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**

- 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

Problem Statement: Solid-State Impurity

Preparation Process:

Dissolving Agomelatine in a solvent like EtOAc → Adding $\text{H}_3\text{PO}_4$ to the solution in step → Isolating and drying the product

Batch-to-Batch Variation:
- Process related
- Polymorphic impurity; any existing forms.
- Detailed investigation

Graph showing peak positions at $10.6^\circ$, $12.8^\circ$, $17.0^\circ$, and $19.5^\circ$. The graph compares different batches (AGLH3857D41, AGLH3857D09, AGLH4337E02).
Indexing of P-XRD Data

- 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.

**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(Å³): 1584.65

**LoD method of 0.5% of F-II in AGL-P**
Thermal Studies: DSC, TGA and Hot stage Microscopy

Solid-solid phase transition ($\approx 42^\circ$ C), supported by hot stage microscopy; no change in morphology.

- AGL-P mp (118.0$^\circ$ C) is higher than AGL form-II (109.3$^\circ$ C).
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 \textit{DSC: Non-isothermal}

**RT-Form → HT-Form**

<table>
<thead>
<tr>
<th>Model</th>
<th>Activation Energy (KJ/Mole)</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kissneger</td>
<td>-41.0</td>
<td>-43.6</td>
</tr>
<tr>
<td>Augies</td>
<td>-43.6</td>
<td></td>
</tr>
<tr>
<td>FWO</td>
<td>-46.2</td>
<td></td>
</tr>
</tbody>
</table>

**HT-Form → RT-Form**

<table>
<thead>
<tr>
<th>Activation Energy (KJ/Mole)</th>
<th>Average</th>
</tr>
</thead>
<tbody>
<tr>
<td>-36.2</td>
<td></td>
</tr>
<tr>
<td>-33.8</td>
<td>-33.8</td>
</tr>
</tbody>
</table>

References: Pharm Dev Technol, 2014
DOI: 10.3109/10887580.2014.982824
Crystal Determination From Powder X-Ray Diffraction

- **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**

**Multimodal Prediction**

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

**MATERIALS STUDIO | Reflex**

- Reflex
- Polymorph Prediction

**Sample Structures**

- AGL-Acetic Acid (Available Crystal Structure)
- AGL-P (Model)

**Structure Solution with the selected model**
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**

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Empirical Formula</td>
<td>C_{15}H_{17}NO_{2}.H_{3}PO_{4}</td>
</tr>
<tr>
<td>Crystal System</td>
<td>Monoclinic</td>
</tr>
<tr>
<td>Space Group</td>
<td>P2_1/c</td>
</tr>
<tr>
<td>a (Å)</td>
<td>21.724(4)</td>
</tr>
<tr>
<td>b (Å)</td>
<td>4.599(1)</td>
</tr>
<tr>
<td>c (Å)</td>
<td>17.173(3)</td>
</tr>
<tr>
<td>β (°)</td>
<td>112.368(1)</td>
</tr>
<tr>
<td>V (Å³)</td>
<td>1584.65</td>
</tr>
<tr>
<td>Z, Z'</td>
<td>4, 1</td>
</tr>
<tr>
<td>Dc (g/cm³)</td>
<td>1.431</td>
</tr>
</tbody>
</table>

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

Good fitting of final Rietveld refinement plot.

(1:1) AGL-P molecular complex.

Crystal packing: segregation of aromatic part and hydrophobic phosphoric part.

PA forming a dimer that connected with AGL and forming 1-D chain, running along c axis.
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 ≤ 2.55 Å can be used as salt/co-crystal criteria

<table>
<thead>
<tr>
<th>Hydrogen bond Matrices</th>
<th>Bond Length (Å), Angle (°)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RT-Form</td>
</tr>
<tr>
<td>C=O....(H)O-P</td>
<td>2.56, 144</td>
</tr>
<tr>
<td>P=O....(H)O-P</td>
<td>2.52, 145</td>
</tr>
<tr>
<td>C-N(H)....O(H)-P</td>
<td>3.11, 130</td>
</tr>
<tr>
<td>C-N(H)....O=P</td>
<td>2.88, 139</td>
</tr>
<tr>
<td>P-O....(H)O-P</td>
<td>2.73, 154</td>
</tr>
</tbody>
</table>

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

✓ 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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