Molecular Complexes of Agomelatine-Phosphoric Acid:

Crystal Structure Determination and Phase Transformation Kinetics by Non-Ambient Powder XRD

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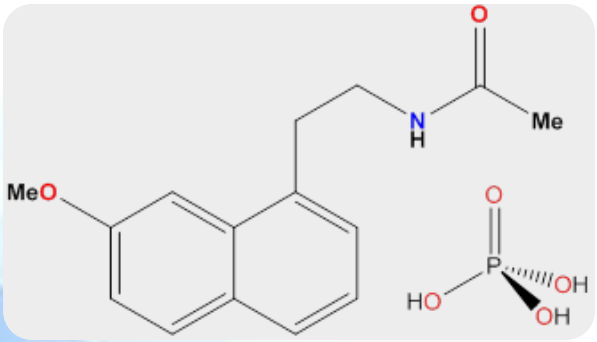
Background of Development



Agomelatine:Phosphoric acid (AGL-P)

- ✓ Novel **antidepressant** developed by Servier Laboratories
- ✓ Thermodynamically **stable form-II**
- ✓ Up to now, **six** polymorphs and several other **solvates/ co-crystal** (Acetic acid, Ethylene glycol, Urea, Citric Acid, Oxalic acid etc) are known
- ✓ Biopharmaceutics Classification System (**BCS**) **class: II**
- ✓ Form-I suffers from **industrial process feasibility** aspect
- ✓ Co-former **screening**, Phosphoric acid **selected**:
  - -- Biopharmaceutical acceptable excipient
  - -- Processeability
  - -- Stability

Decreasing Solubility

Acetic acid Solvate
($P2_1/c$, $Z'=1$
Mp: 76° C)

Form III
($Pna2_1$, $Z'=1$
Mp: 100.4° C)

Form I
($Pca2_1$, $Z'=2$
Mp: 99.1° C)

Form II
($P2_1/c$, $Z'=2$
Mp: 109.3° C)

References: EP 2743 255 A1; Cryst. Growth & Des: 2011, **11**, 466; Cryst. Growth & Des: 2012, **12**, 2226; and AJPS: 2013, **8**, 181

Problem Statement: *Solid-State Impurity*

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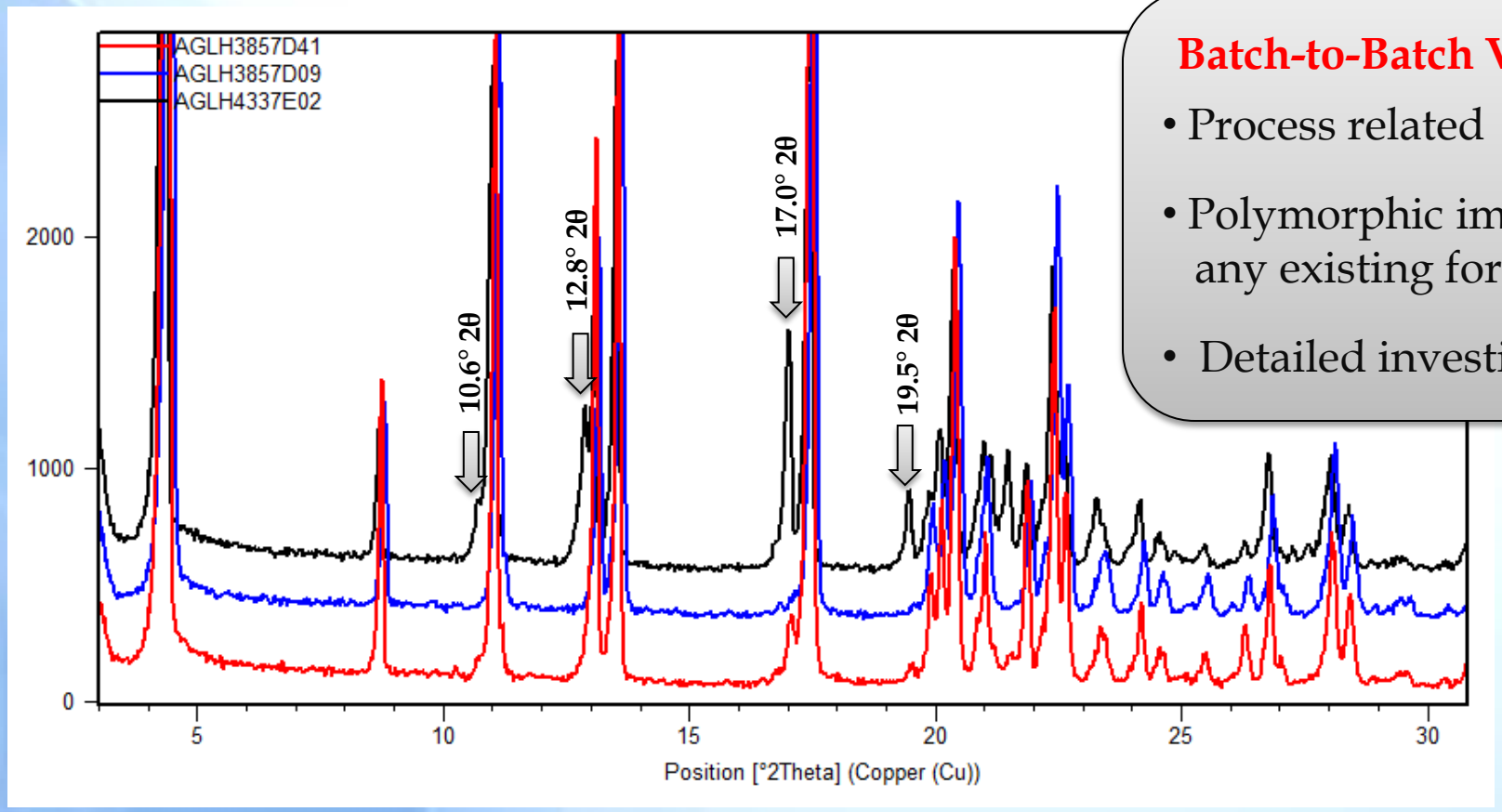
Preparation Process

Dissolving Agomelatine in a solvent like EtOAc → **Adding H_3PO_4 to the solution in step** → Isolating and drying the product



Batch-to-Batch Variation

- Process related
- Polymorphic impurity; any existing forms.
- Detailed investigation

Indexing of P-XRD Data

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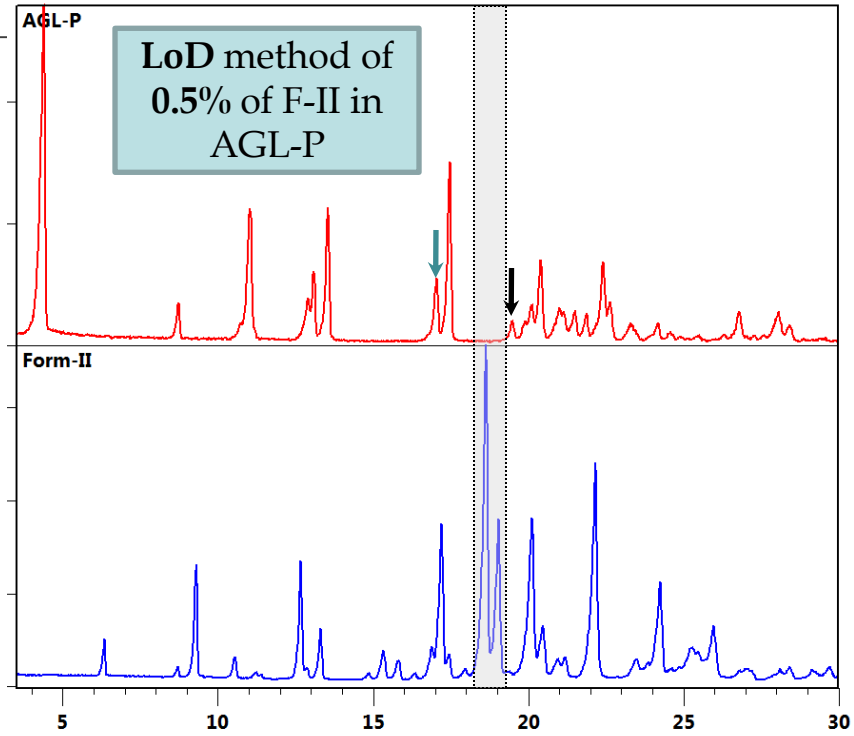
AGL:P- 1:1	
Crystal System: Monoclinic	
Space Group: $P2_1/C$	
R_{wp}: 22.25%	
a (Å)	22.150(2)
b (Å)	4.708(9)
c (Å)	17.502(3)
β (°)	112.296(6)
V(Å^3)	1584.65

: Experimental
: Simulated
: Difference
: Observed Reflection



LoD method of **0.5%** of F-II in AGL-P

✓Indexing is possible with (1:1) AGL:H_3PO_4 molecular complex.

✓ Extra peaks from-II is coincident, missing of main characteristic peaks like 18.6° 2θ.

✓ Possibility of new crystalline phase.

Thermal Studies: *DSC,TGA and Hot stage Microscopy*

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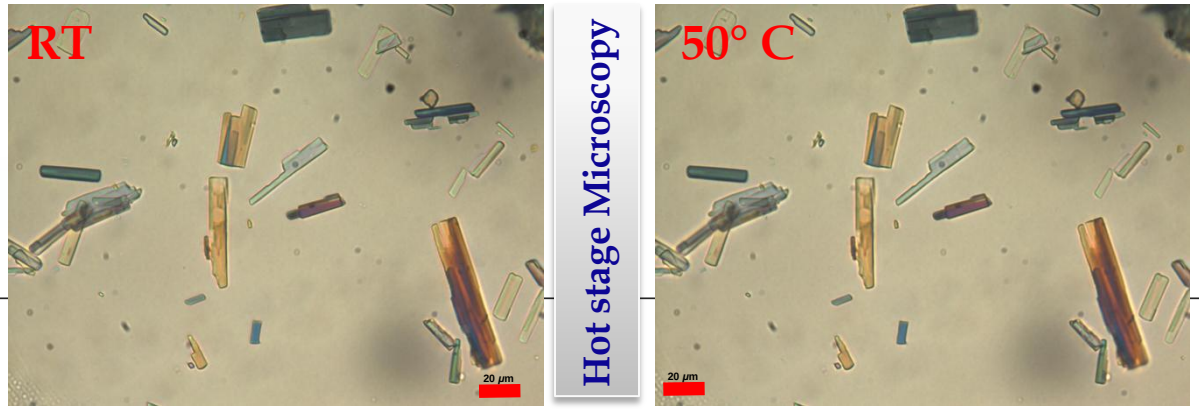

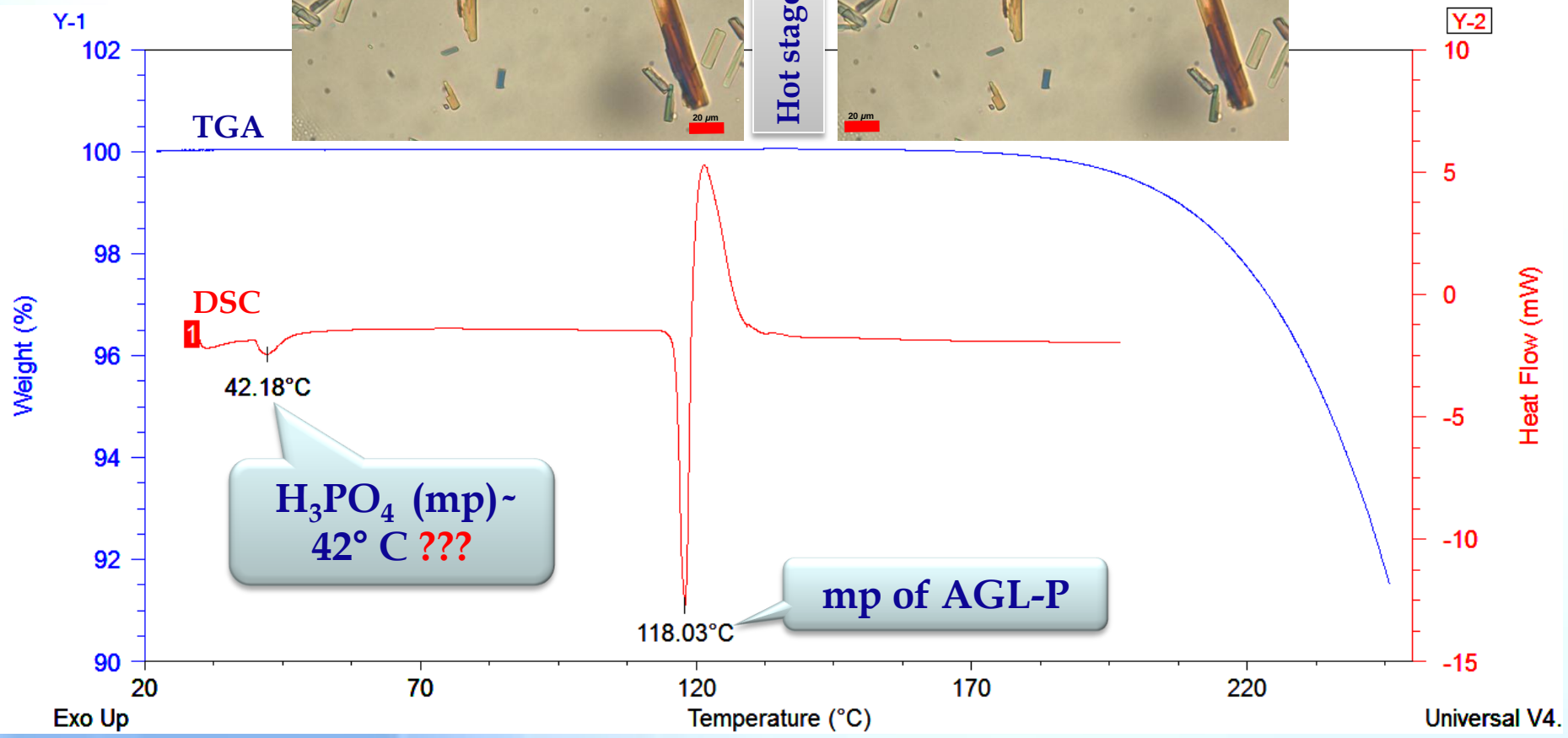

✓ **Solid-solid phase transition** (≈42° C), supported by hot stage microscopy; no change in morphology.

✓ AGL-P mp (118.0°) C is higher than AGL form-II (109.3° C).

Variable Temperature PXRD Studies

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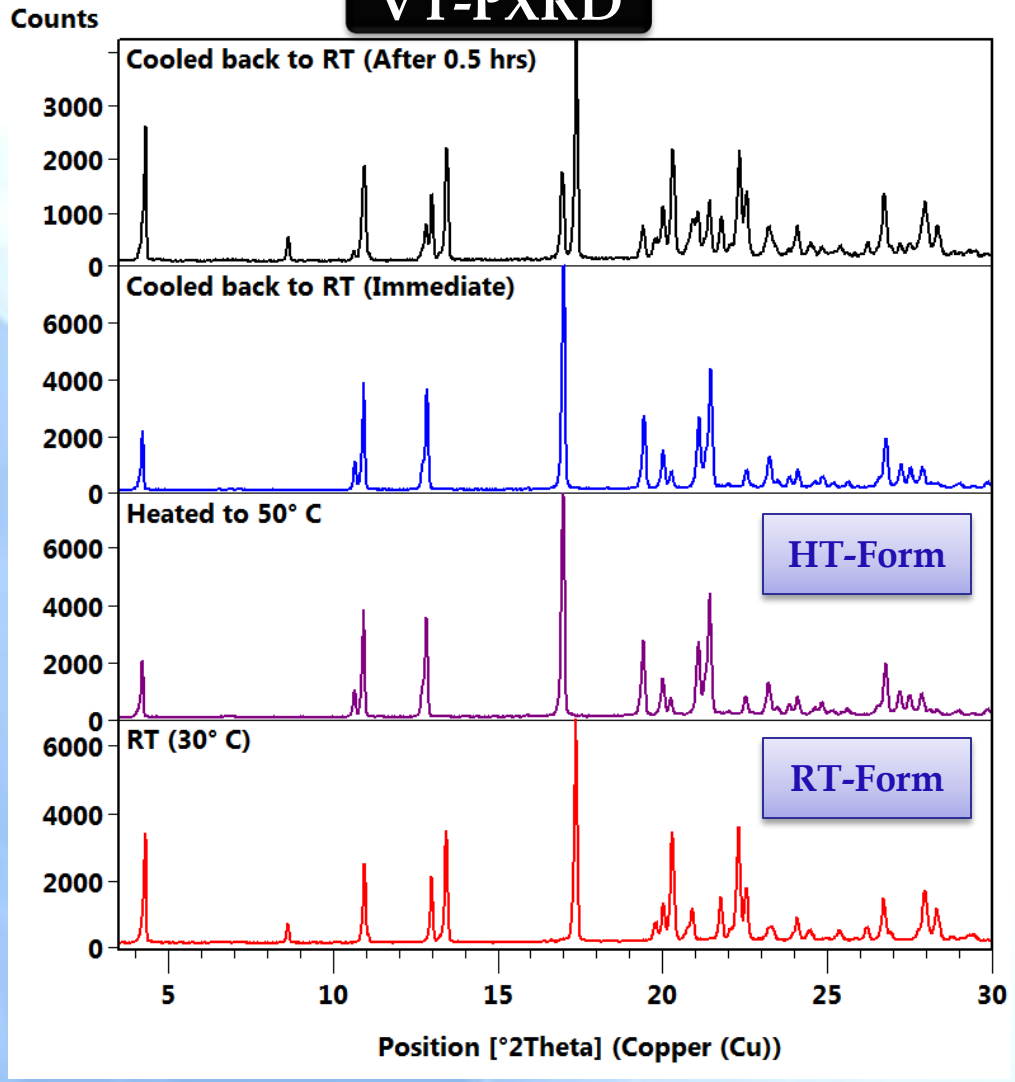
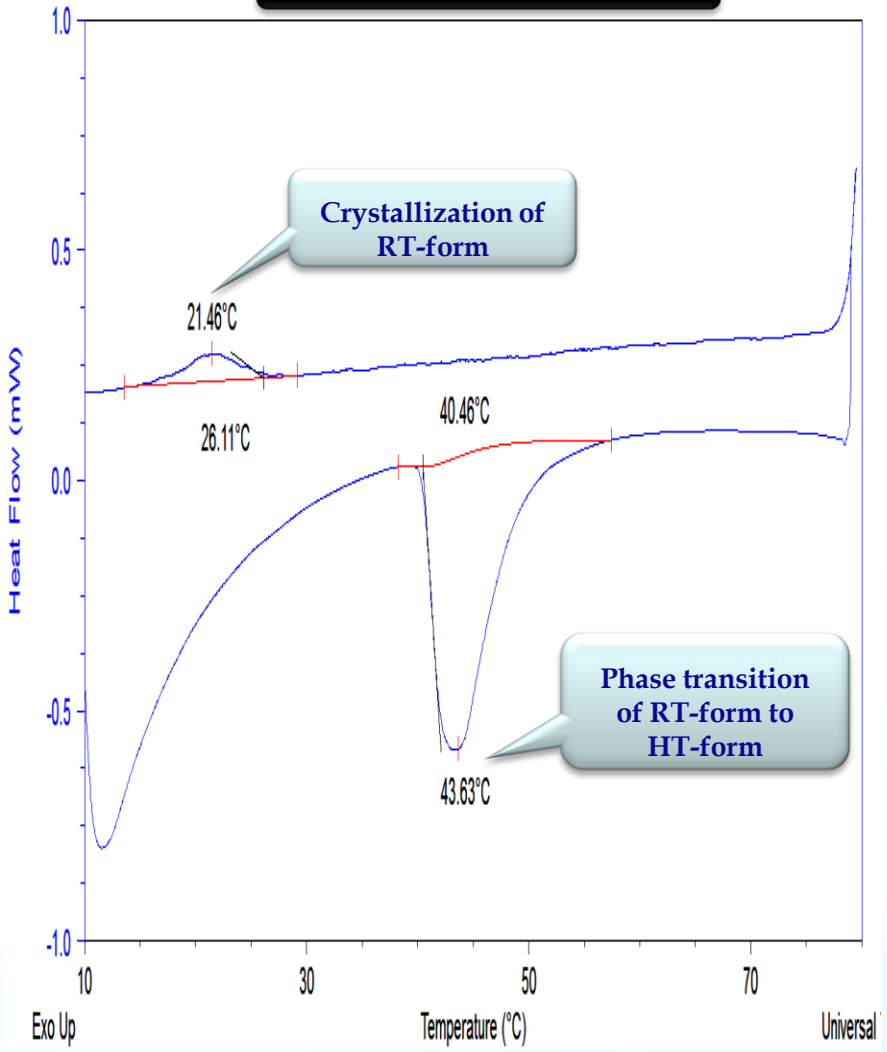
VT-PXRD



Heat-Cool-DSC



✓ Solid-solid phase transition leads to **new polymorph** (HT-Form). They are **enantiotropic** in nature; crystallization of RT-form happens at ≈22° C.

Kinetic Studies by *DSC: Non-isothermal*

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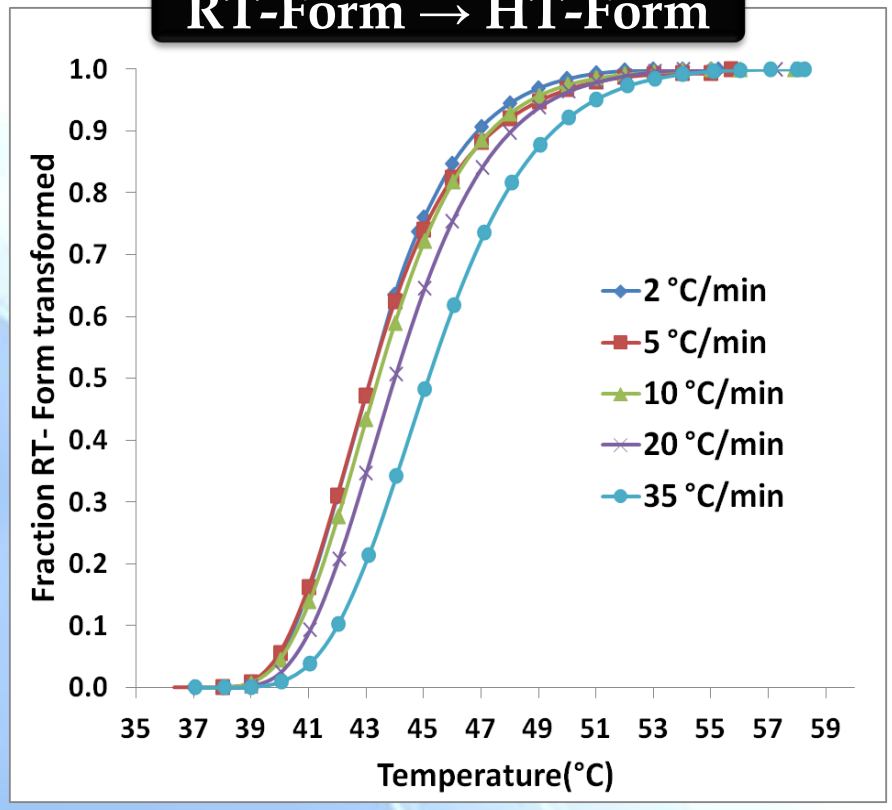
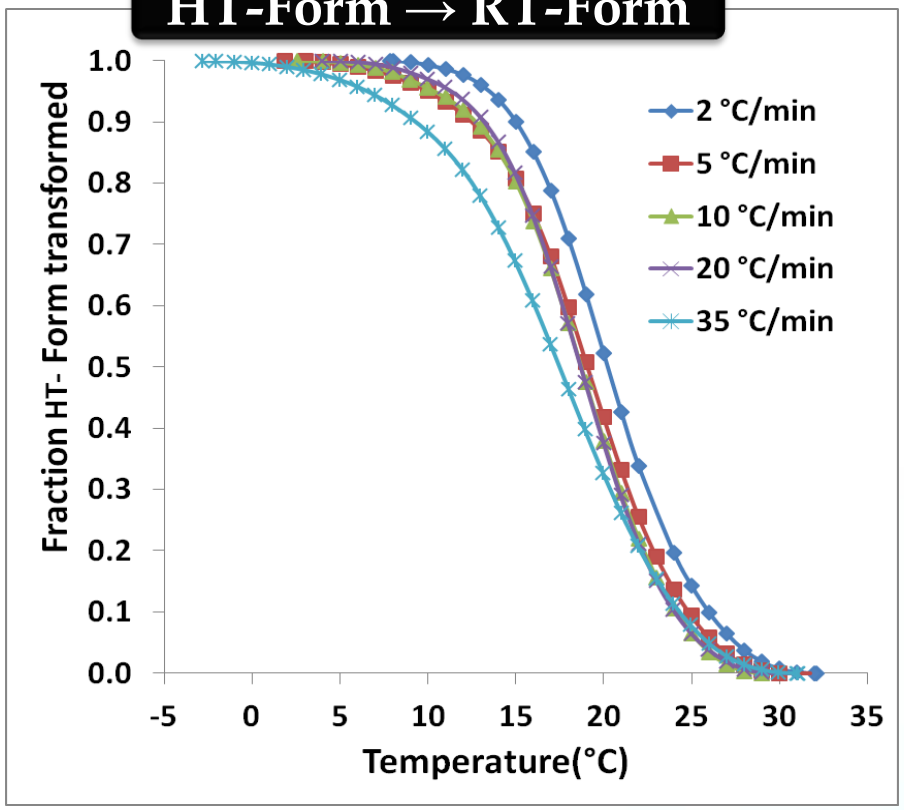
RT-Form → HT-Form



HT-Form → RT-Form



Model	RT-Form → HT-Form		HT-Form → RT-Form	
	Activation Energy (KJ/Mole)	Average	Activation Energy (KJ/Mole)	Average
Kissnger	-41.0	**-43.6**	-36.2	**-33.8**
Augies	-43.6		-33.8	
FWO	-46.2		-31.4	

References: Pharm Dev Technol, 2014
DOI: 10.3109/10837450.2014.962824

Crystal Determination From Powder X-Ray Diffraction

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Indexing
- Unit Cell Parameters Determination
- Space Group Search
- Refinement

Structure Solution
- Model Selection
- Solution (Simulating Annealing)

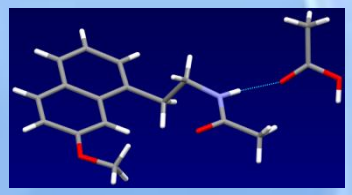
Structure Refinement
- Rietveld Refinement
- Analysis of Crystal Structure in terms of Hydrogen Bonding Interaction
- Fine Tune the Structure
- Refinement

Appropriate **Model Selection** is the key part of successful structure determination for multi-components crystal

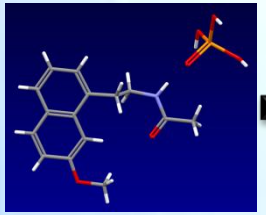
MATERIALS STUDIO | Reflex

Reflex

Polymorph Prediction



AGL-Acetic Acid
(Available Crystal Structure)



AGL-P
(Model)

- Crystal Structure Prediction with indexed Space group
- Model selection on the basis of cell dimension and H-bonding interaction profile

Structure Solution with the selected model

Data Collection Strategies

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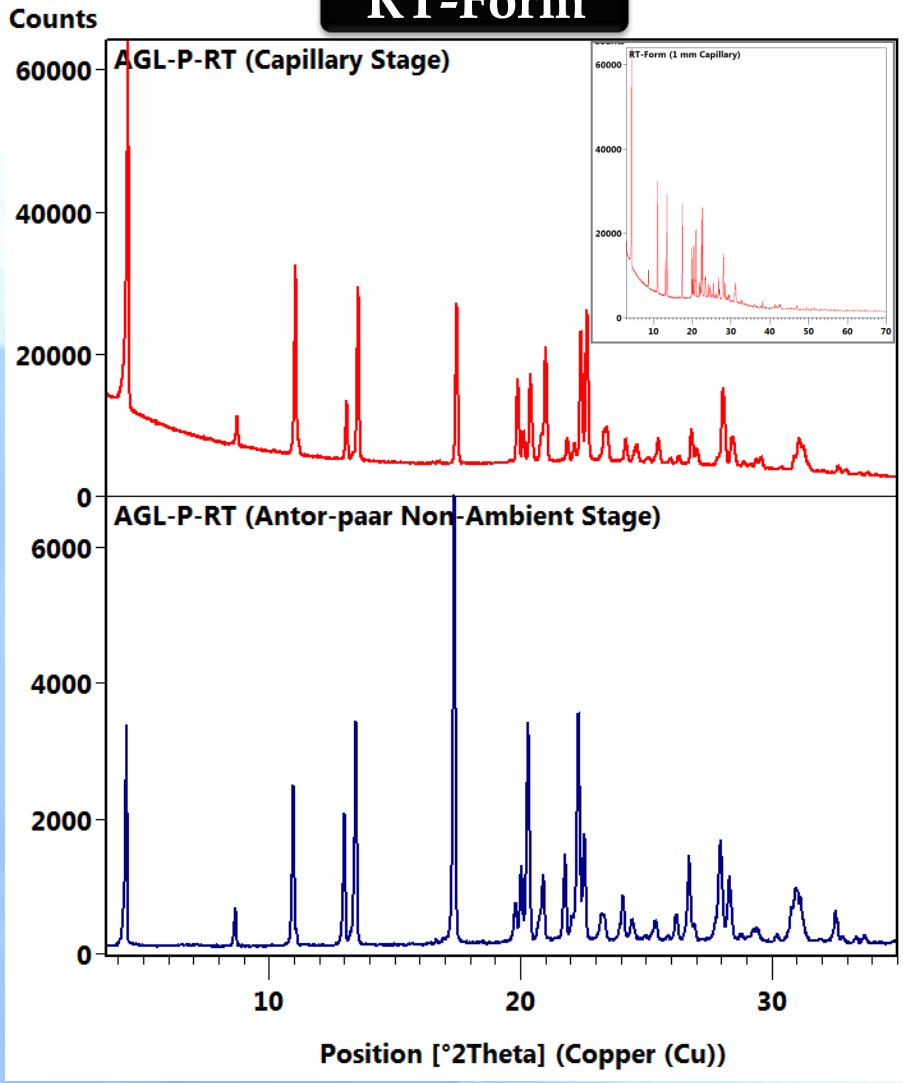
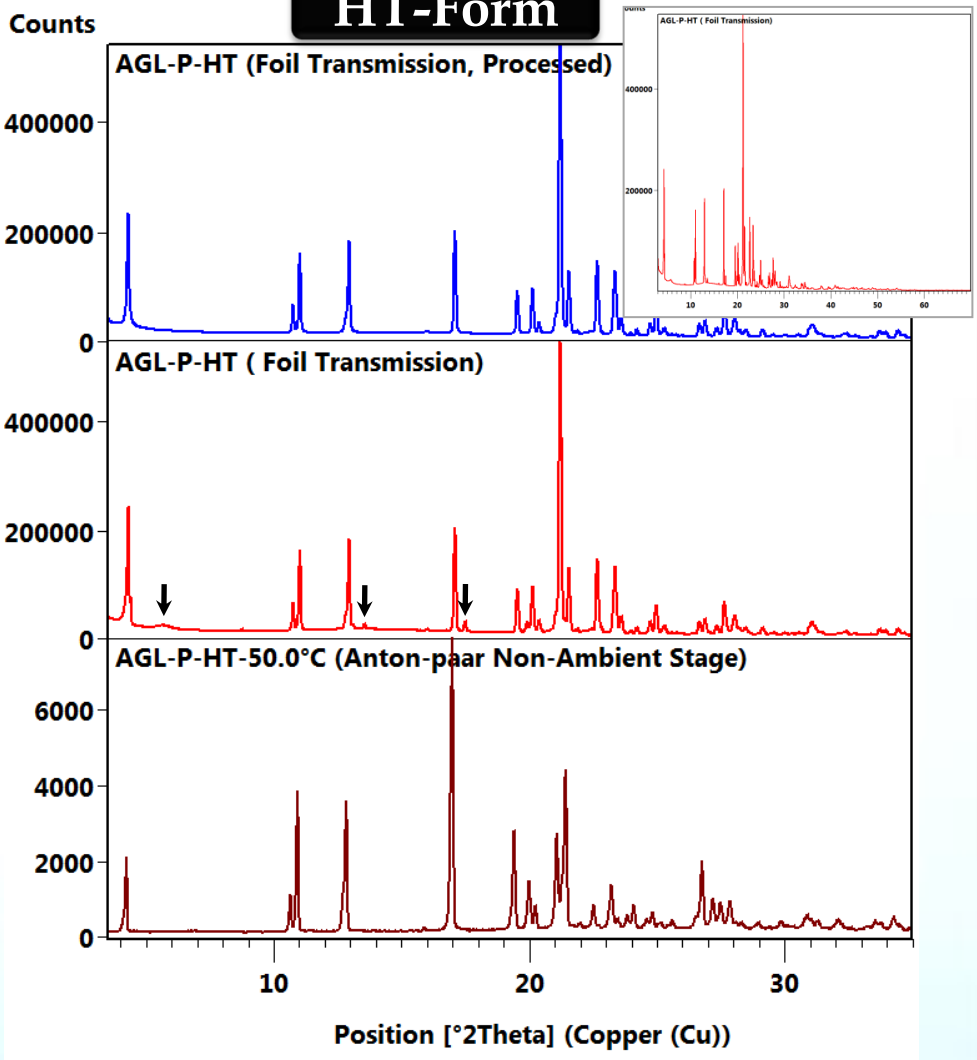
RT-Form



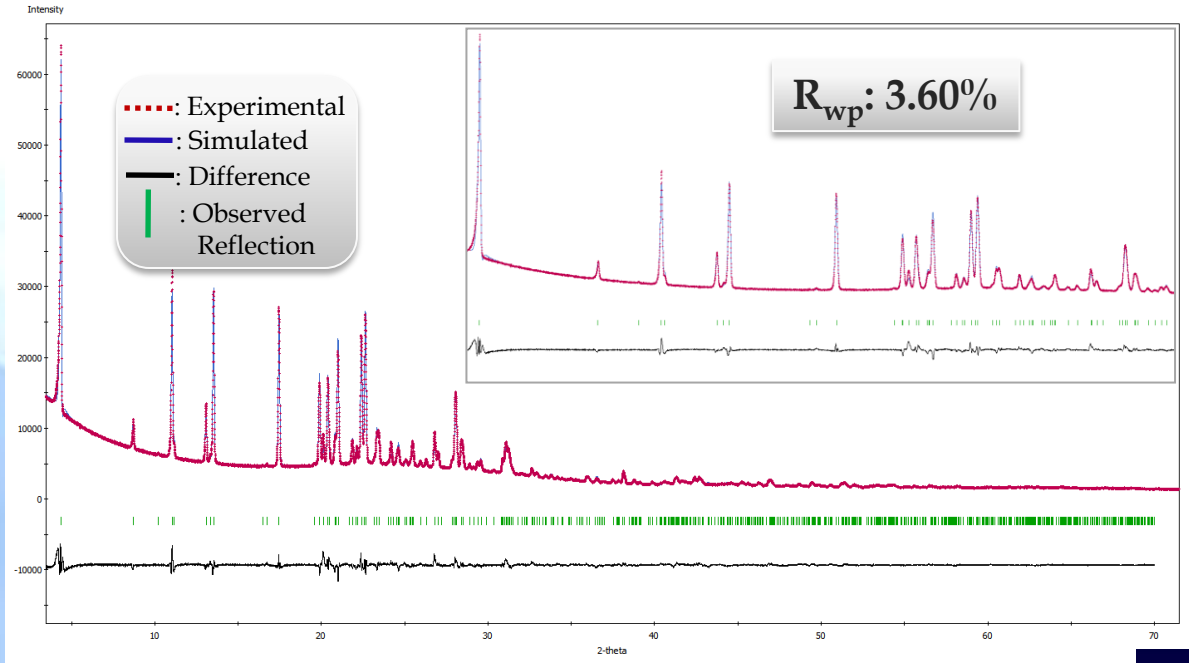
HT-Form



✓Antor-paar Non-Ambient stage data **were not suitable** for Structure Determination, due to **extensive preferred orientation**.

✓ Data collection for meta-stable HT-Form in transmission mode is challenging. RT-Form is converted to HT-Form externally and data is collected in **foil-transmission mode**. Still, few peaks of RT-Form observed; excluded for structure determination.

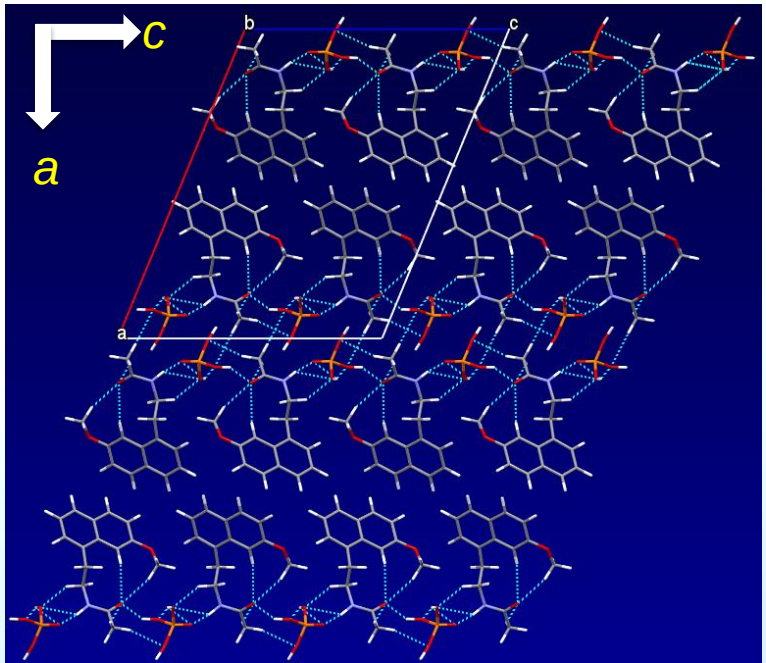
Crystal Structure of RT-Form



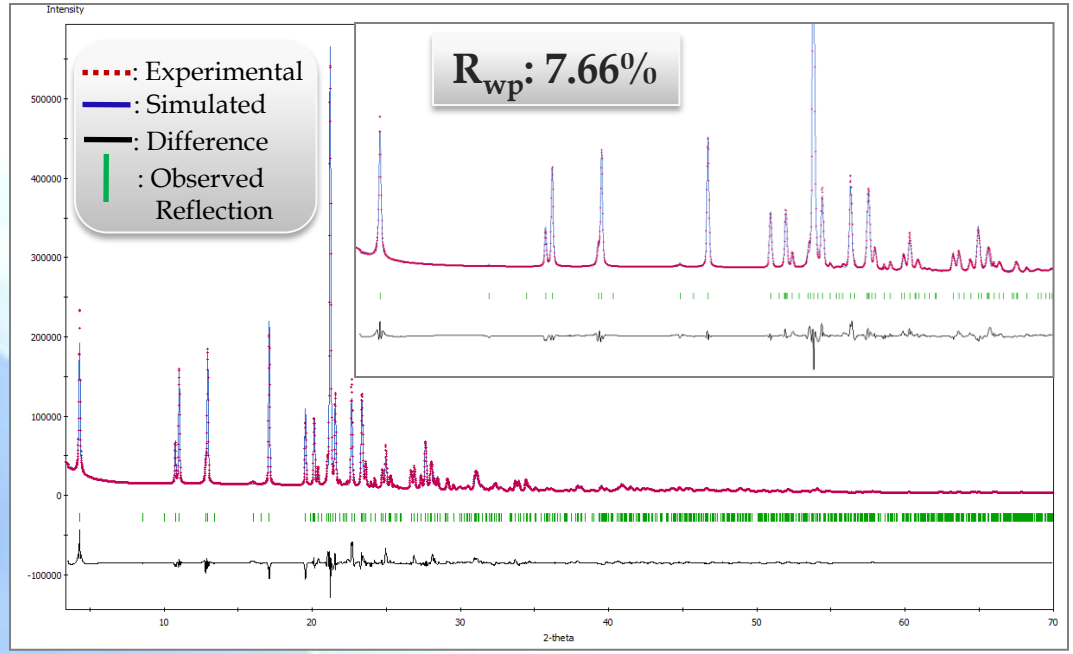
Crystallographic Data

Empirical Formula	$C_{15}H_{17}NO_2.H_3PO_4$
Crystal System	Monoclinic
Space Group	$P2_1/c$
a (Å)	21.724(4)
b (Å)	4.599(1)
c (Å)	17.173(3)
β (°)	112.368(1)
V (Å^3)	1584.65
Z, Z′	4, 1
Dc (g/cm^3)	1.431

- ✓ Good fitting of final Rietveld refinement plot.
- ✓ (1:1) AGL-P molecular complex.
- ✓ Crystal packing: segregation of aromatic part and hydrophlic phosphoric part.
- ✓ AGL and PA forming 1-D chain running along c axis.



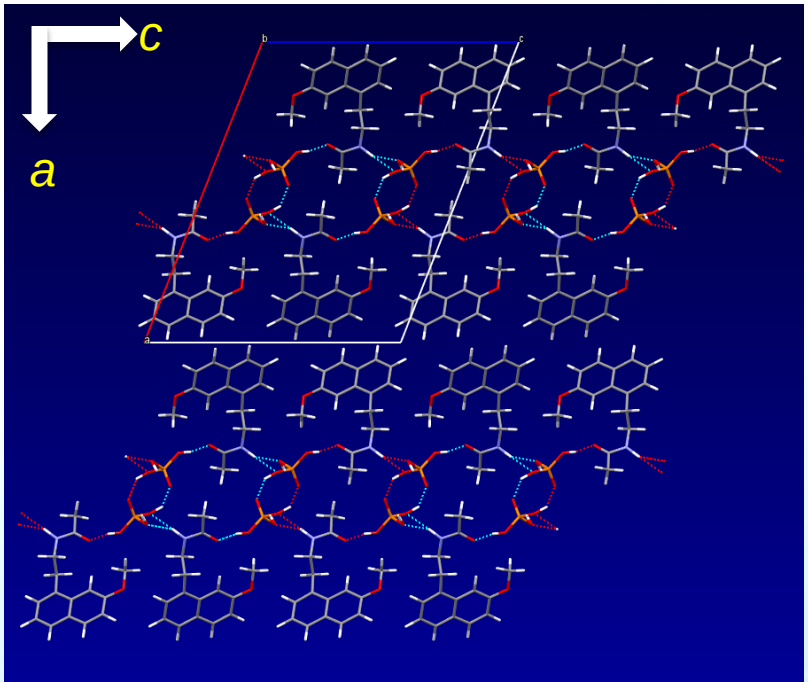
Crystal Structure of HT-Form



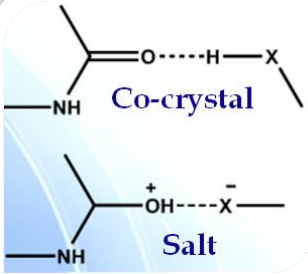
Crystallographic Data

Empirical Formula	$C_{15}H_{17}NO_2.H_3PO_4$
Crystal System	Monoclinic
Space Group	$P2_1/c$
a (Å)	22.413(1)
b (Å)	4.598(2)
c (Å)	17.797(9)
β (°)	111.468(2)
V (Å^3)	1706.99
Z, Z′	4, 1
Dc (g/cm^3)	1.328

- ✓ Good fitting of final Rietveld refinement plot.
- ✓ (1:1) AGL-P molecular complex.
- ✓ Crystal packing: segregation of aromatic part and hydrophlic phosphoric part.
- ✓ PA forming a dimer that connected with AGLand forming 1-D chain, running along c axis.



Crystal Structure Analysis



CrystalEngComm 2013,15, 8941

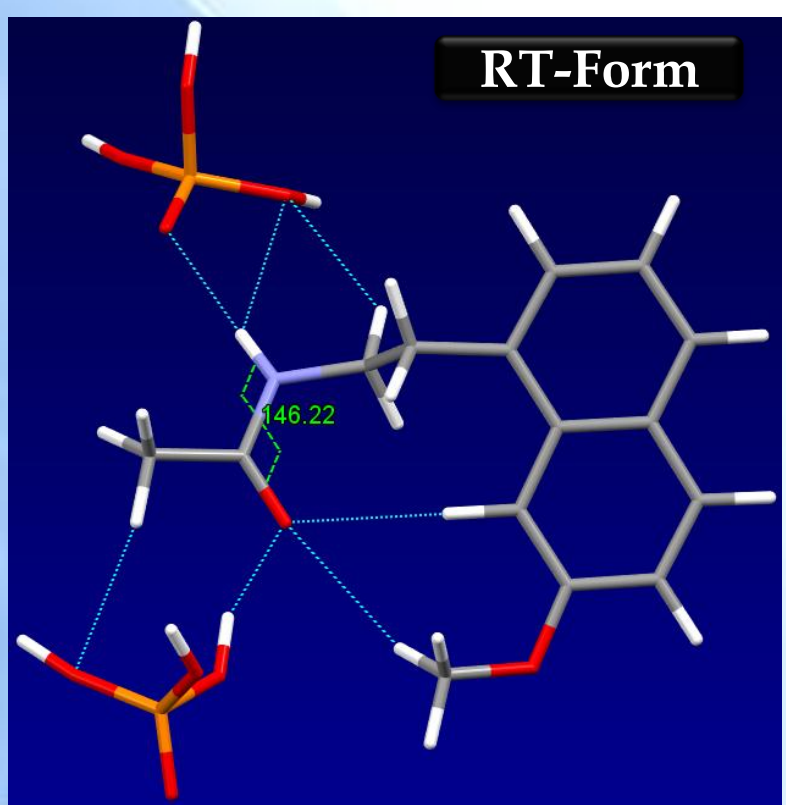
Possibility of salt formation of AGL-PA **is low**

-- as being with **weakly ionizable** amide functionality

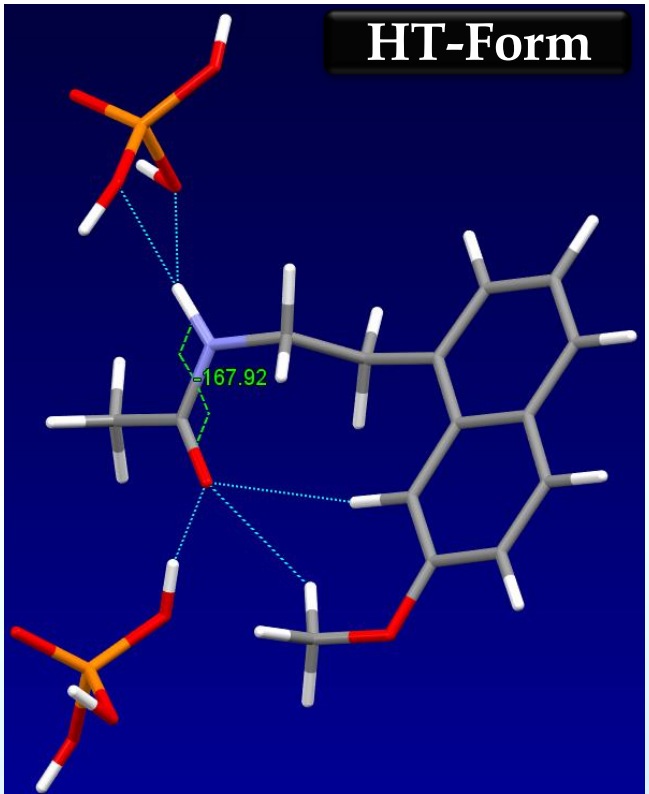
-- with pka difference is also ≤ 1

-- Strong H-Bond length ≤2.55Å can be used as salt/co-crystal criteria

Hydrogen bond Matrices	Bond Length (Å), Angle (°)	
	RT-Form	HT-Form
C=O….(H)O-P	**2.56, 144**	**2.46, 167**
P=O….(H)O-P	2.52, **145**	2.4, 141
C-N(H)….O(H)-P	3.11, 130	3.24,145/ 3.07,142
C-N(H)…. O=P	2.88, 139	-
P-O….(H)O-P	**2.73, 154**	2.44,125



The common H-N-C=O torsion angle of AGL is in the range of 162-180°



Summary and Conclusions

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✓ Crystal Structure Determination confirms

-- Both the molecular complexes of (1:1) molecular complexes of AGL-P are **co-crystal**, showing enantiotropic **polymorphism**.

✓ Correlation between kinetics and molecular level structural understanding reveals

-- **Conformational switching** is the triggering factor of solid-solid phase transformation.

-- At ambient temperature half life of **RT-form is more than HT-form**.

✓ The proposed **protocol of model selection** with help of Polymorph prediction could simplify the co-crystal structure determination from PXRD data.

✓ AGL-P co-crystal is a "pharmaceutical co-crystal" and **the best** alternative of AGL Form-II is terms of enhance processability as well as stability with comparable solubility.

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Thanks....