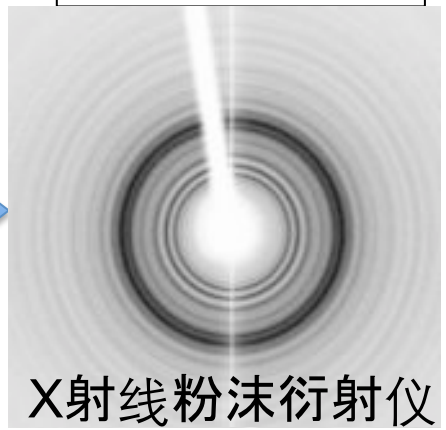
Powder structure analysis of dehydration process

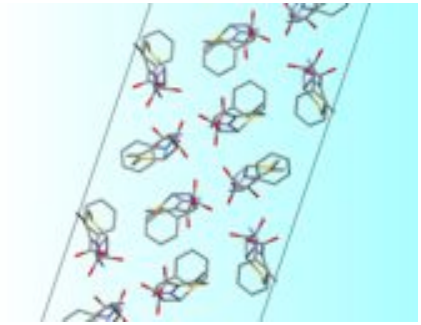


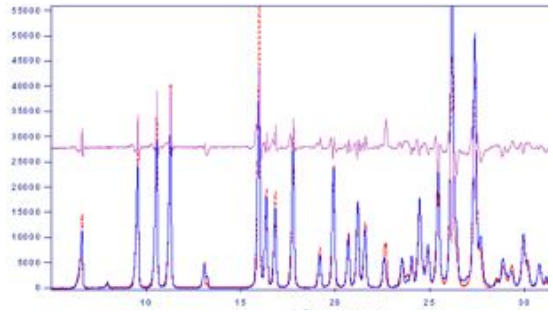
Single crystal



Powder crystal





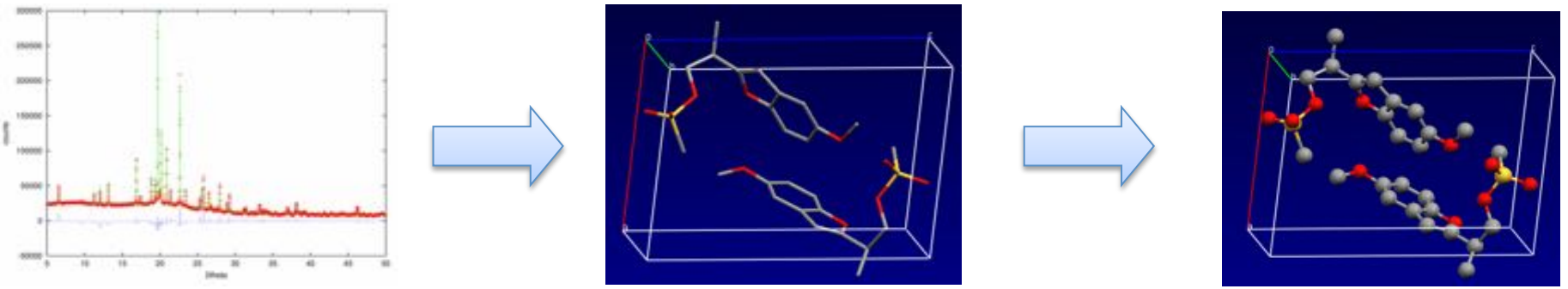


Structure **D**etermination from **P**owder **D**ata technique resolves such problems

What is SDPD?

ab initio Structure analysis from powder data (XRD)

- Structure Determination from Powder Diffraction Data (SDPD) – *determination & Rietveld refinement*



Indexing
- lattice parameters

Extraction
- diffraction intensities

Structure solution

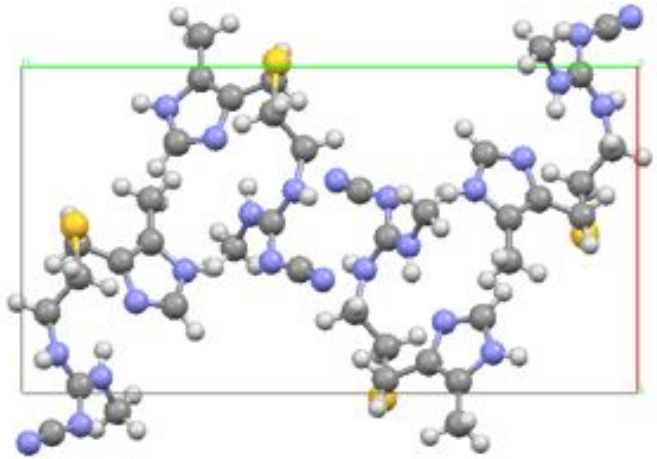
Direct space method: simulation of crystal structure which reproduce PXRD

Structure refinement

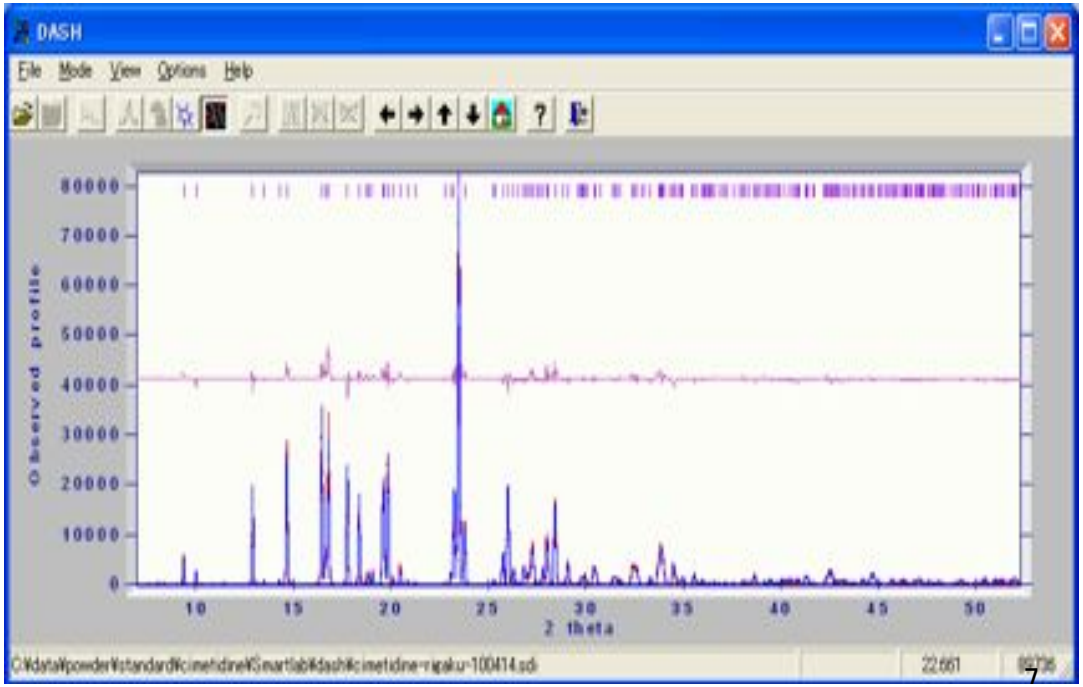
Rietveld method: refine atomic and profile parameters to fit XRD pattern by least-square method.

How to solve the structure from XRD pattern ?
Direct space method

- We can Build a crystal structure model (simulation) and calculate XRD pattern(blue) to compare with observed XRD(red) and then see the difference! (central violet plot to become flat)
- Bond lengths and angles are fixed, but torsion angles are free to rotate. Molecular position, orientation, and torsions are free.

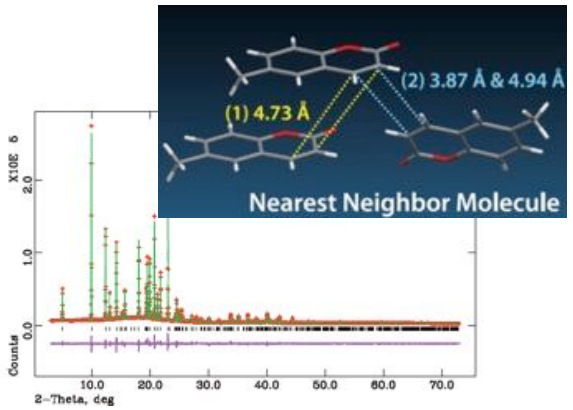


Correct!

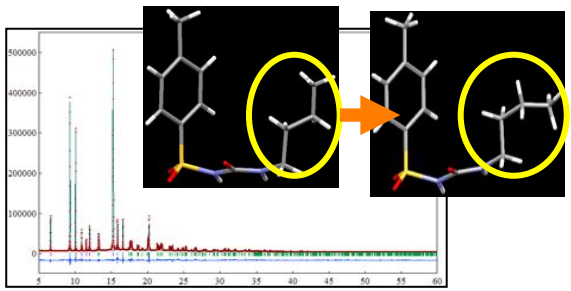


Our previous works

Twin Crystal

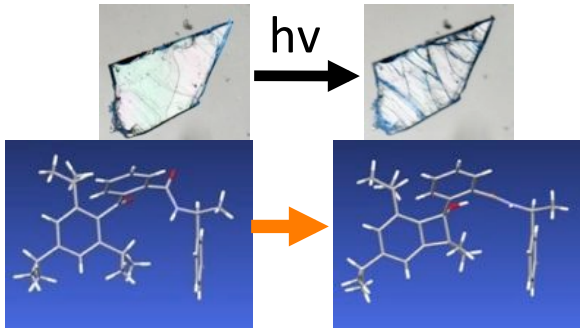


Phase Transition of Pharmaceuticals



Int. J. Pharm., **2009**, 369, 12

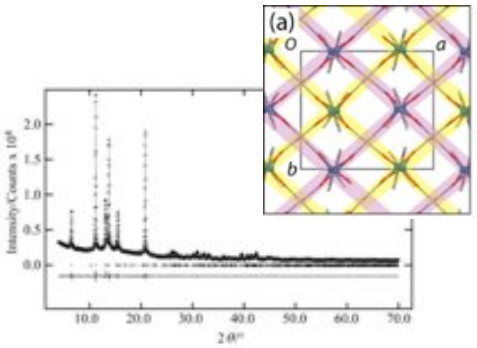
Photoreaction in Crystalline State



CrystEngComm,**2011**, *13, 3197*

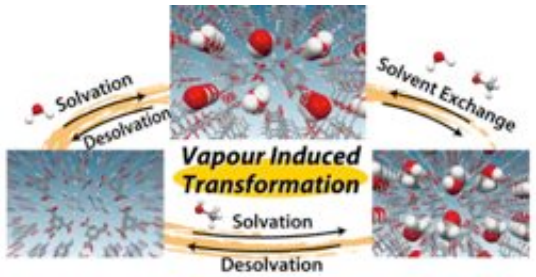
All structures were analyzed by SDPD technique

Mechanochemical reaction (MOF)



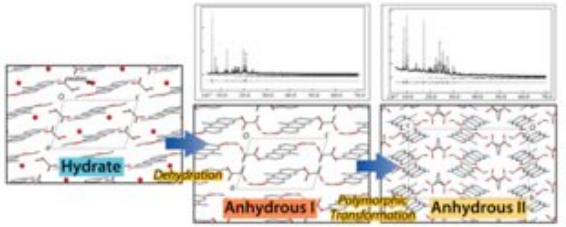
Chem.Comm.,**2010**,46, 7572

Vapor Induced Transformations



Angew.Chem.Int.Ed.,**2006**,45,6013
Cryst.Growth&Des.,**2009**, 9, 1201
Chem.Comm,**2010**, 46, 4264

Dehydration Phase Transition of Pharmaceuticals

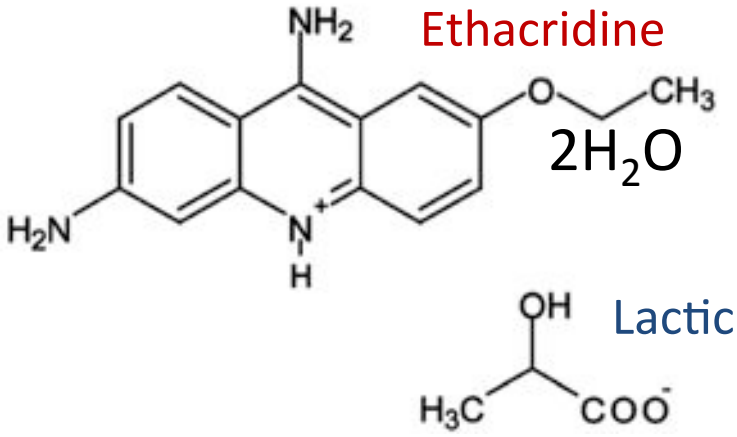


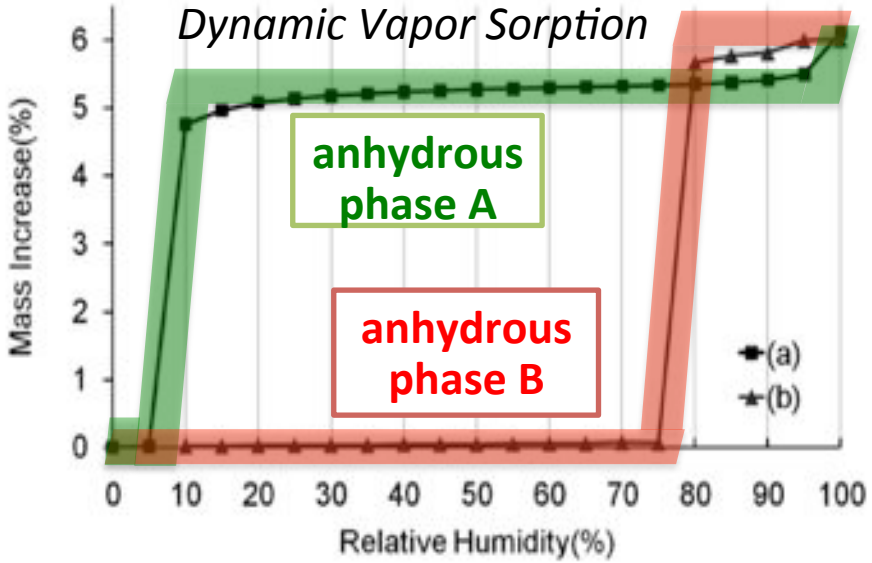
Cryst.Growth&Des.,**2012**,12, 6165
Cryst.Growth&Des.,**2010**,10,3176
J.Phys.Chem C.,**2010**,114,580

J.Phys.Chem C.,**2010**,114,580

Acrinol (crystal structure and cRH)

Acrinol (Antiseptics)





Dihydrate → (Dehydration @400K) → Anhydrate A → (Thermal transition @470K) → Anhydrate B

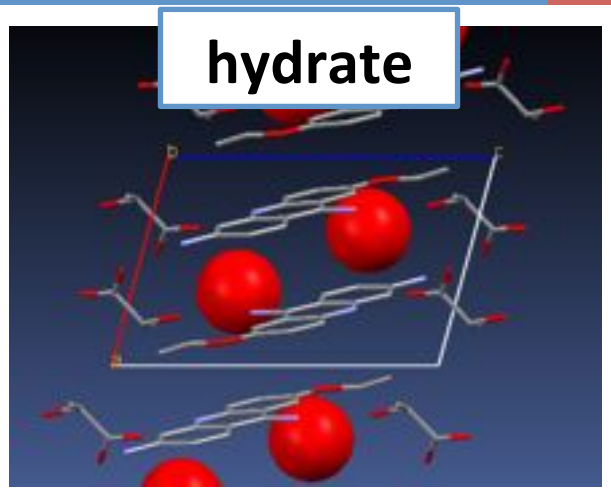
Anhydrous A and B have different hydration characters

A: easily hydrates around R.H. 5%

B: stable up to R.H. 75%

} Crystal structure difference? SDPD!

Crystal structure and hydration property

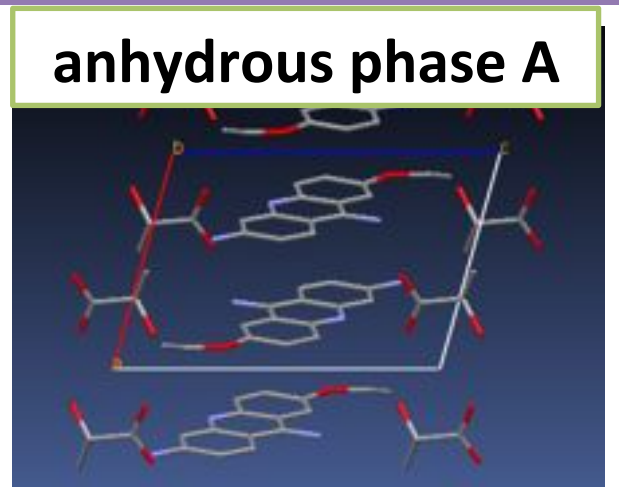


hydrate

dehydration

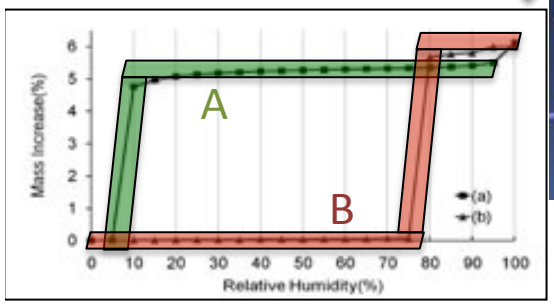
Easy and smooth

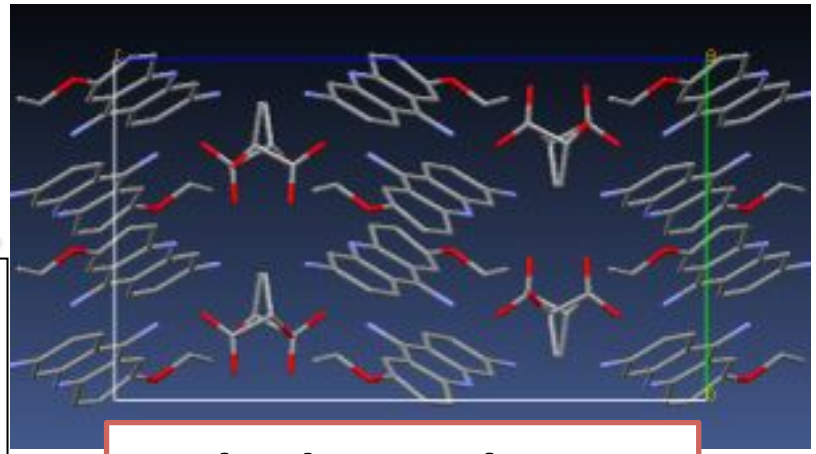
re-hydration



anhydrous phase A

Difficult to hydrate



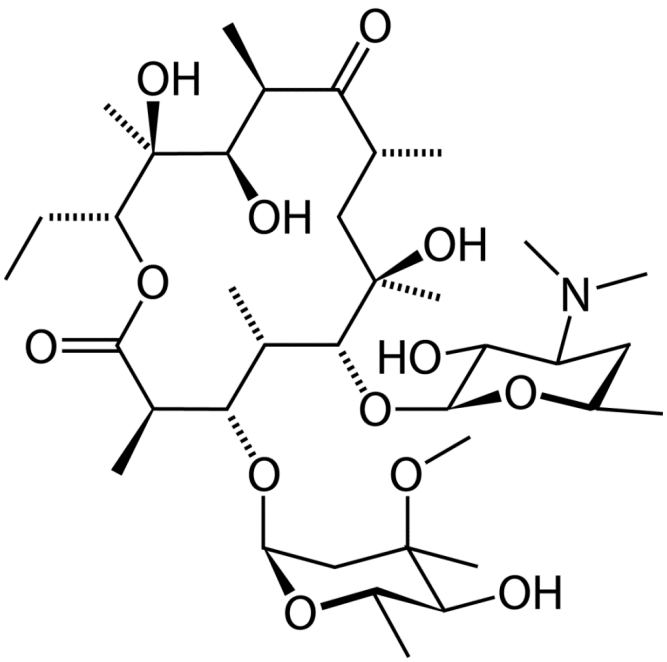


anhydrous phase B

Crystal structure similarity and difference explain the dehydration / hydration property

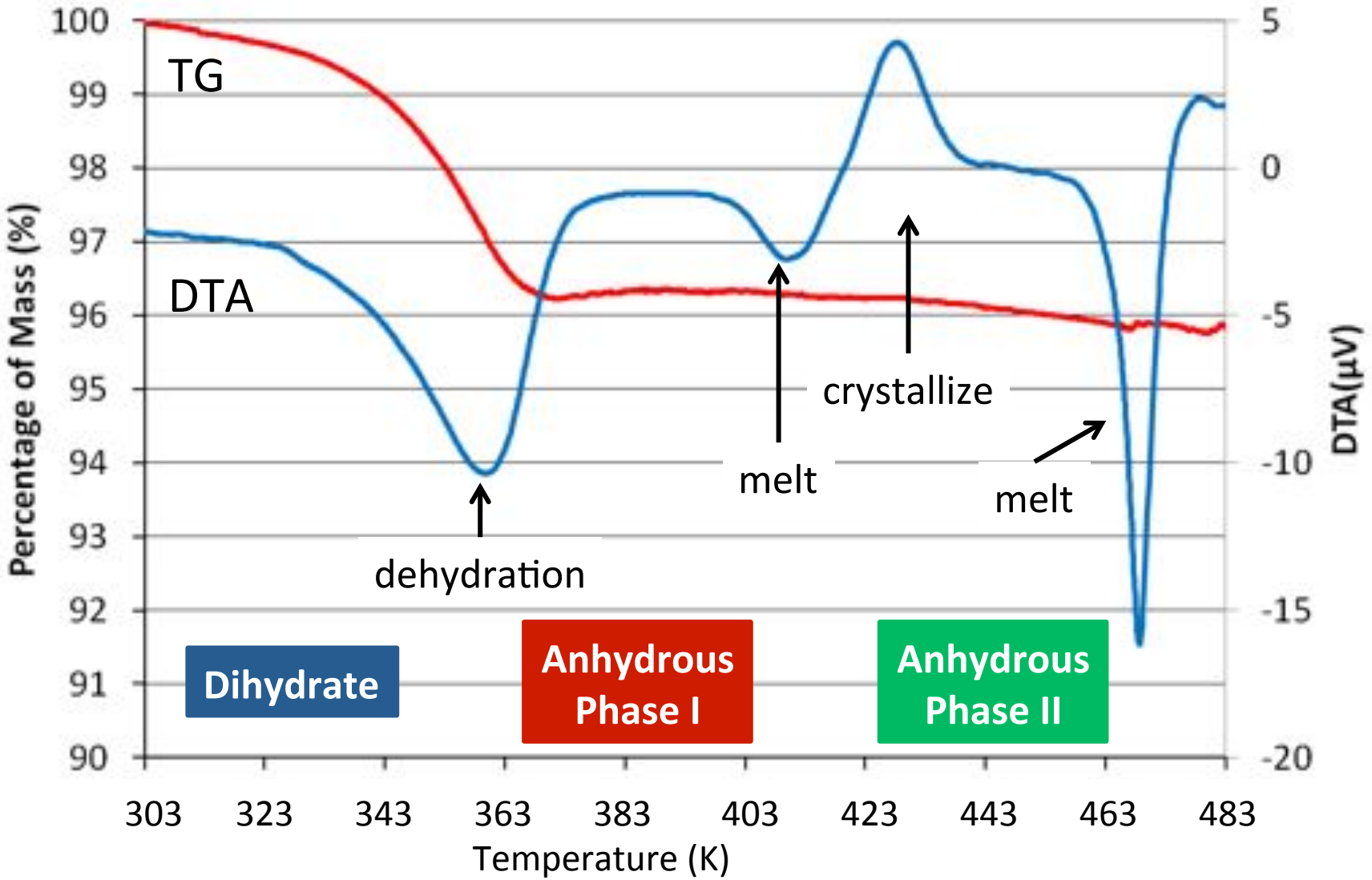
Erythromycin A
– *Isomorphic Desolvates* –

Crystal Growth & Design, 2013, 13 (5), pp 2060–2066



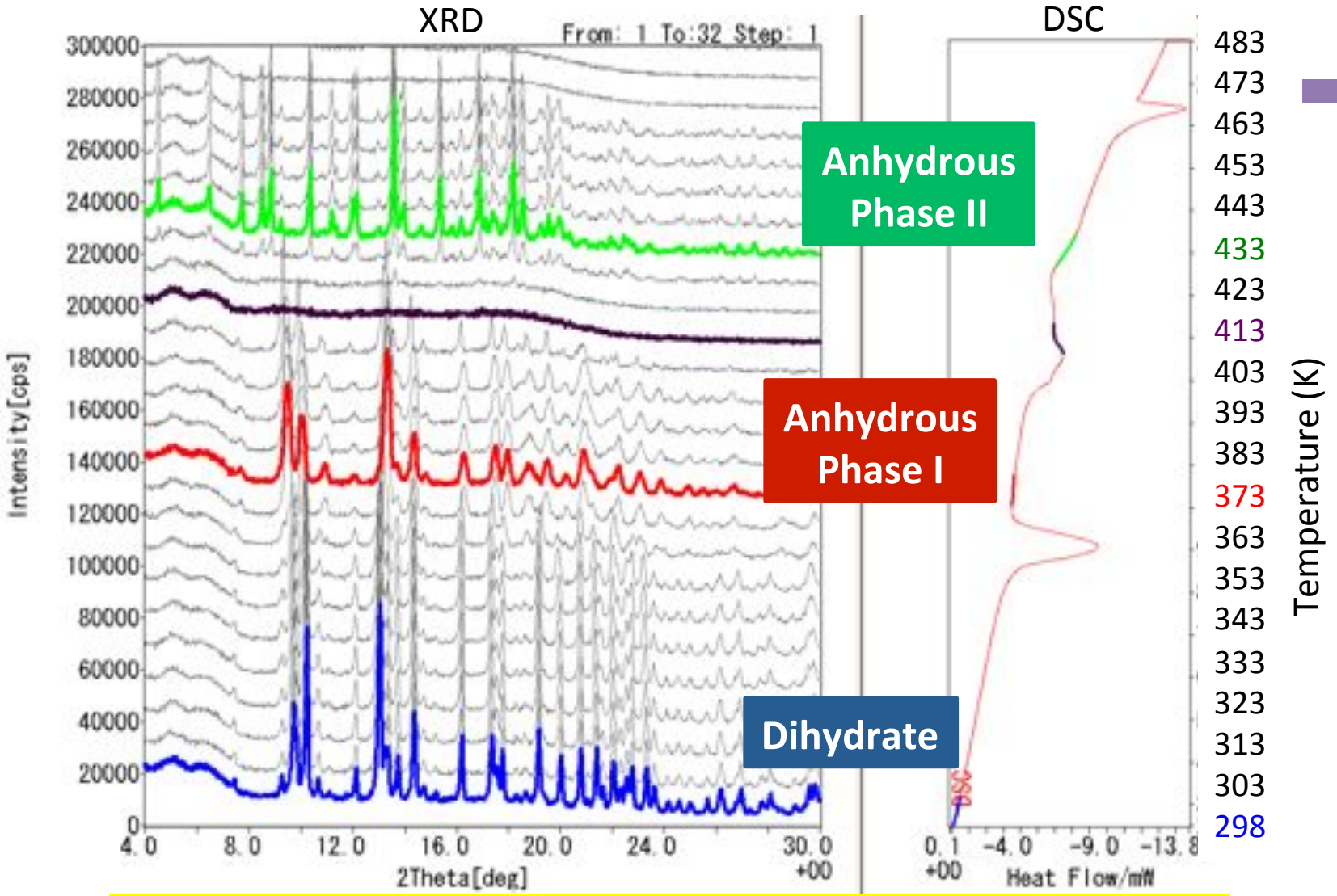
- ✓ Macrolide class of antibiotics
- ✓ $C_{37}H_{67}NO_{13}$, m.w. 733.93 g/mol
- ✓ dihydrate form is marketed

Erythromycin A dihydrate / TG-DTA



Dihydrate → Dehydration @360K → Anhydrate I → Thermal transition @430K → Anhydrate II

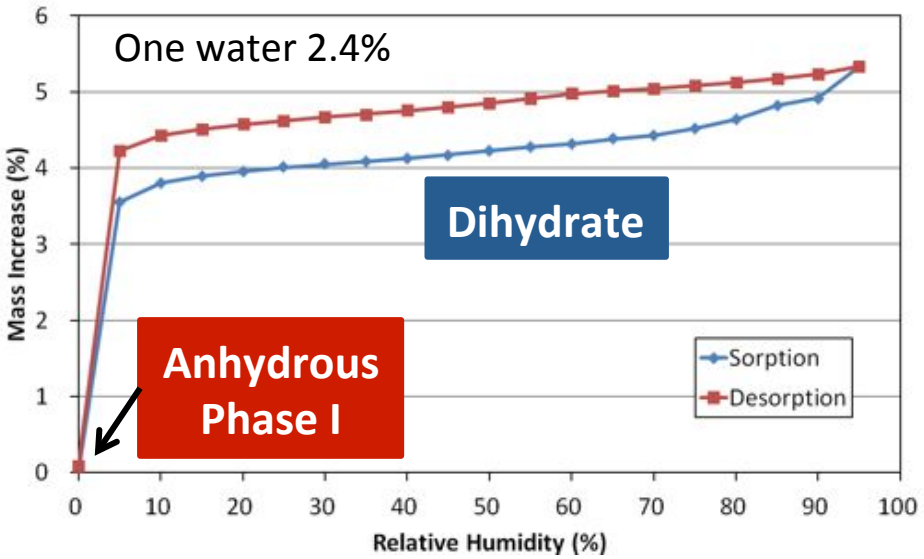
Erythromycin A / XRD-DSC



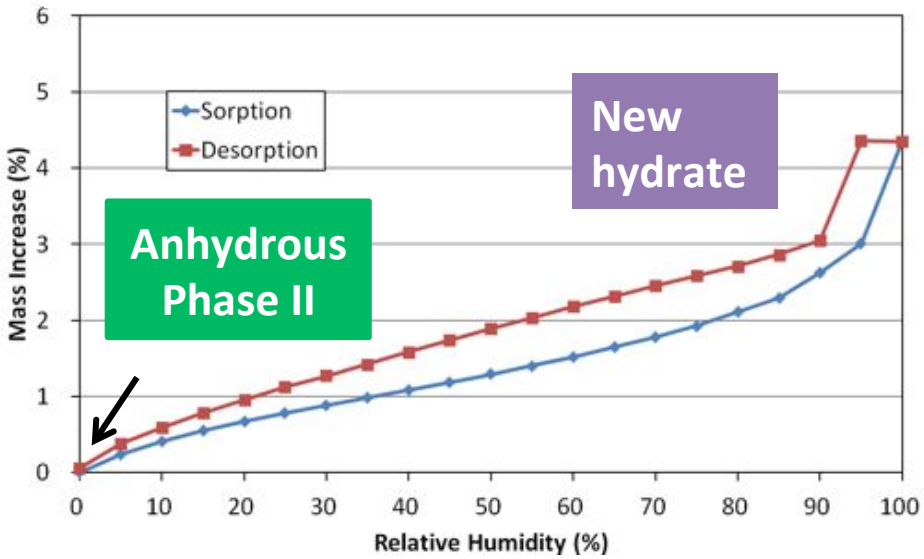
Two anhydrous phases are crystalline states

Erythromycin A / Dynamic vapor sorption

DVS plot of anhydrous phase I



DVS plot of anhydrous phase II



Anhydrous Phase I ⇄ (> RH 5% / < RH 5%) Dihydrate

stoichiometric hydration

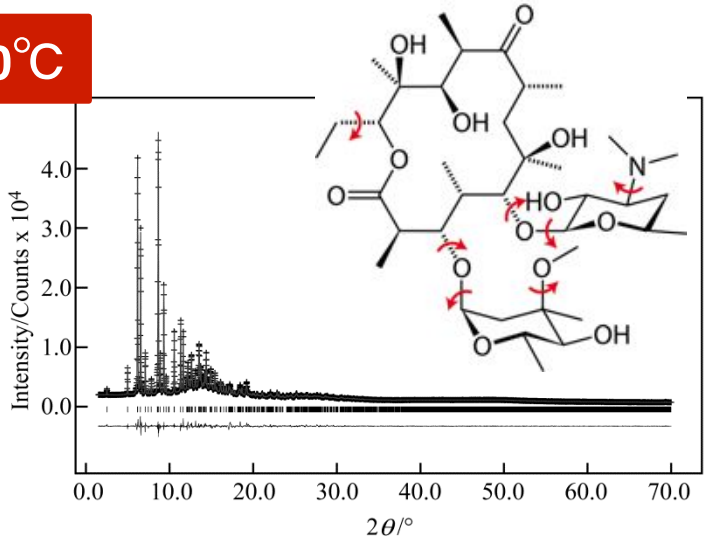
Anhydrous Phase II → (Humidity) New hydrate

nonstoichiometric hydration

SDPD for anhydrous phases I and II to reveal structural change

SDPD of Erythromycin A / phase I and II

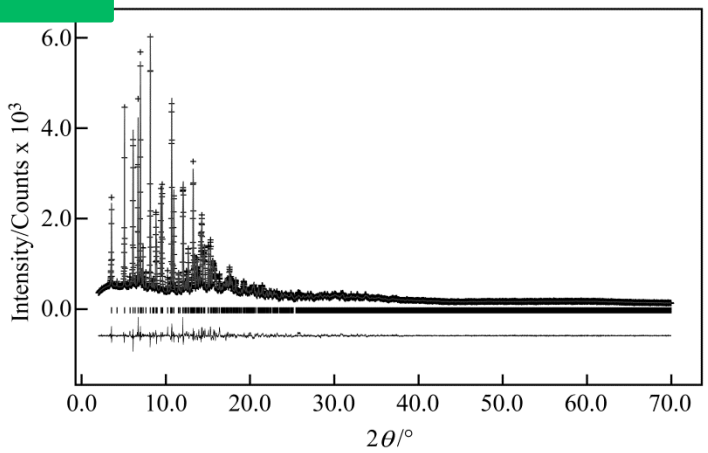
Anhydrous Phase I @ 100℃



space group $P2_12_12_1$

a/Å	9.5162(3)
b/Å	9.5449(3)
c/Å	46.255(1)
V/Å^3	4201.4(3)
$Z(Z')$	4(1)
Rwp	0.0374

Anhydrous Phase II @ RH 3%



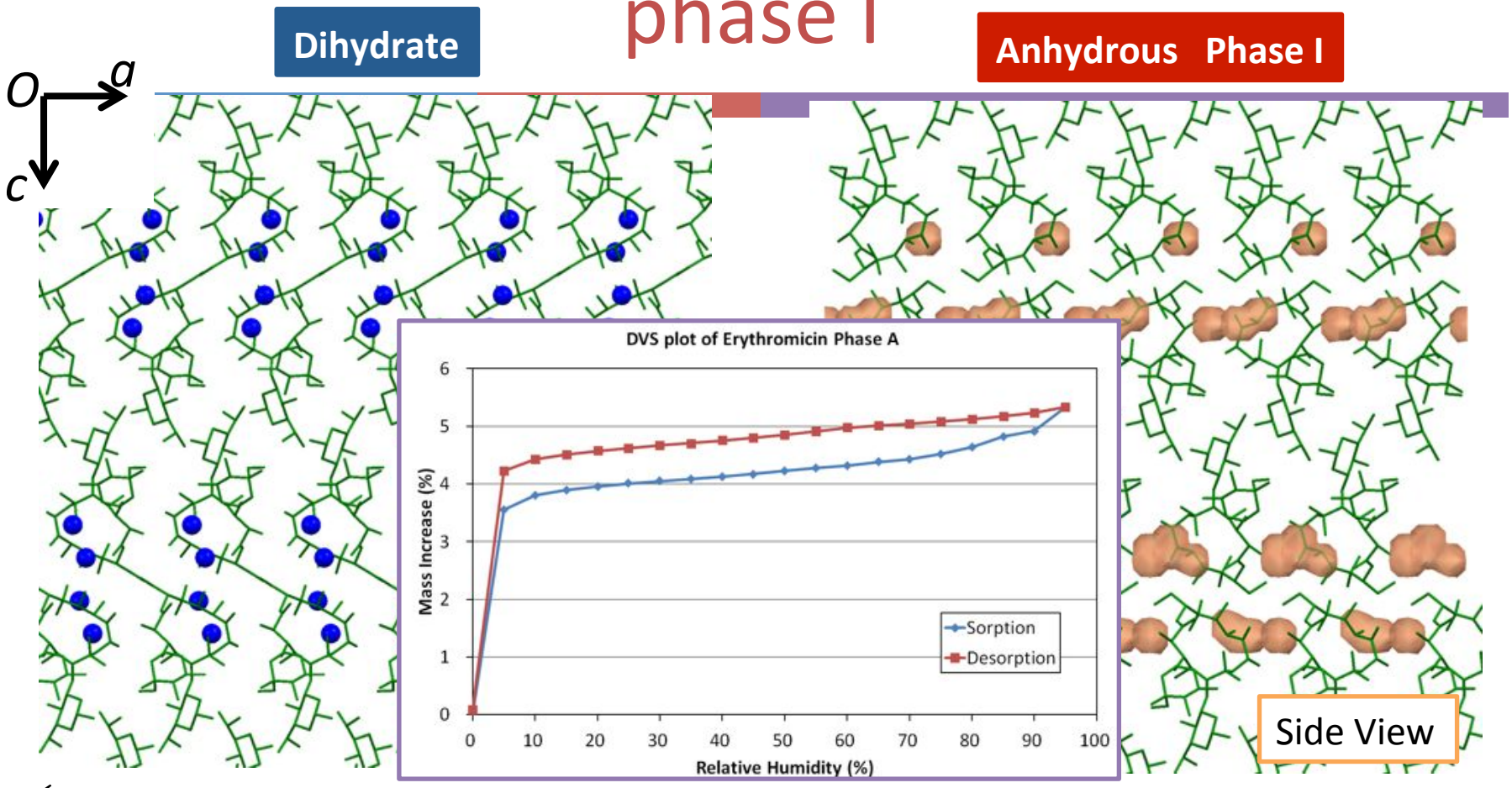
space group $P2_12_12$

a/Å	32.5162(9)
b/Å	23.8539(7)
c/Å	10.7657(2)
V/Å^3	8350.3(5)
$Z(Z')$	**8(2)**
Rwp	0.0528

26 parameters in direct space method

[Software]
DICVOL04, DASH, GSAS

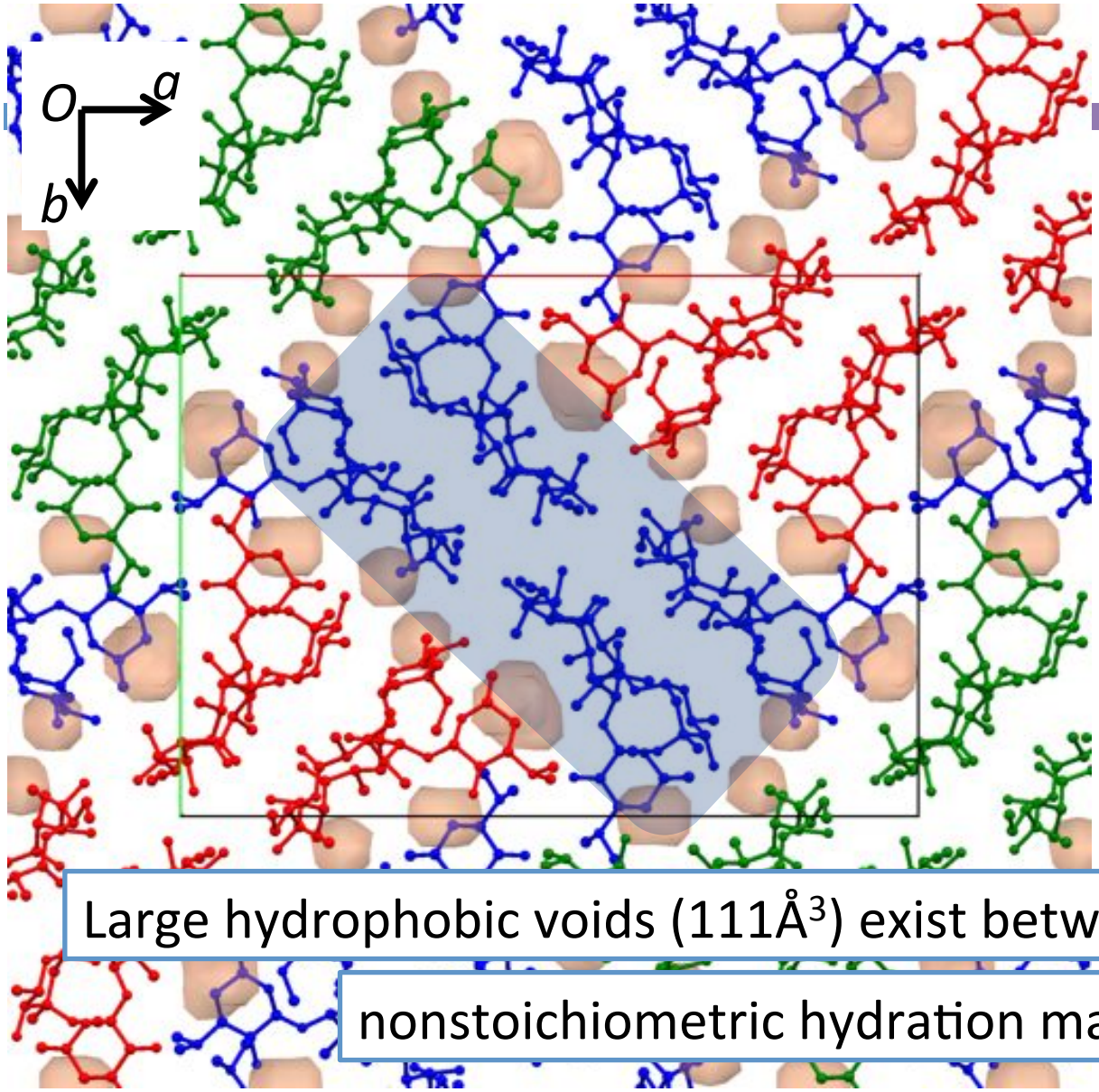
Voids observed in the anhydrous phase I

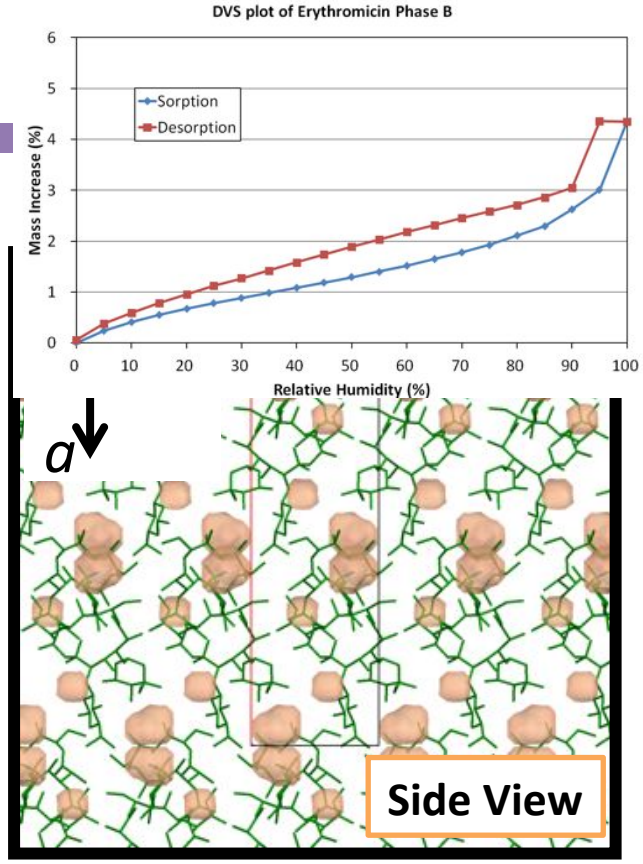


- ✓ Anhydrous phase I has voids (Isolated)
- ✓ Void positions are same as water positions in dihydrate

Anhydrous phase I easily hydrates stoichiometrically

Voids observed in the anhydrous phase II



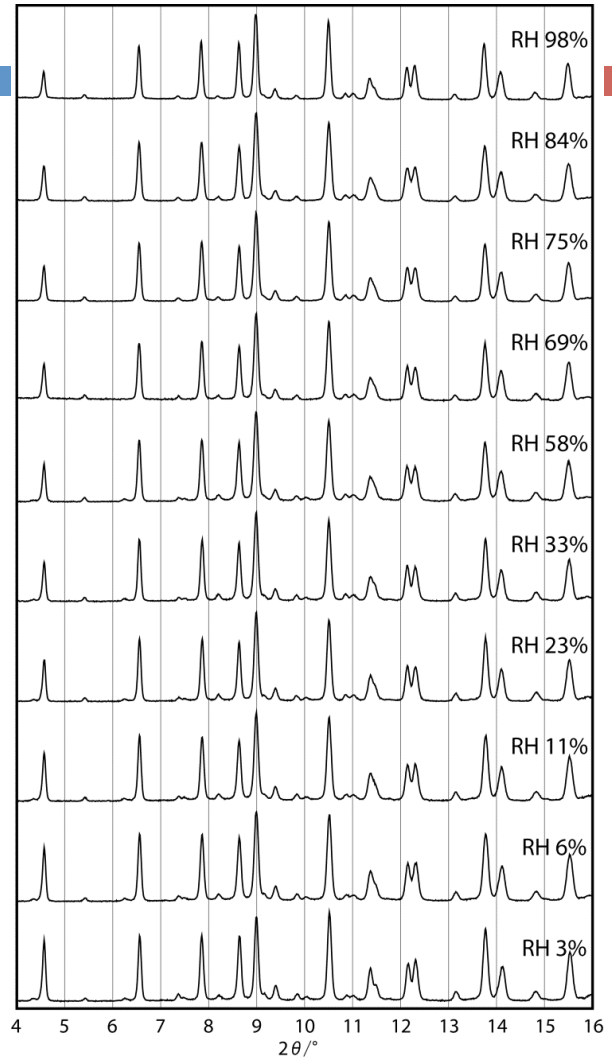


Large hydrophobic voids (111Å^3) exist between HB tetramer units

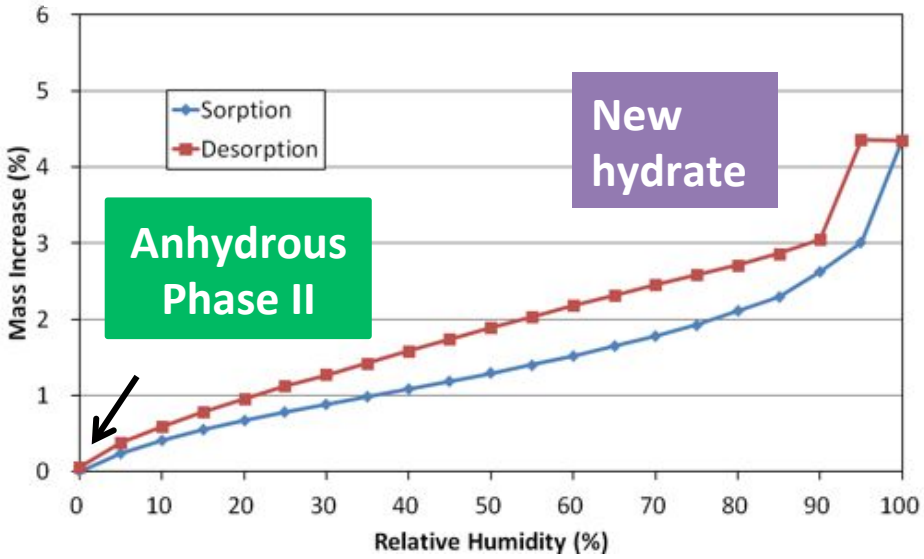
nonstoichiometric hydration may occur in these voids

Anhydrous II – nonstoichiometric hydration

Little PXRD change !



DVS plot of anhydrous phase II



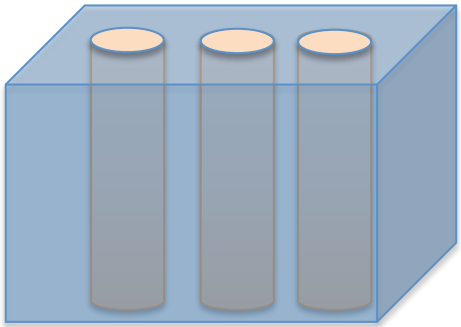
Anhydrous Phase II → (Humidity) → New hydrate

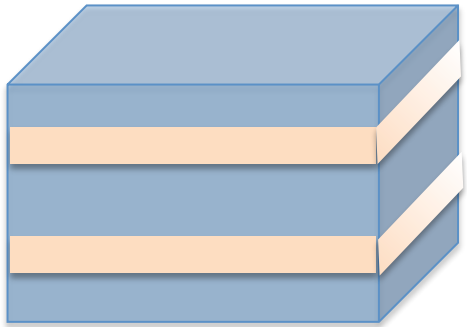
nonstoichiometric hydration

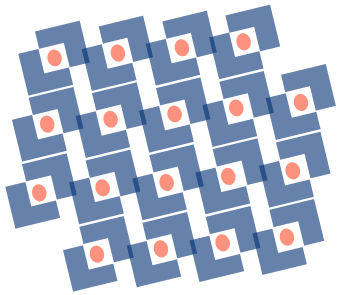
Isomorphic de/hydration. Powder structure analysis (SDPD)!

isomorphic desolvates summary

In textbook,
the idea is linked up with “water channel or water sheet” structure.

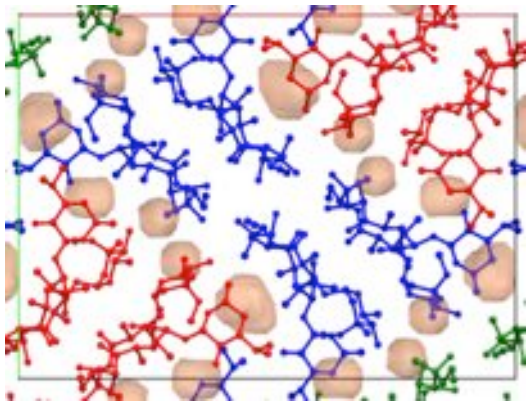


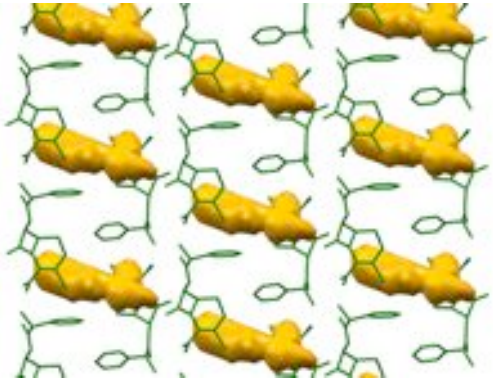




…and, they open and close dynamically.

Now, we suggest “sponge-like” structure with voids can also be “isomorphic desolvates”, which is only revealed by SDPD analysis.

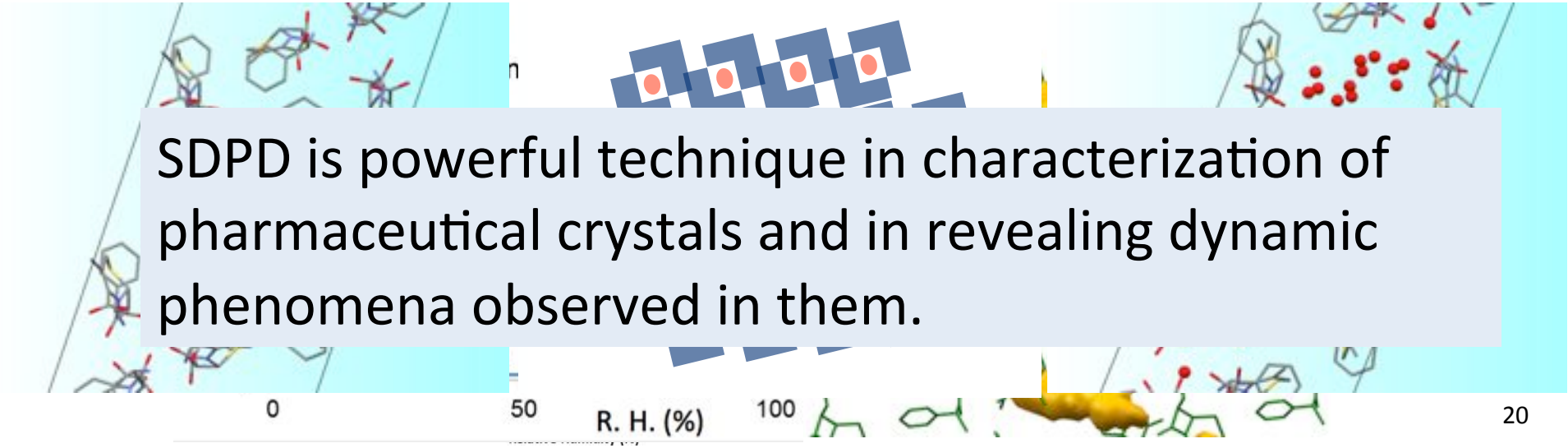




Summary

Pharmaceutical Pseudo-polymorphic phase transition
- hydration / dehydration structural change

Acrinol – two anhydrous phases, different hydration property
Cefalexin – channel water, block sub-structure slides
Cefaclor, Erythromycin A(II) – *void structure, nonstoichiometric*
– Isomorphic Desolvates –



SDPD is powerful technique in characterization of pharmaceutical crystals and in revealing dynamic phenomena observed in them.