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



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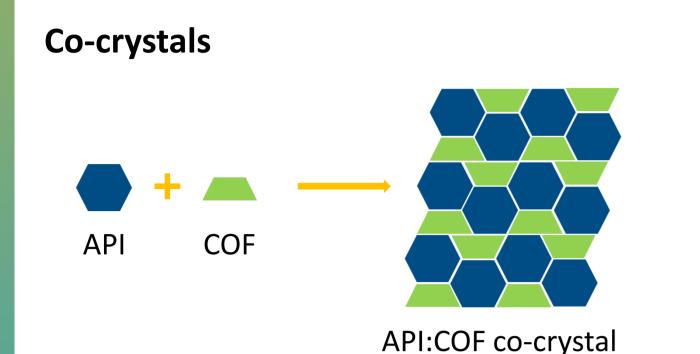
d Univ. Rouen Normandie, Normandie Univ, SMS, UR 3233, F-76000 Rouen, France Univ. Bordeaux, CNRS, Bordeaux INP, CBMN, UMR 5248, F-33600 Pessac, France

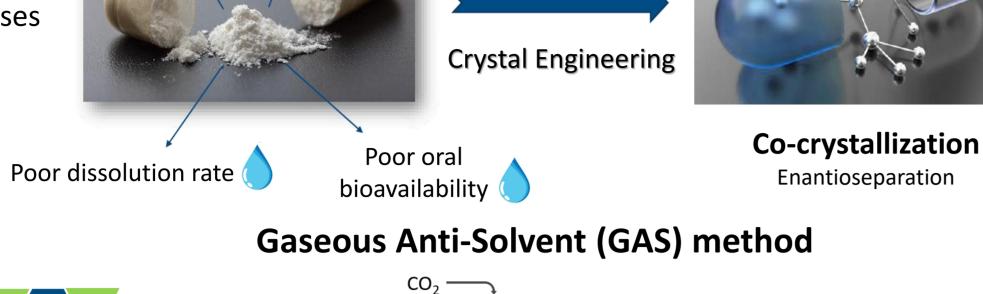
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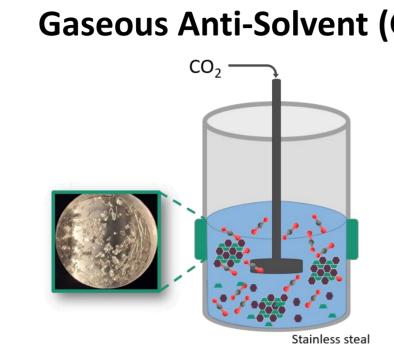
Solubility Screening



Active Pharmaceutical Ingredient (API) Poor solubility Chirality Improved properties Supercritical Fluids Crystallization = key unit operation in separation and purification processes in the pharmaceutical industry **Crystal Engineering**







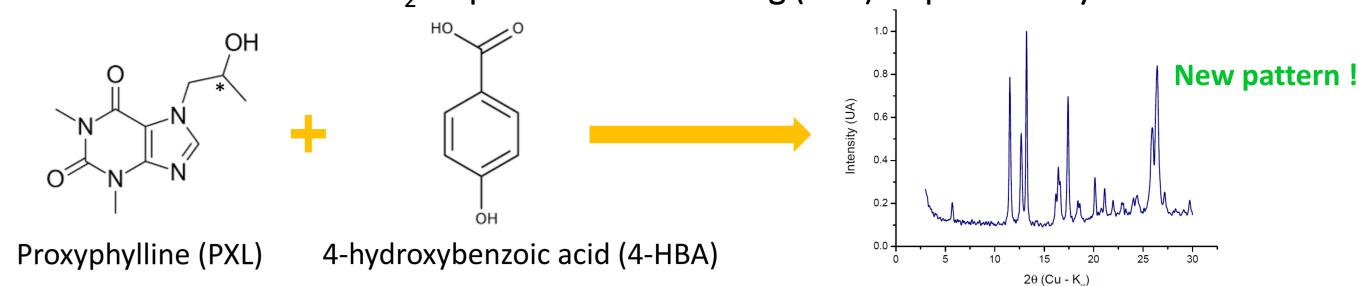
✓ Eco-friendly ✓ A fast and single-step process ✓ Dry powder

Main objective

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

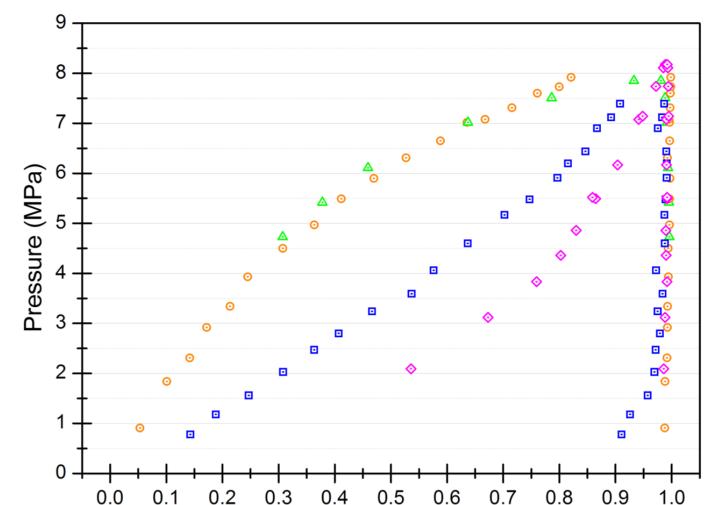
Methodology

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



Isobutanol

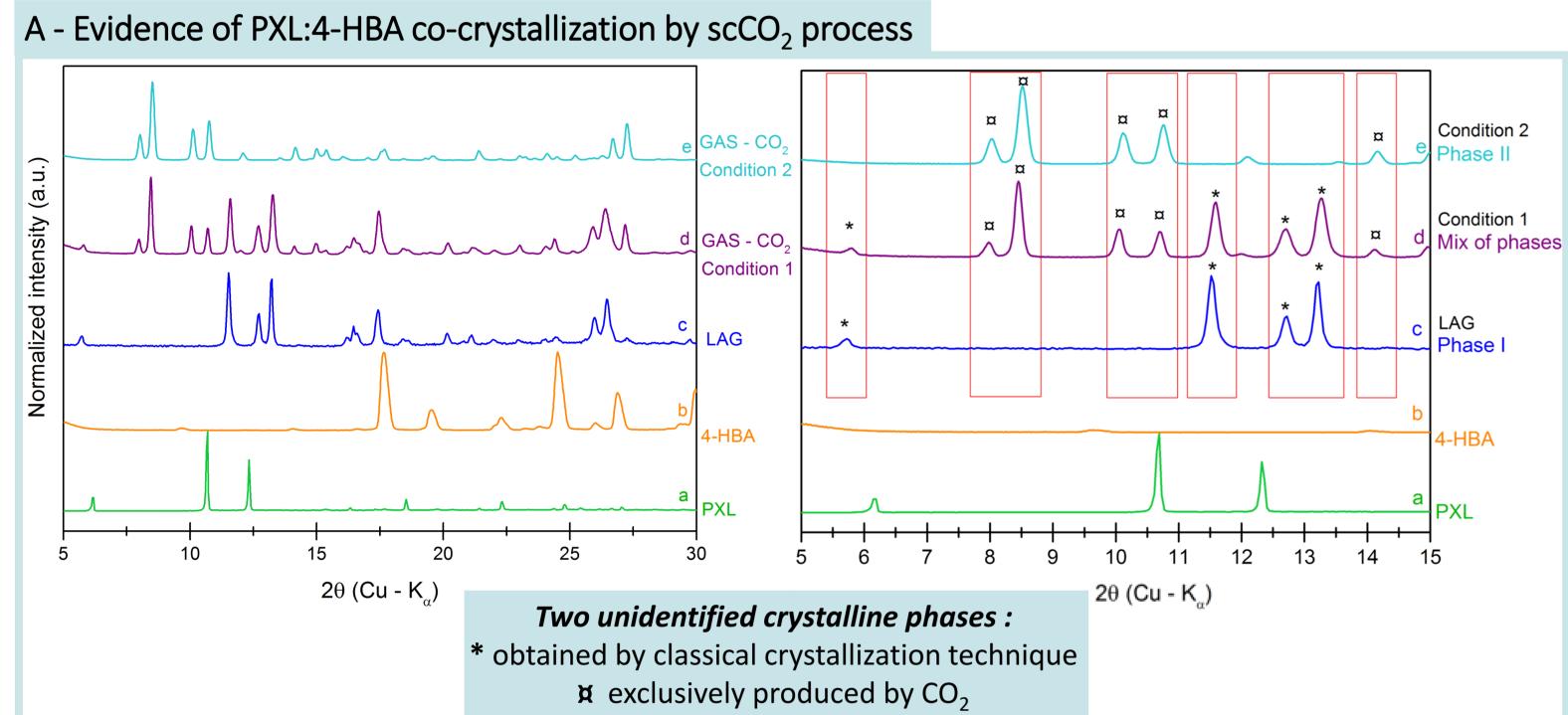
- Solvent selection for GAS co-crystallization: VLE & Solubility Screening



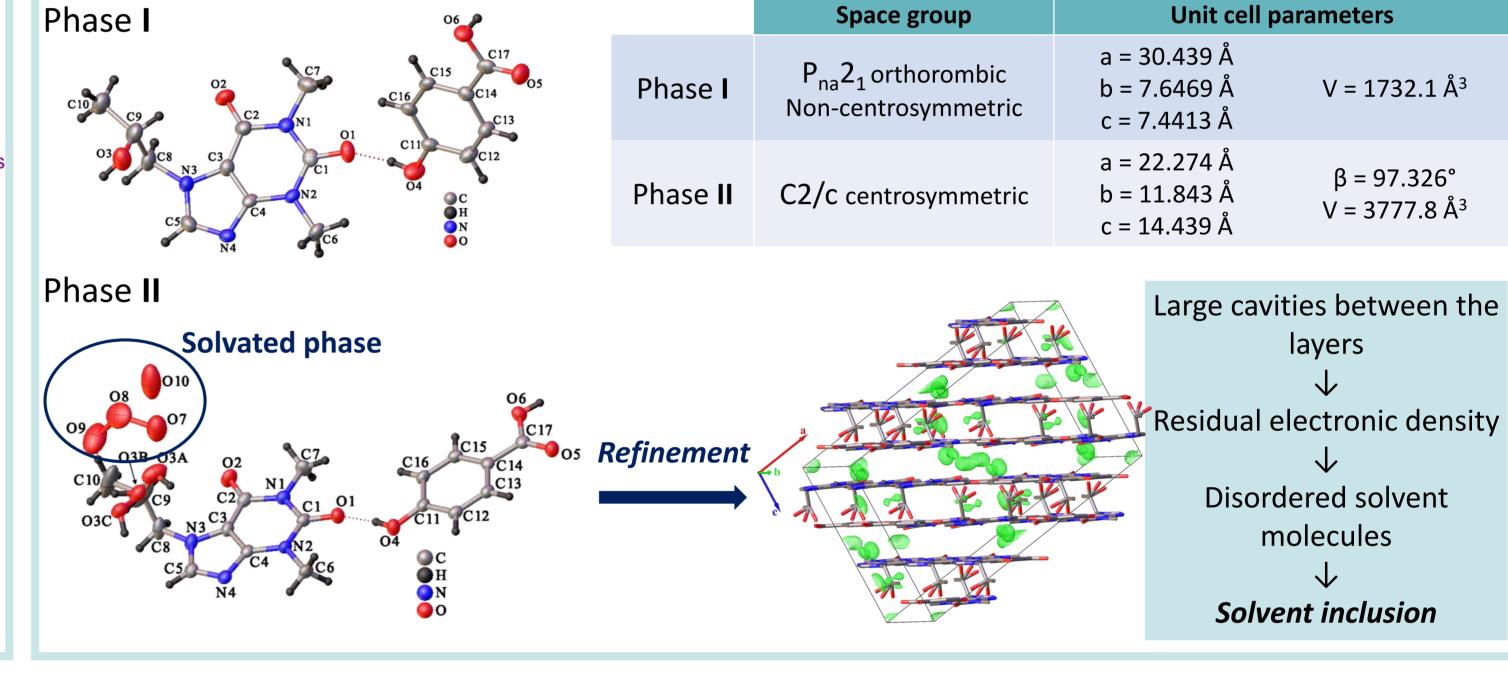
Wang et al. (2009) C_{sat} 4-HBA Solvent Sol. Ethyl acetate 53.2 3.8 14 Acetone 11.4 Ethyl acetate 69.7 11.4 **Ethanol** 10.4 24.4 2.3 Isobutanol

Vapor-Liquid Equilibrium of CO₂solvents mixtures at 40°C. x,y_{CO2}

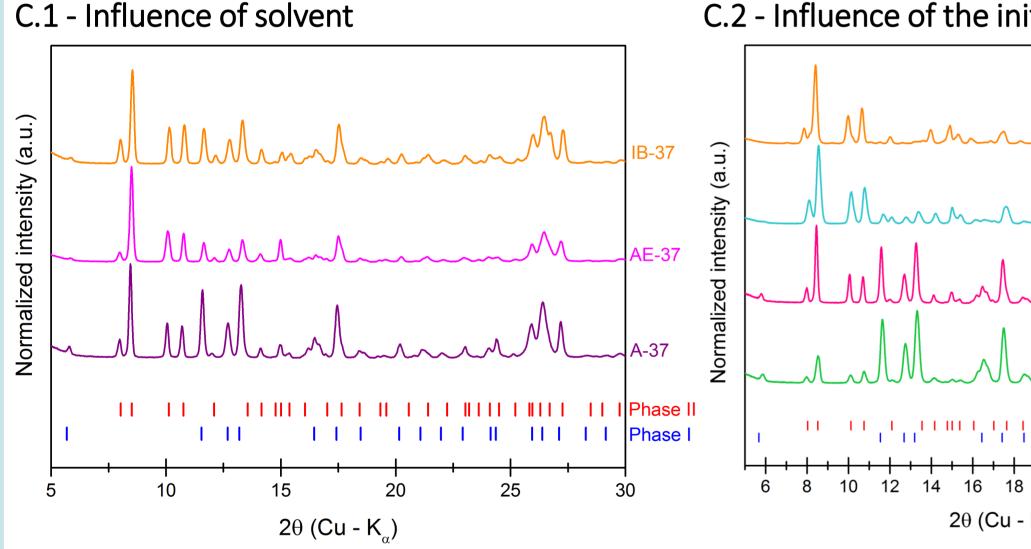
Results



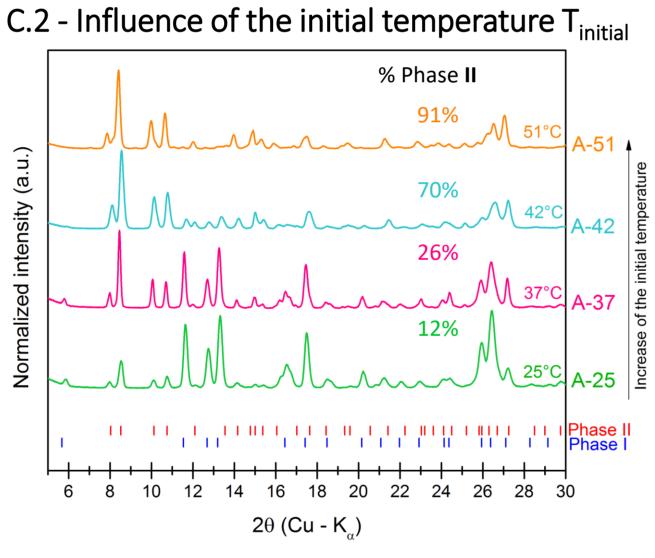
B - Crystal structure determination of the unknown phases



C – Effect of operating conditions

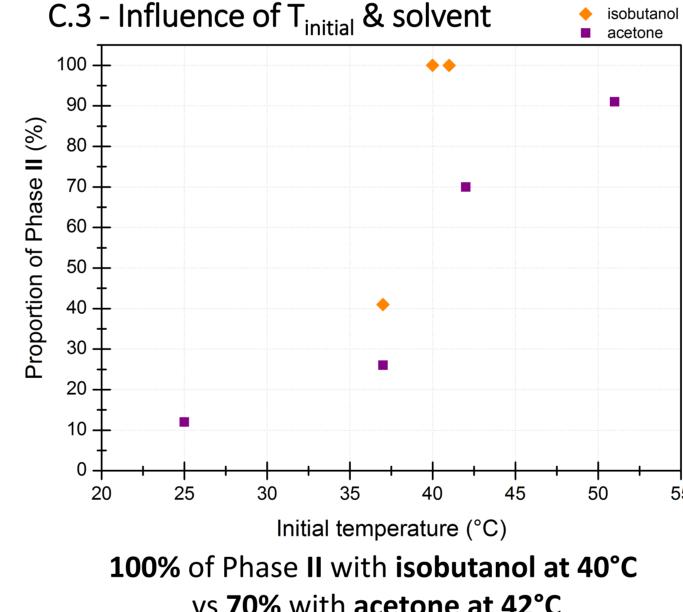


Same diffraction pattern of CO₂-processed samples in acetone (A-37), ethyl acetate (AE-37) and isobutanol (IB-37) by GAS at 37°C.



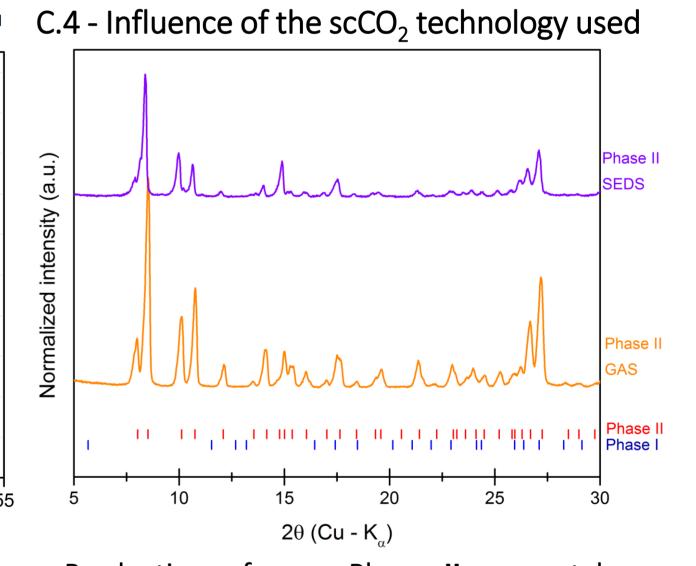
PXRD patterns of CO₂-processed samples in acetone at different initial temperatures.

7 % Phase II with
7 T_{initial}



vs 70% with acetone at 42°C

↗ purity with combination solvent & **↗** T_{initial}



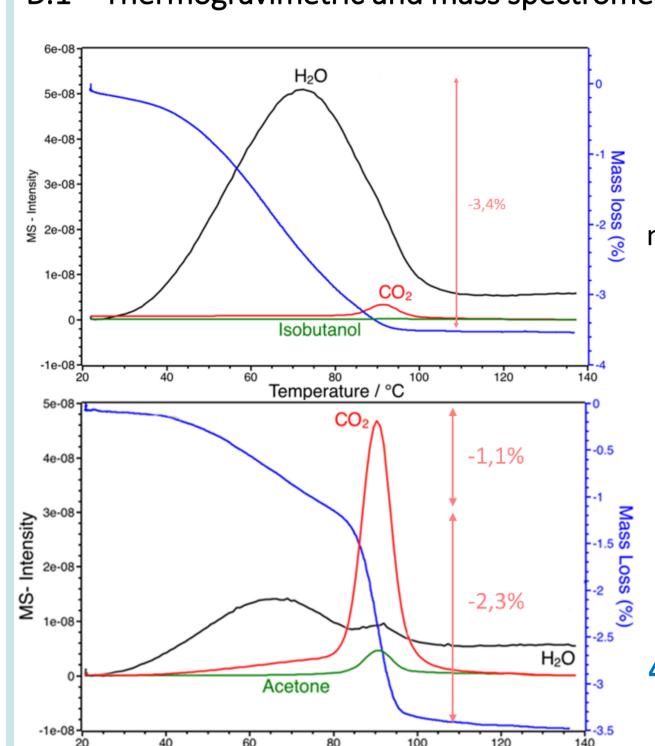
Production of pure Phase II co-crystals with SEDS (Solution Enhanced Dispersion by Supercritical fluids) technique

Minor conclusions:

- ➤ Phase II is only produced by CO₂ techniques
- > No solvent effect at 37°C
- ➤ Purity of Phase II depends on both solvent + initial temperature effects

D – Transformations of solid phases

D.1 – Thermogravimetric and mass spectrometry analyses



Pure Phase II (isobutanol sample IB-41) Unique mass loss event mainly water, low proportion of CO₂ 91% water / 9% CO₂ No trace of isobutanol

> Mix of Phase I + II (acetone sample A-37) Two-step mass loss event

1st removal of water **2**nd removal of high amount of CO₂ 40% water / 54% CO₂ / 6% acetone

D.2 – Powder evolution with time at room conditions

Acetone (A-37)		Ethyl acetate (AE-37)		Isobutanol (IB-40)	
storage	Phase I	storage	Phase I	storage	Phase I
D+3	75 %	D+1	49 %	D+2	0 %
D+11	99 %	D+9	100 %	D+12	1%
D+14	100 %			D+28	100 %

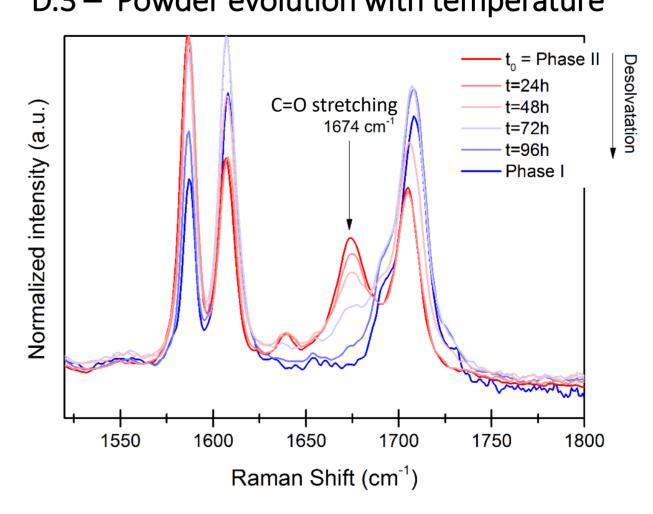
iransformation to Phase I within few days regardless of the solvent used

→ Phase II is metastable

- Transition rate depends on the initial Phase I content \rightarrow + % Phase I + transition fast

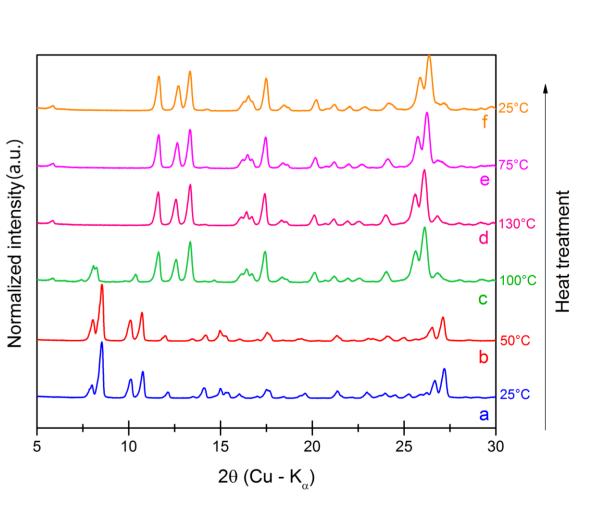
Stability effect of the solvent inserted into the cavities > water

D.3 – Powder evolution with temperature



Monitoring of the structural reorganization of Phase II to Phase I in 4 days by in situ Raman spectroscopy.

 $I_{1674 \text{ cm}}^{-1}$, C=0 bond \searrow with time and temperature from the laser beam



In situ PXRD patterns of the CO₂processed pure Phase II sample (IB-41) upon heat treatment.

> 7 T : Phase II → Phase I T = 100°C : Transient phase

> **↘** T : Phase I remains stable

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
 - \triangleright Phase II = metastable, kinetic phase, only produced by CO₂ crystallization techniques
- ✓ Layer structure of Phase II \rightarrow cavities where CO₂, H₂O, and acetone can be trapped
- ✓ CO_2 -operating conditions determine the purity of Phase II:
 - ➤ GAS : isobutanol at 40°C / acetone above 50°C > SEDS : acetone at 50°C

- naturally evolve over time towards Phase I ✓ The transition is accelerated by the initial content

✓ CO₂-produced powders (Phase II or Phase I+II)

of Phase I and/or by heat treatment



F. Ercicek 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.









