

# Crystallization process development of Febuxostat most stable polymorph and of a soluble salt thereof

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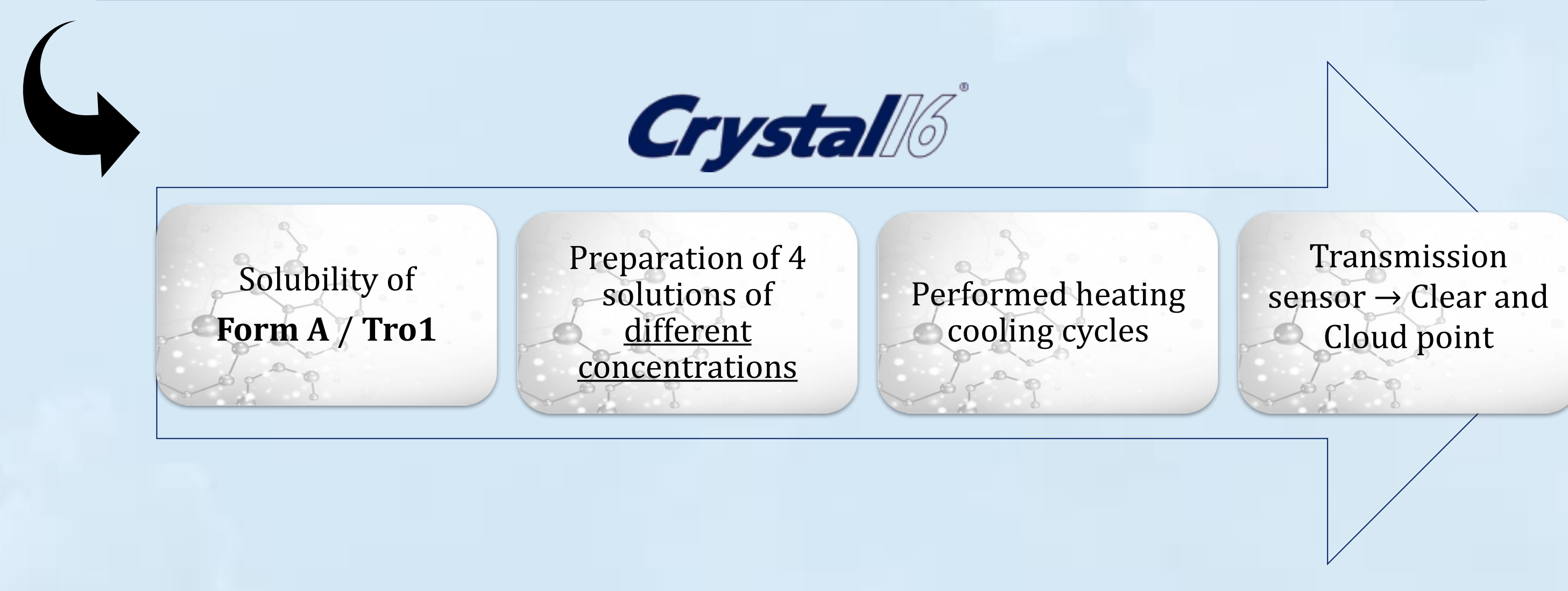
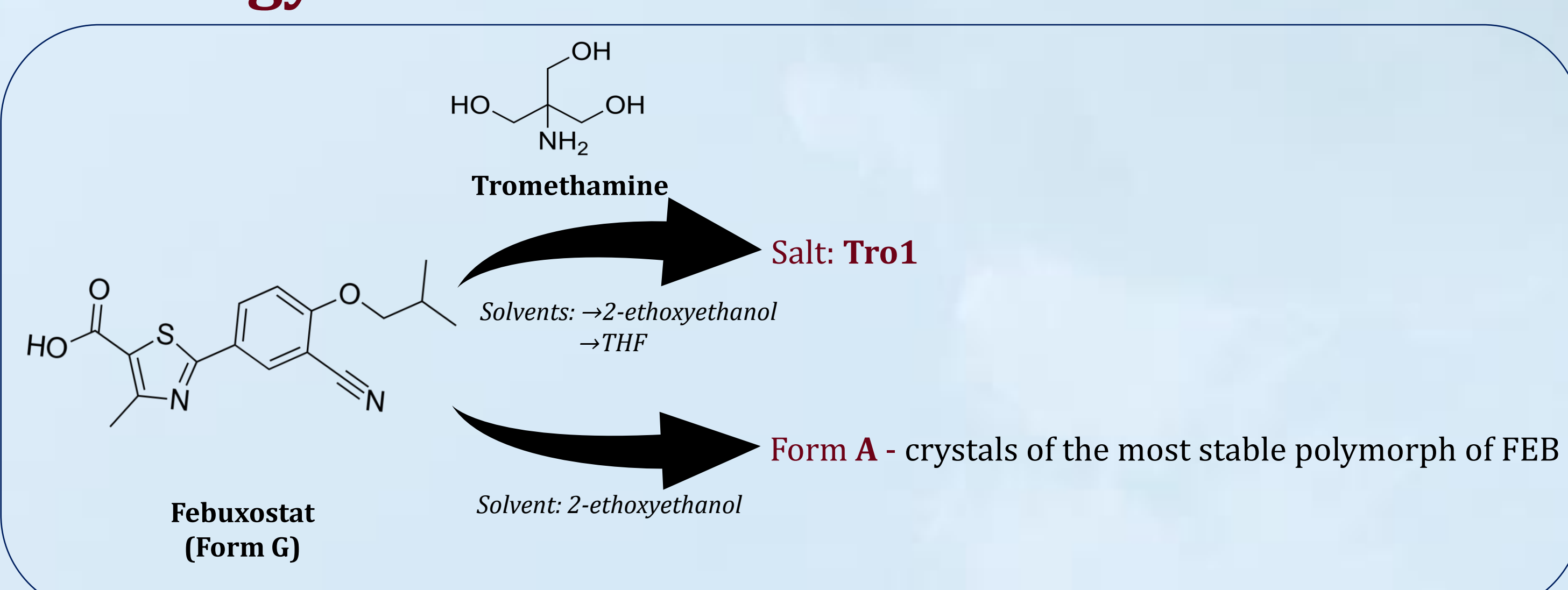
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## Introduction

Febuxostat (FEB) is an active pharmaceutical ingredient (API), poorly water-soluble and therefore poorly bioavailable. FEB is used for the treatment of hyperuricemia in gout, as inhibitor of xanthine oxidase, to reduce uric acid production. With the aim of improving the aqueous solubility, we investigated the crystallization process of the FEB tromethamine salt (Tro1). In addition, we were able to grow crystals of the most stable polymorph of FEB, designated as form A in the literature. The crystallization process development of the Tro1 and form A was performed in a controlled manner using the Crystal16™.

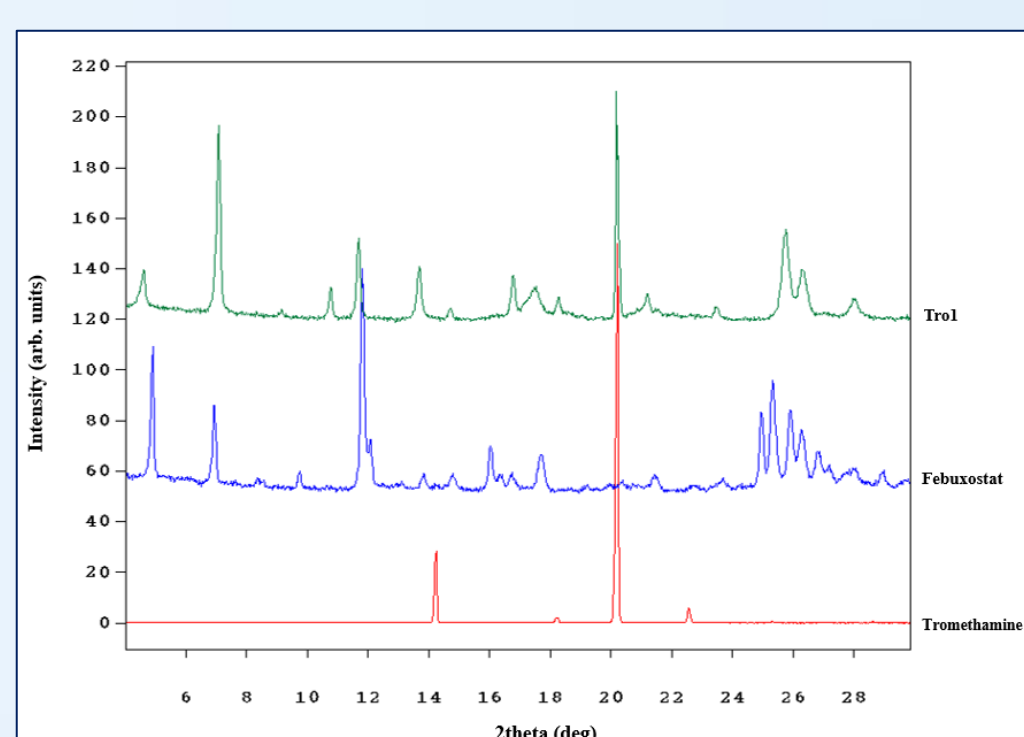
The crystallization process parameters were established by determining the Meta-stable Zone Width (MSZW) while performing two thermal cycles in a suitable solvent system (2-ethoxyethanol) using a broad temperature range (5 - 90°C) and different concentrations. The formation of Tro1 and form A was evidenced by X-ray powder diffraction. We can conclude that Tro1 can be reliably crystallized in 2-ethoxyethanol by using high starting concentrations (> 200 mg/mL). Furthermore, crystals of form A were successfully grown in the same solvent at concentrations above 100 mg/mL. Crystal structure determination of form A will be attempted in a future work.

## Strategy

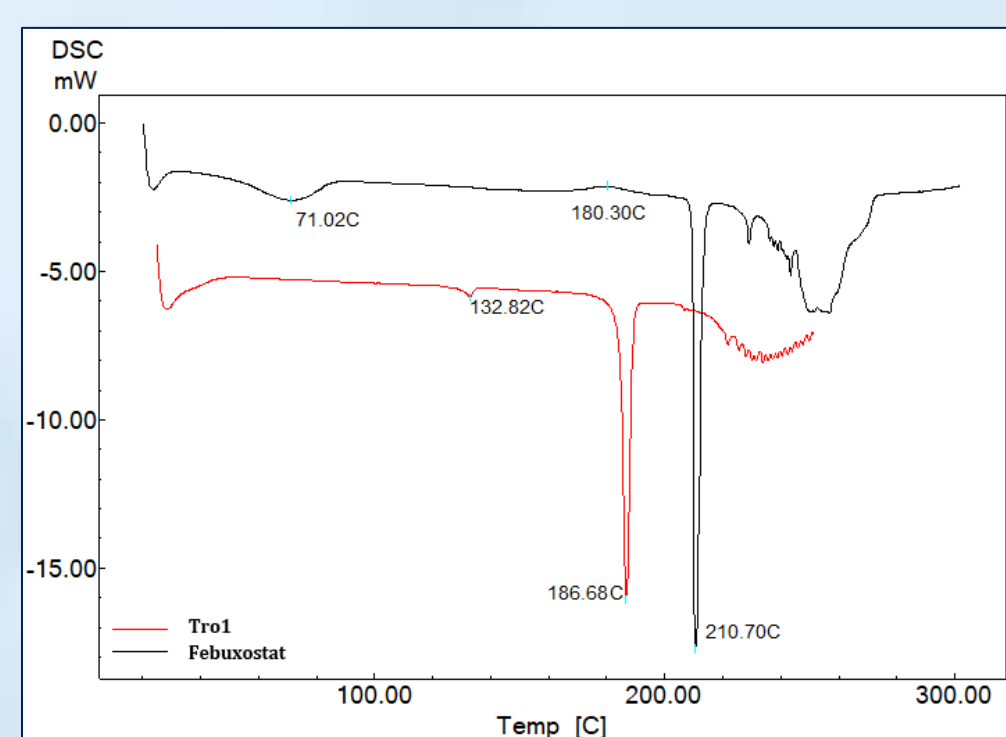


## Characterization

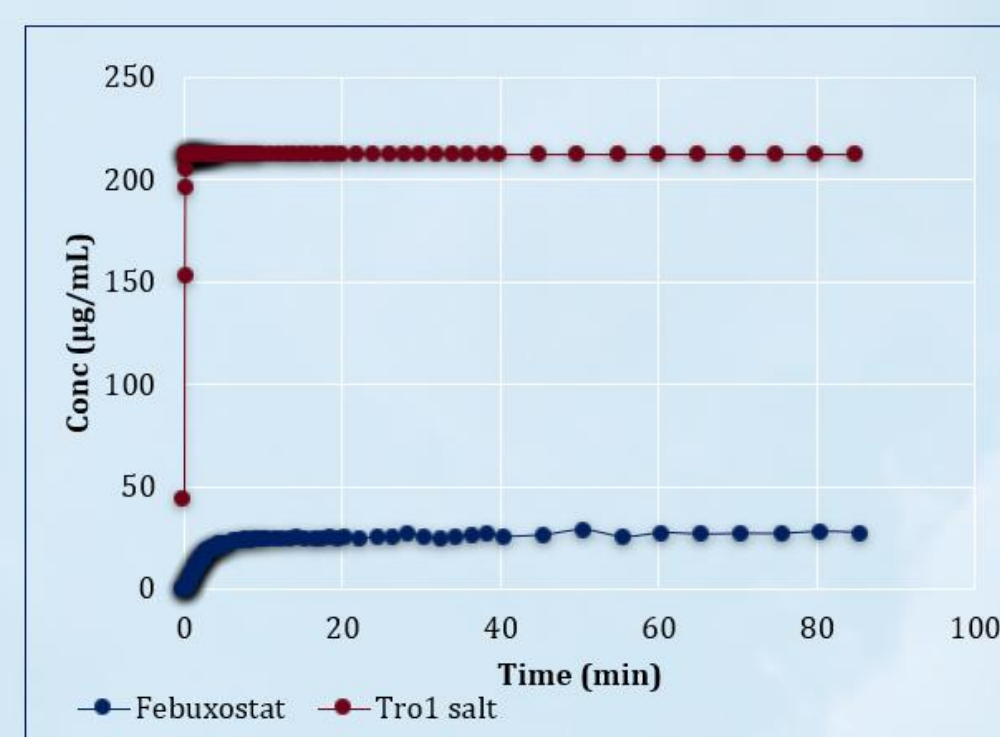
### 1. Tro1



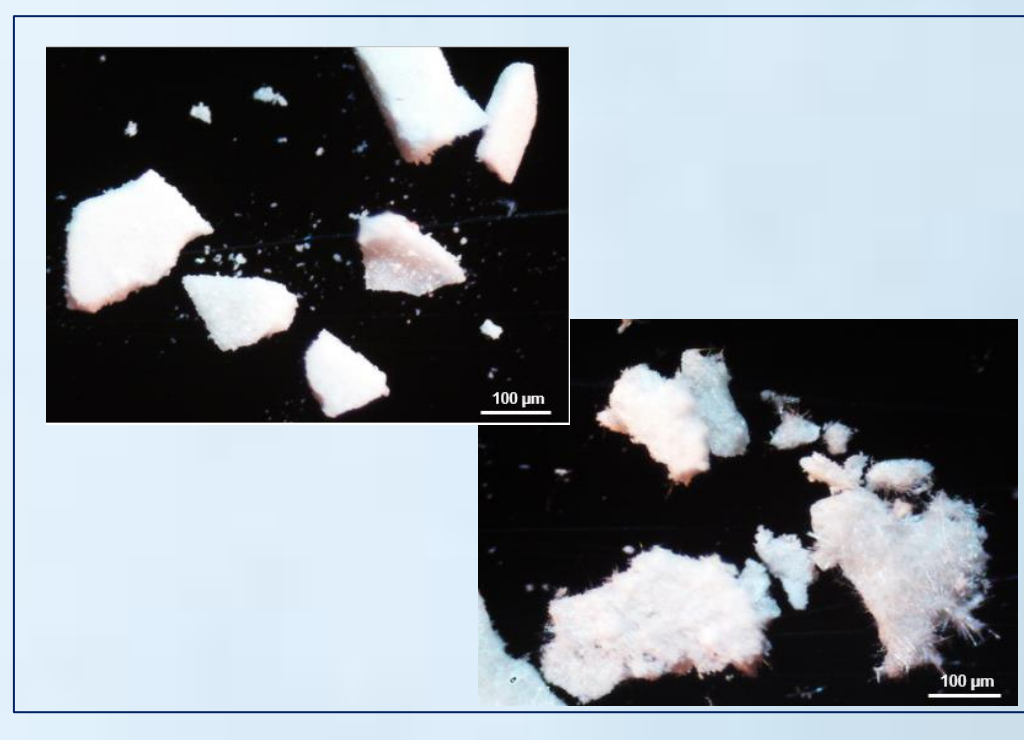
XRPD pattern of Tro1 compared to the starting material (FEB) and Tromethamine



DSC trace of Tro1 compared to the starting material (FEB)



The dissolution curves of the Tro1 salt and the starting material (FEB) in water



Microscope images of Tro1

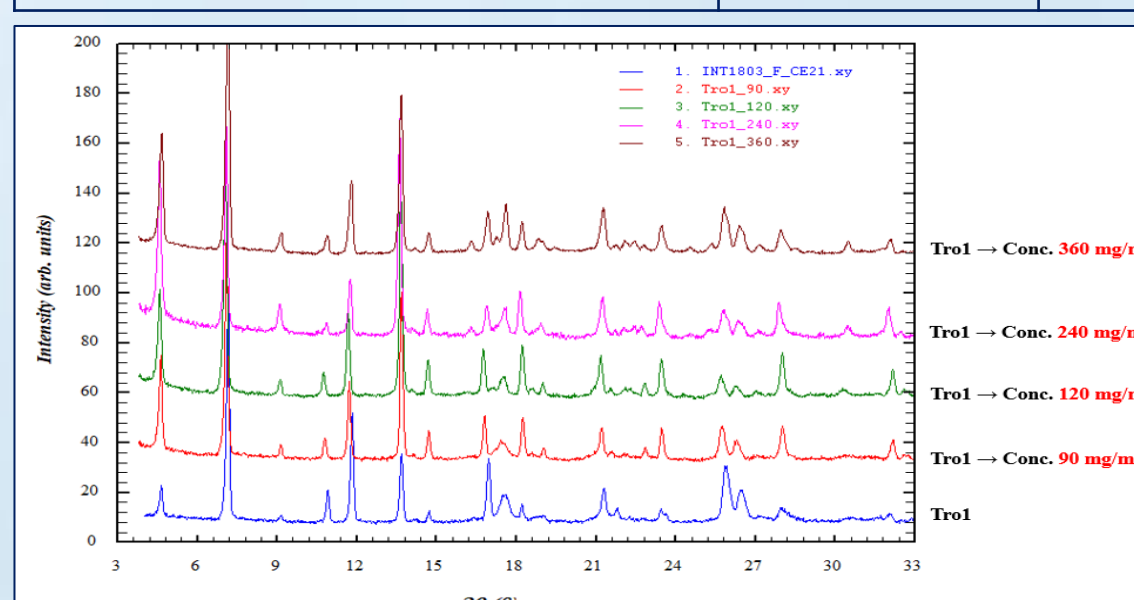
|                                    |  |
|------------------------------------|--|
| <b>Starting material</b>           | Febuxostat (Form G)                      |
| <b>Counter-ion</b>                 | Tromethamine                             |
| <b>Ratio (FEB:Tro)</b>             | 1:1                                      |
| <b>Experiment</b>                  | ✓ grinding<br>✓ slow cooling-evaporative |
| <b>Solvents</b>                    | 2-ethoxyethanol<br>THF                   |
| <b>New salt</b>                    | Tro1                                     |
| <b>Endothermic melting points</b>  | 132.82°C<br>186.68°C                     |
| <b>Solubility in Water</b>         | 212.11 µg/mL                             |
| <b>Stability (40°C and 75% RH)</b> | Stable                                   |



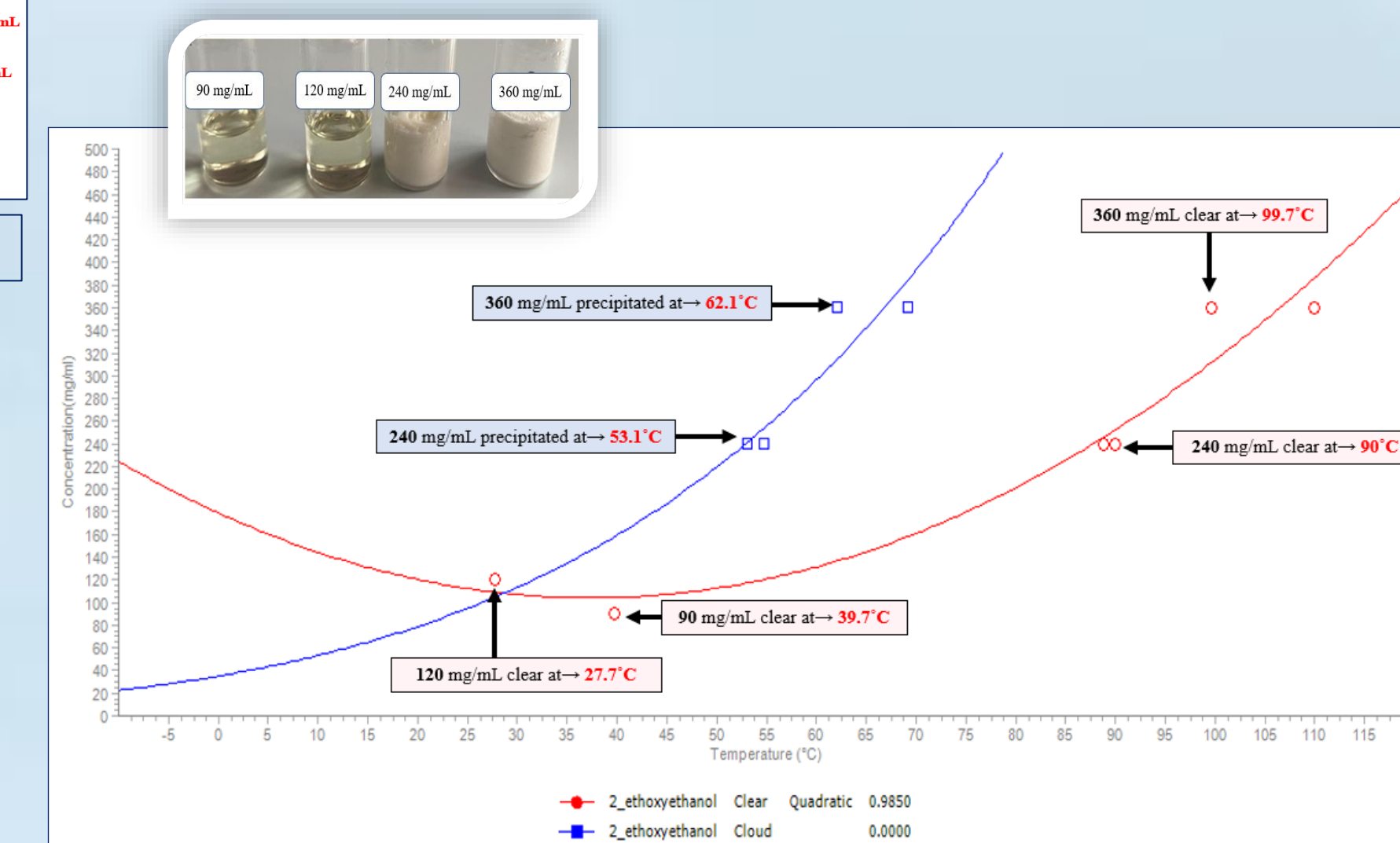
## Crystallization using Crystal16™

### 1. Tro1

| Concentration of FEB (mg/mL) | Ratio Feb:Tro | Solvent         | Observations after analysis at Crystal16™ | Form by XRPD |
|------------------------------|---------------|-----------------|---|--------------|
| 90                           | 1:1           | 2-ethoxyethanol | Clear solution                            | Tro1         |
| 120                          |               |                 | Clear solution                            | Tro1         |
| 240                          |               |                 | Slurry                                    | Tro1         |
| 360                          |               |                 | Slurry                                    | Tro1         |

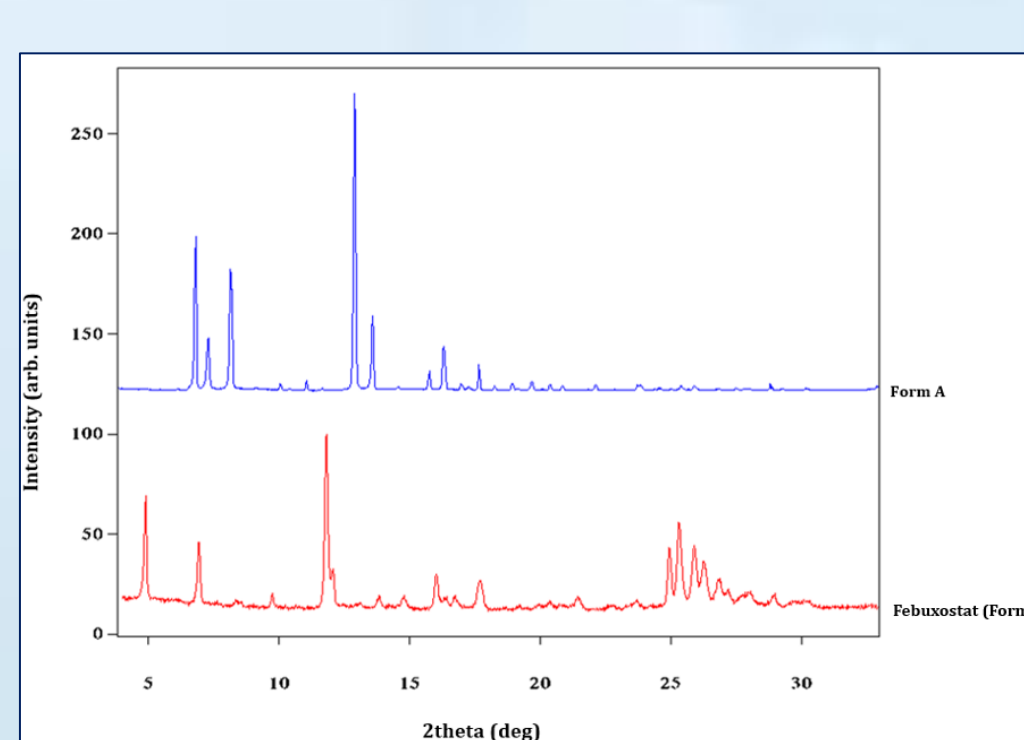


XRPD patterns of Tro1 after Crystal16™

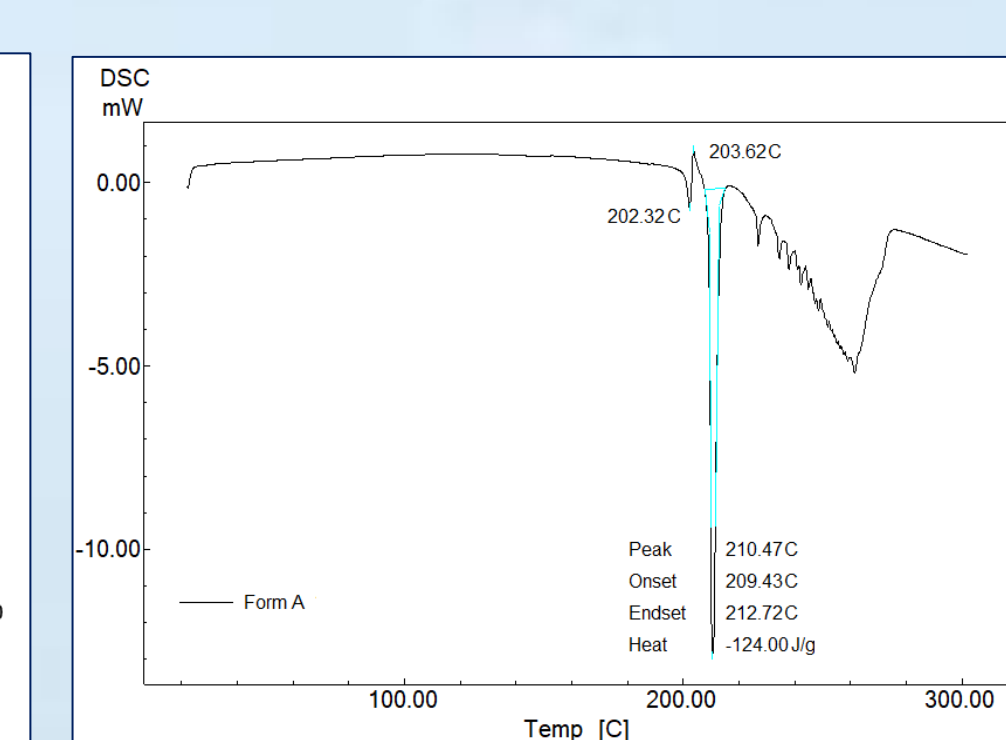


Solubility and Meta-stable Zone Width for Tro1

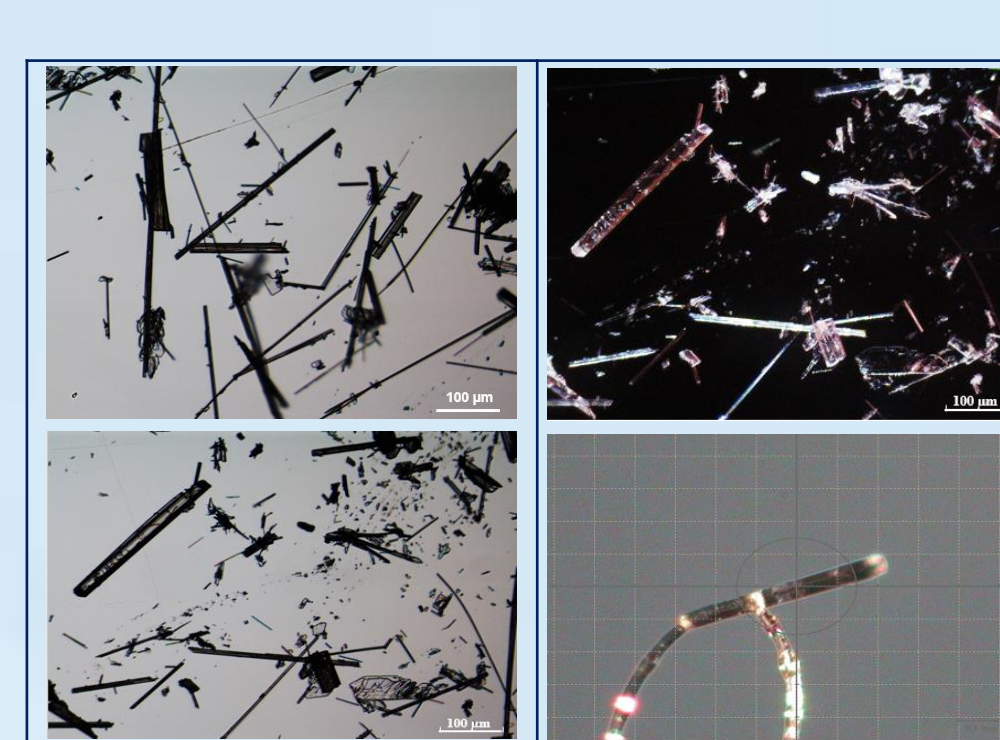
### 2. Febuxostat - Form A



XRPD pattern of form A compared to form G

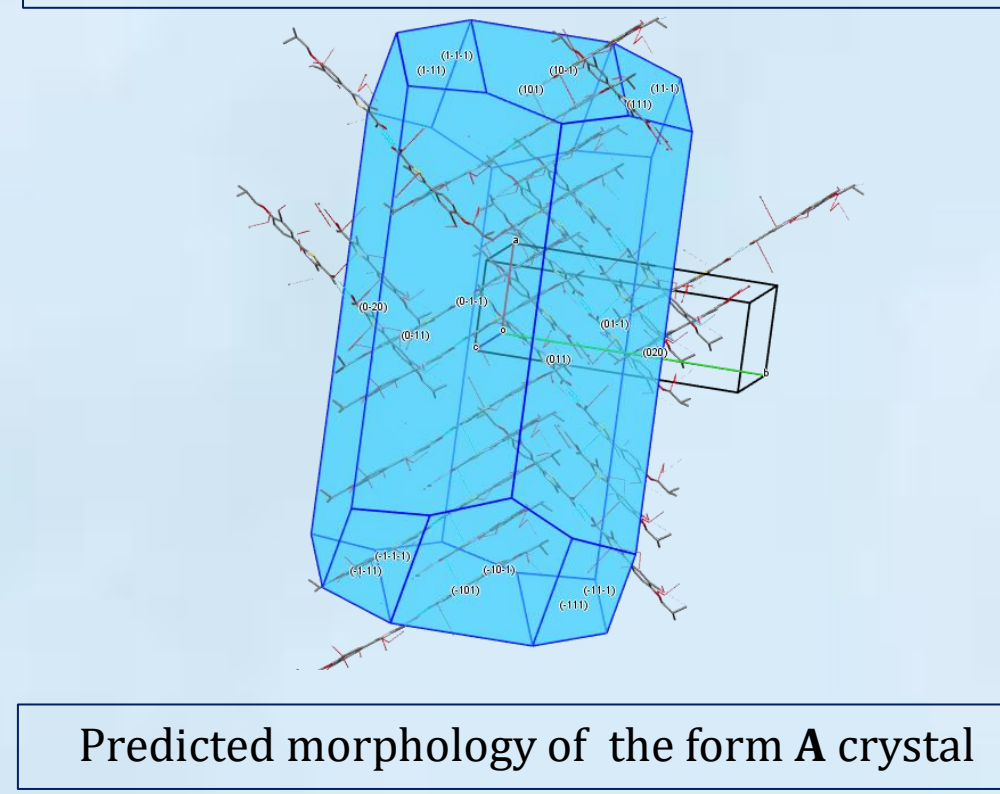


DSC trace of form A



Microscope images of form A

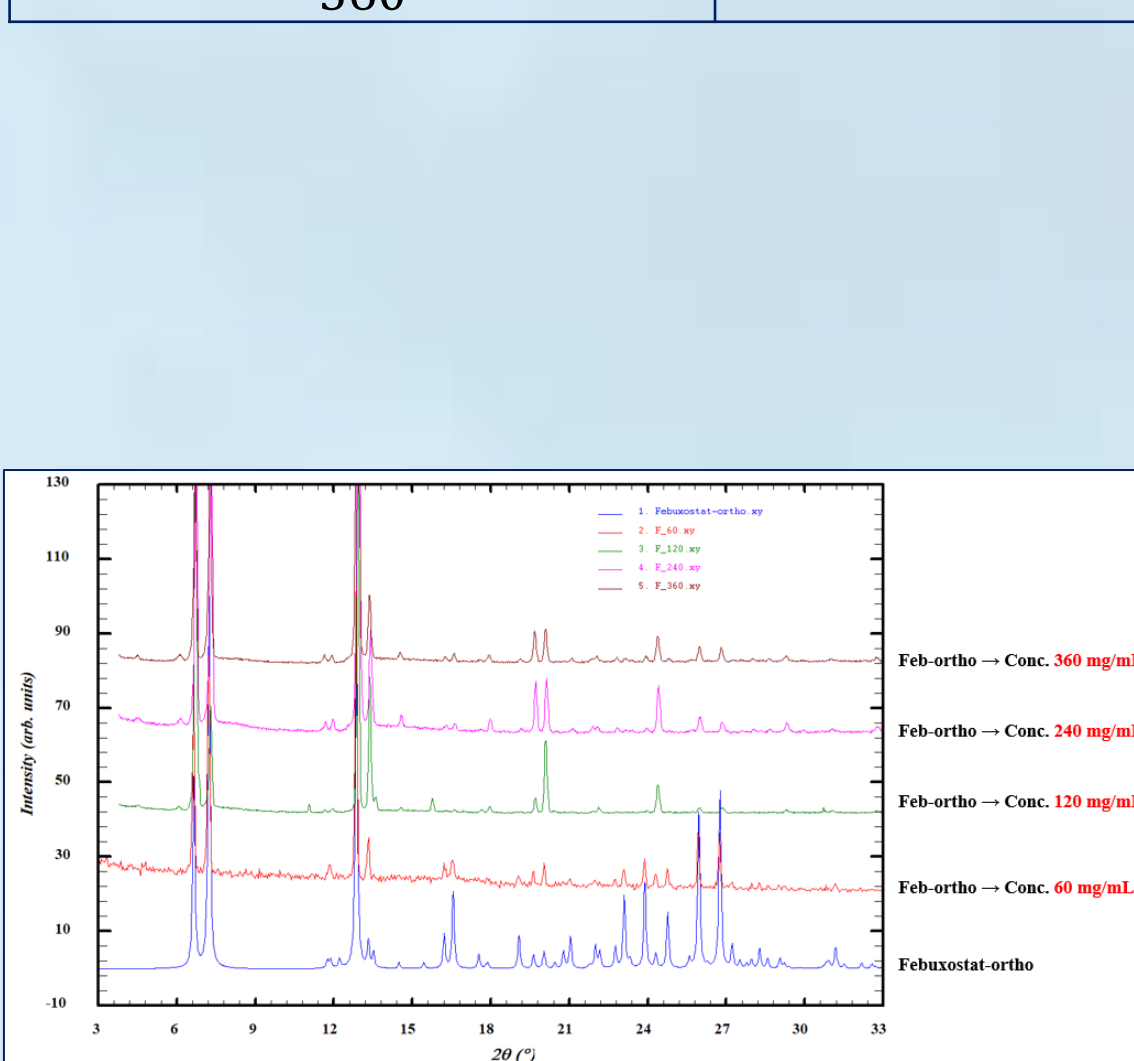
|                                    |                            |
|------------------------------------|----------------------------|
| <b>Starting material</b>           | Febuxostat (Form G)        |
| <b>Experiment</b>                  | ✓ slow cooling-evaporative |
| <b>Temperatures</b>                | 5°C, 25°C, 60°C            |
| <b>Solvent</b>                     | 2-ethoxyethanol            |
| <b>Form</b>                        | Form A                     |
| <b>Endothermic melting points</b>  | ~202.3°C<br>209.43°C       |
| <b>Stability (40°C and 75% RH)</b> | Stable                     |



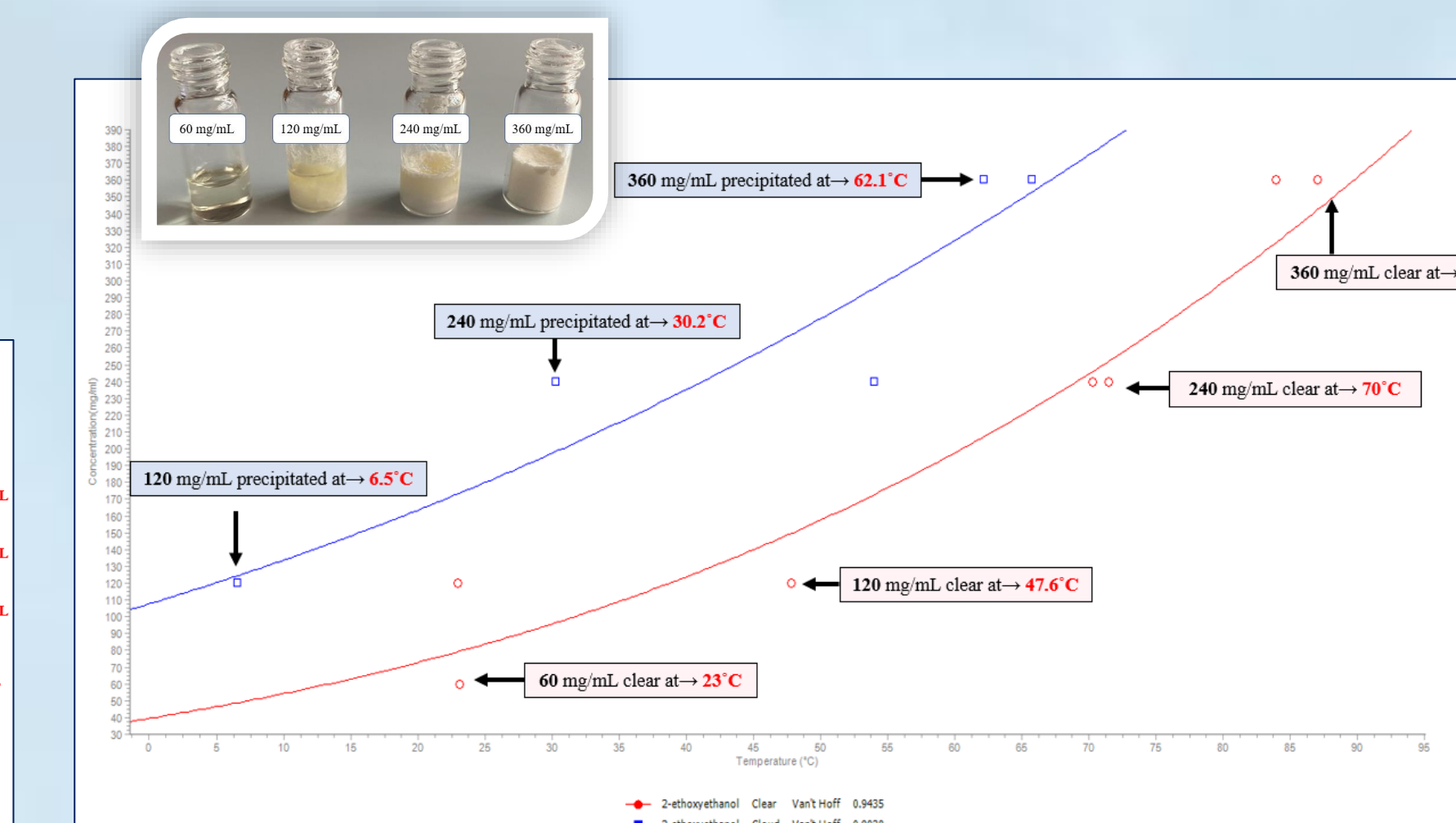
Predicted morphology of the form A crystal

### 2. Febuxostat - Form A

| Concentration of FEB (mg/mL) | Solvent         | Observations after analysis at Crystal16™ | Form by XRPD |
|------------------------------|-----------------|---|--------------|
| 60                           | 2-ethoxyethanol | Clear solution                            | Form A       |
| 120                          |                 | Clear solution + precipitate ↓            | Form A       |
| 240                          |                 | Slurry                                    | Form A       |
| 360                          |                 | Slurry                                    | Form A       |



XRPD patterns of form A after Crystal16™



Solubility and Meta-stable Zone Width for Febuxostat (form A)

## Conclusions

⊗ A novel salt and crystal form of FEB were obtained in a controlled manner using the Crystal16™ platform.

⊗ Making use of the integrated transmission technology together with 16 parallel reactors at a volume of 1 mL, the Crystal16™ easily allowed to assess salt and crystal formation.

⊗ The formation of Tro1 and form A can be reliably crystallized in 2-ethoxyethanol by using high starting concentrations: > 200 mg/mL for Tro1, respectively > 100 mg/mL for form A.

## References

- [1] Groom C. R., Bruno I. J., Lightfoot M. P. and Ward S. C., "The Cambridge Structural Database", *Acta Cryst.*, **2016**, *B72*, 171-179.
- [2] Karimi-Jafari, M., Padrela, L., Walker, G. M., & Croker, D. M., *Cryst. Growth Des.*, **2018**, *18*(10), 6370-6387.
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