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Unveiling novel phases: CO₂ assisted co crystallization of proxyphylline with 4 hydroxybenzoic acid

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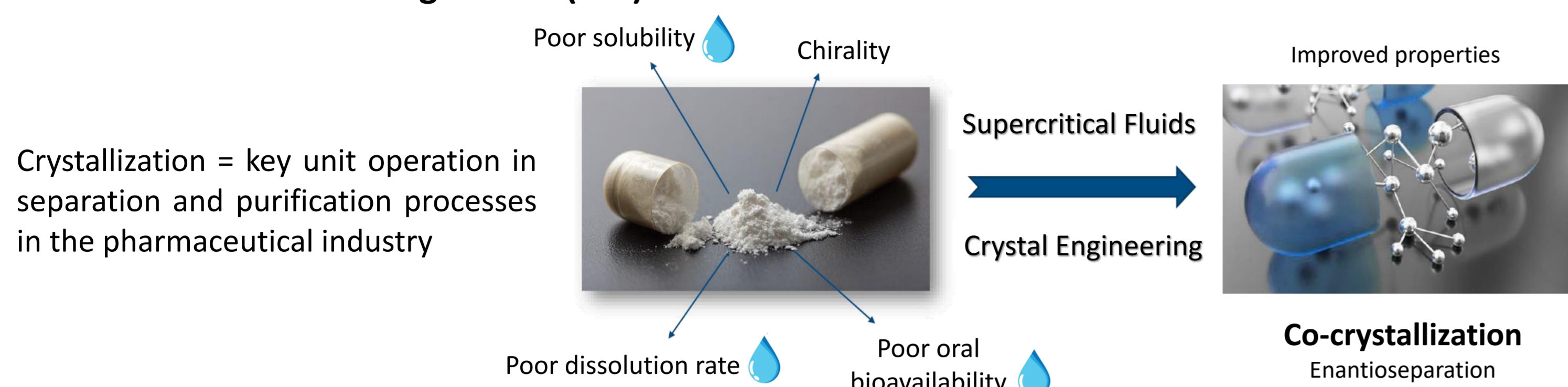
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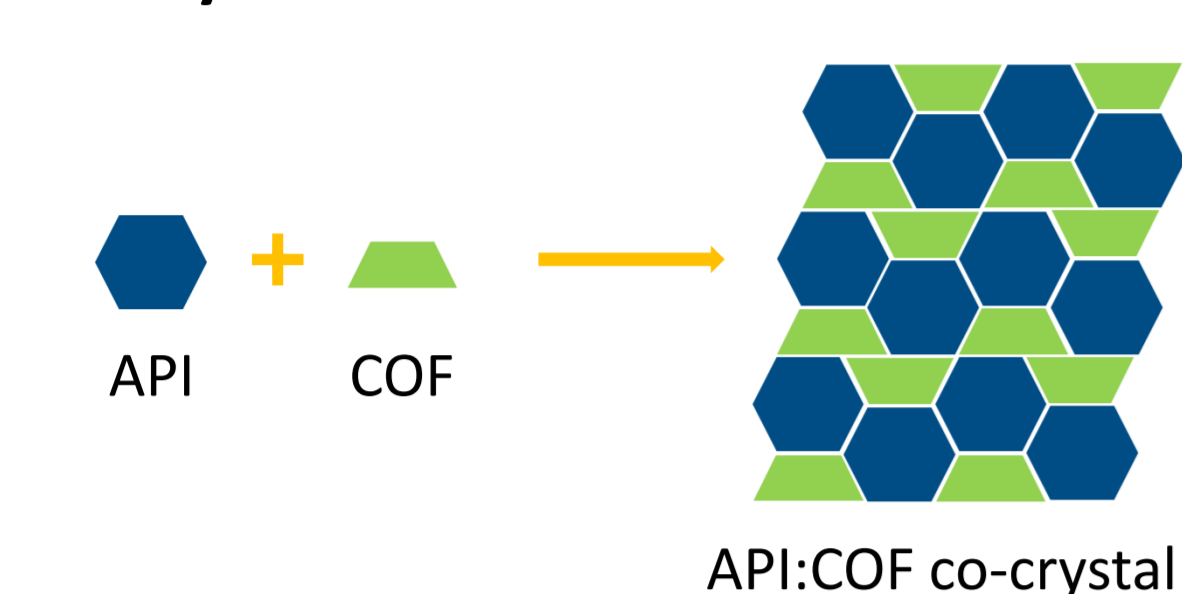
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Context

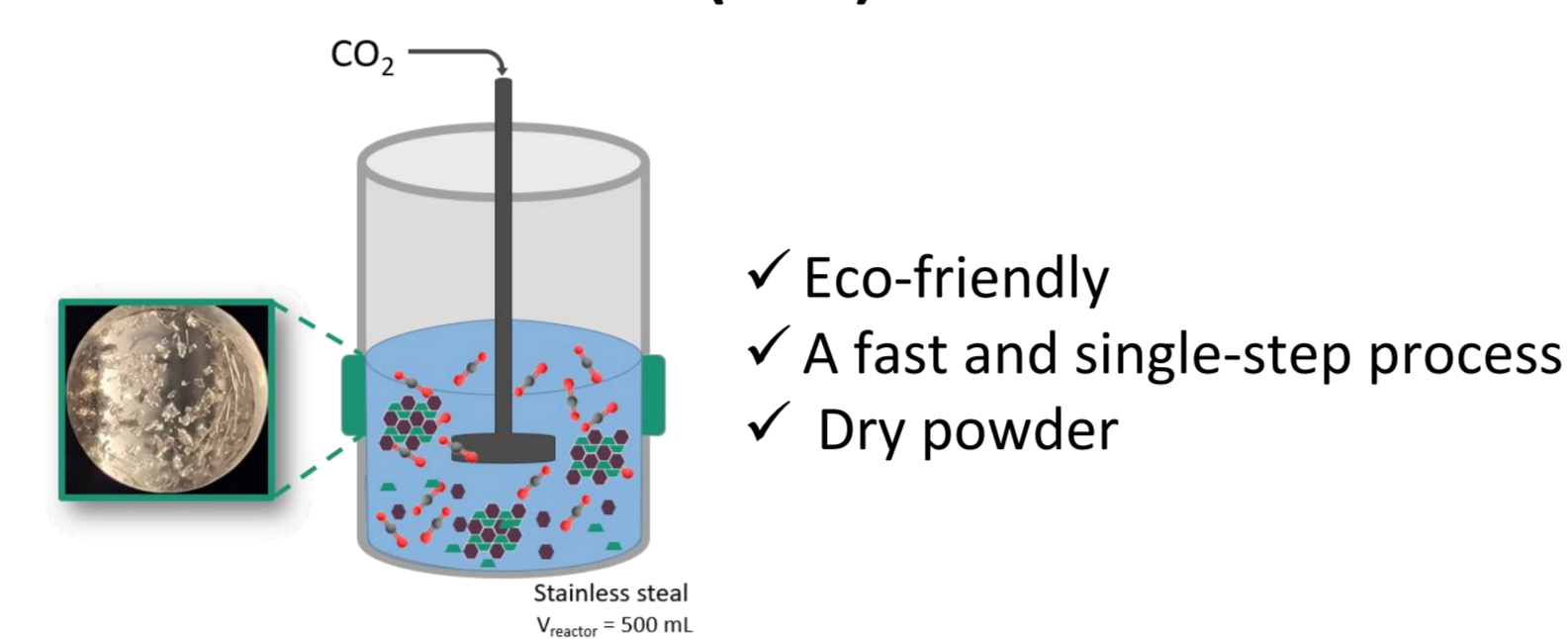
Active Pharmaceutical Ingredient (API)



Co-crystals



Gaseous Anti-Solvent (GAS) method

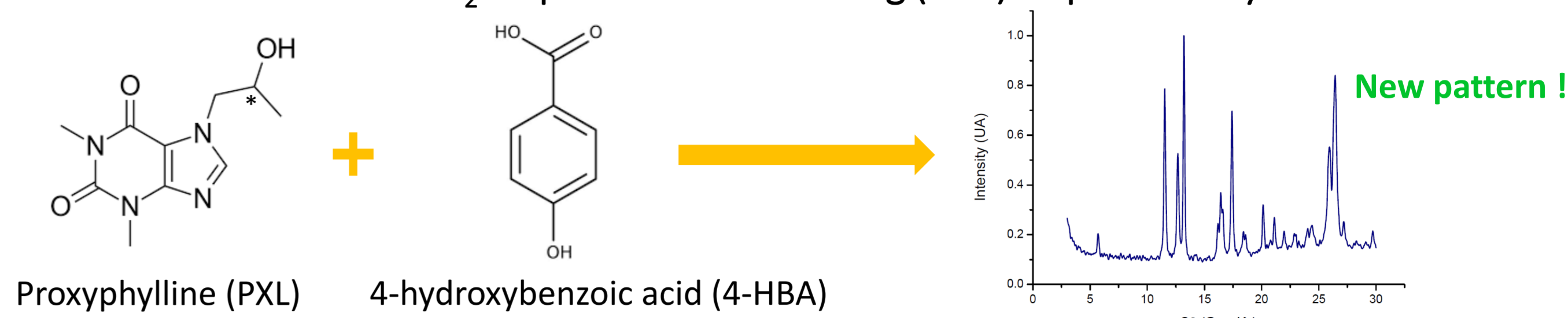


Main objective

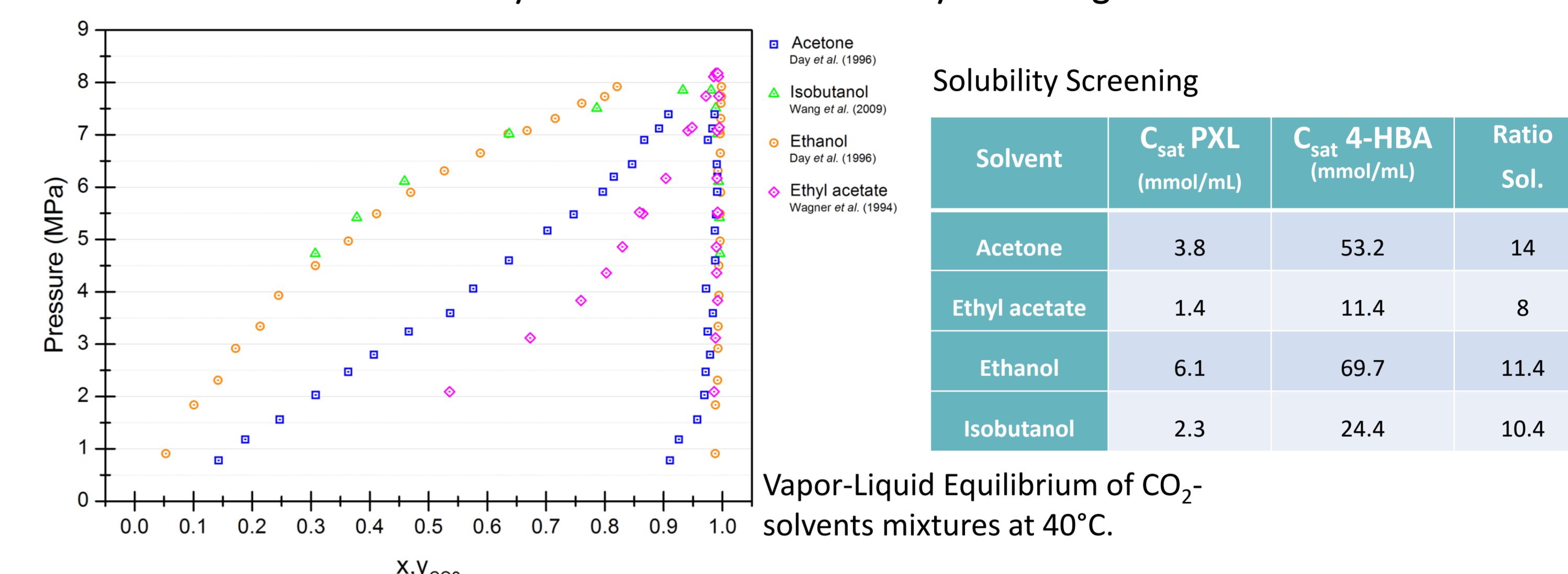
Understand the dynamics of PXL:4-HBA co-crystallization assisted by scCO₂ technology

Methodology

- Co-crystallization trials without CO₂: Liquid Assisted Grinding (LAG) --- preliminary result

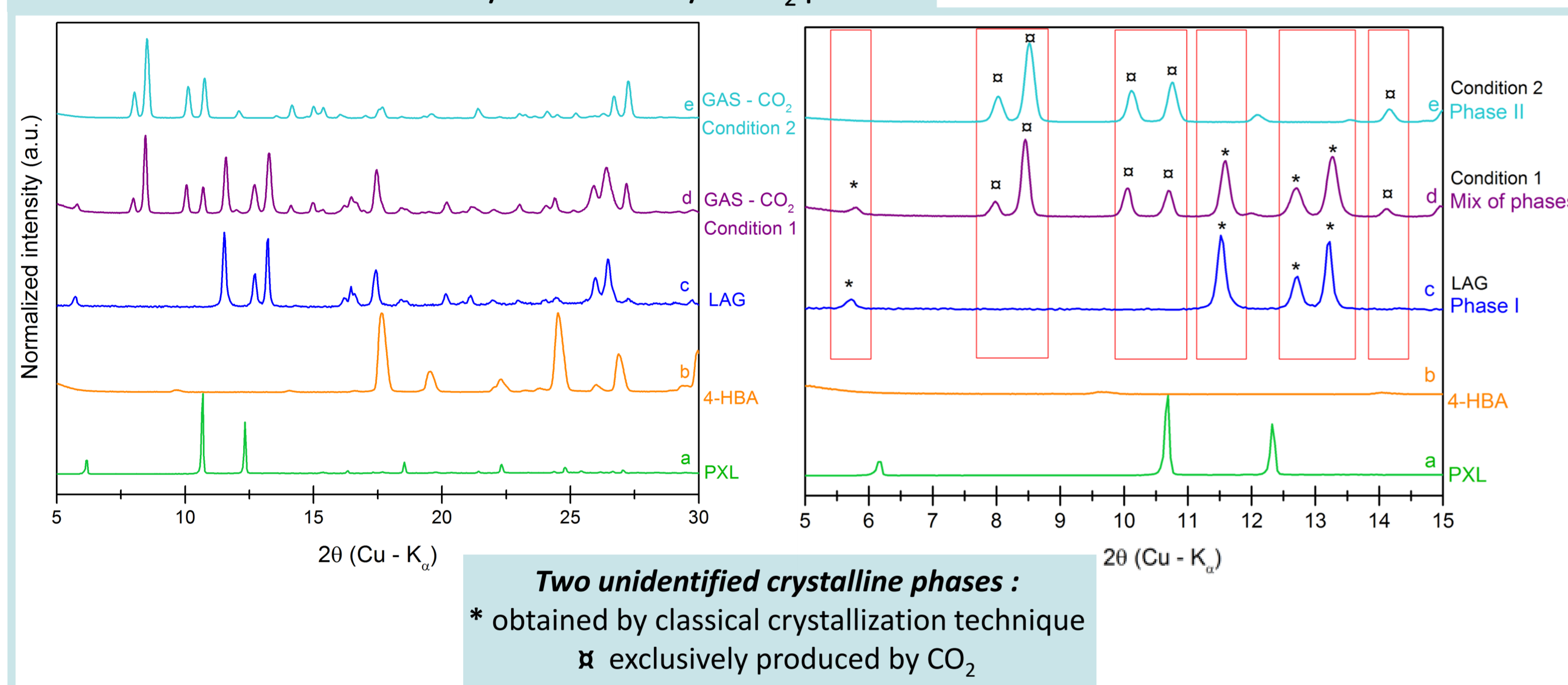


- Solvent selection for GAS co-crystallization: VLE & Solubility Screening

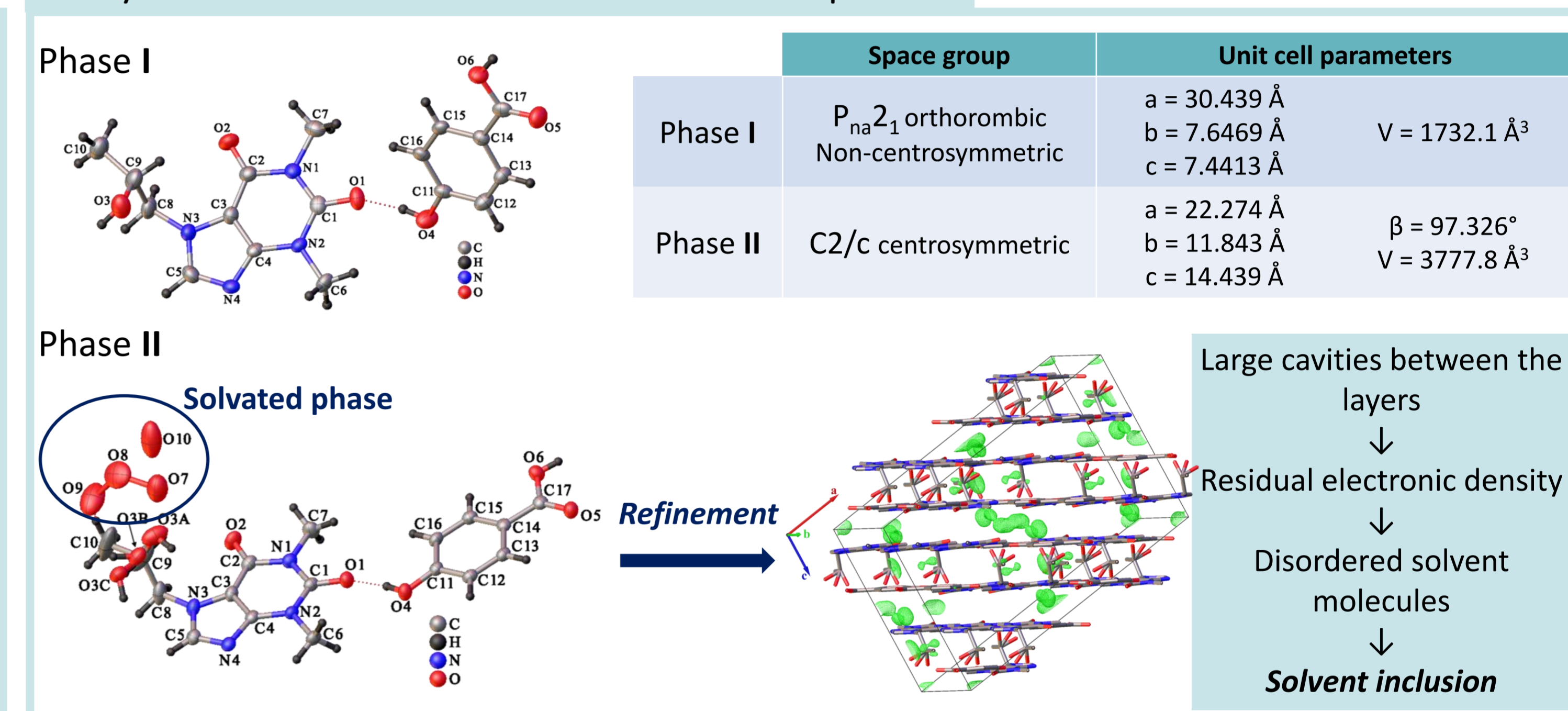


Results

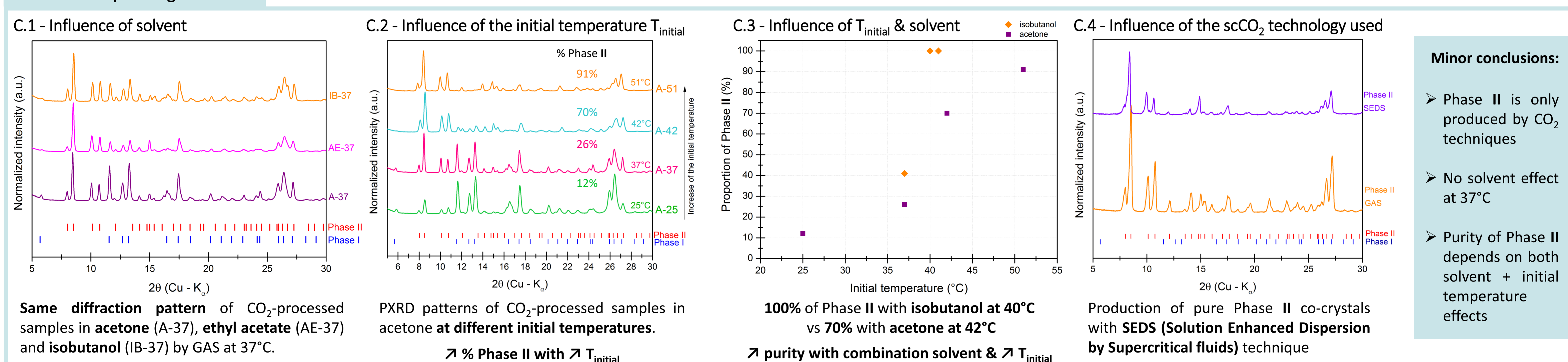
A - Evidence of PXL:4-HBA co-crystallization by scCO₂ process



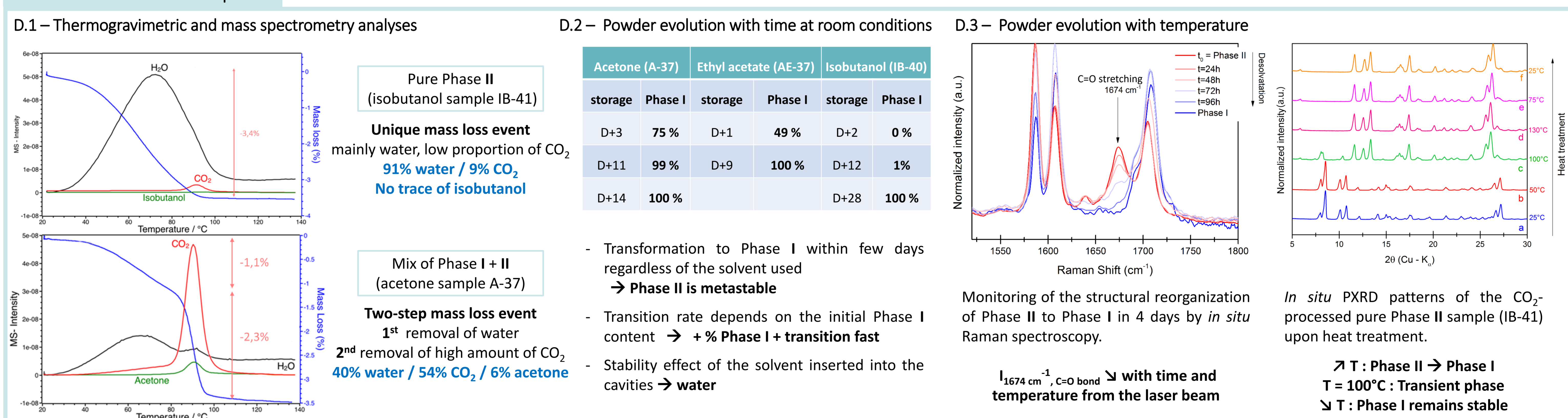
B - Crystal structure determination of the unknown phases



C - Effect of operating conditions



D - Transformations of solid phases



Conclusions

- Formation of a new co-crystal PXL:4-HBA by LAG and scCO₂ techniques
- Two solid phases :
 - Phase I = stable, easily produced by LAG and can be produced by GAS
 - Phase II = metastable, kinetic phase, only produced by CO₂ crystallization techniques
- Layer structure of Phase II → cavities where CO₂, H₂O, and acetone can be trapped
- CO₂-operating conditions determine the purity of Phase II :
 - GAS : isobutanol at 40°C / acetone above 50°C
 - SEDS : acetone at 50°C
- CO₂-produced powders (Phase II or Phase I+II) naturally evolve over time towards Phase I
- The transition is accelerated by the initial content of Phase I and/or by heat treatment

REFERENCES

F. Ericcek et al., « Unraveling a Unique Metastable Phase of a Proxyphylline Cocrystal Exclusively Produced by Compressed Carbon Dioxide », *Crystal Growth & Design*, May 2024, doi: 10.1021/acs.cgd.4c00279.

ACKNOWLEDGEMENTS

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