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# TAILOR-MADE POLYMORPH SELECTION USING ADDITIVES

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## INTRODUCTION

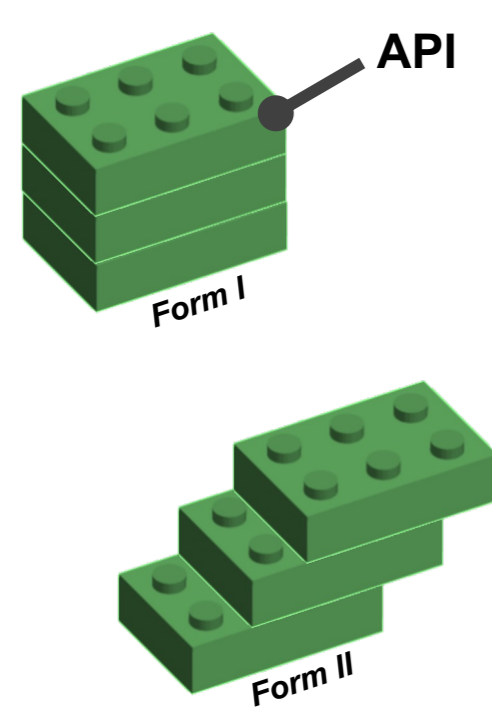


Fig. 1 Polymorphism of a given compound.

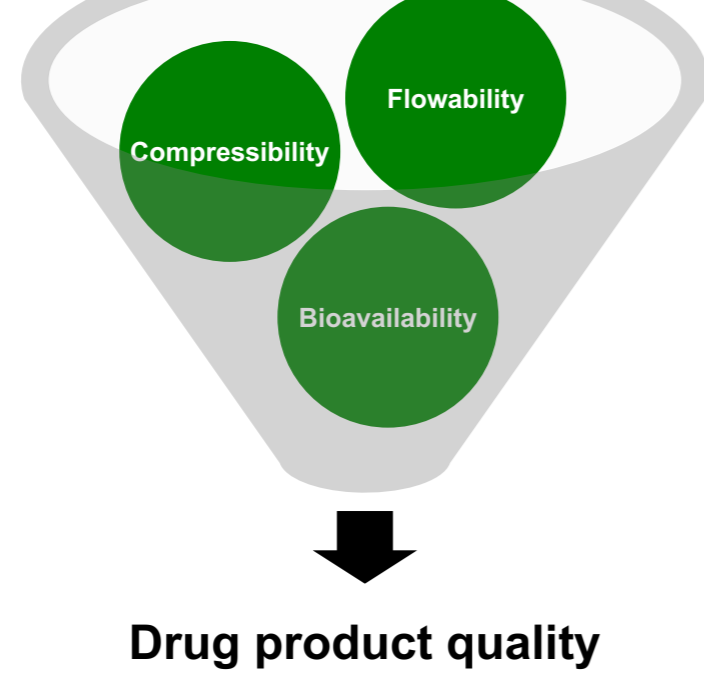


Fig. 2 Challenge of polymorphism selection for the development of pharmaceuticals.

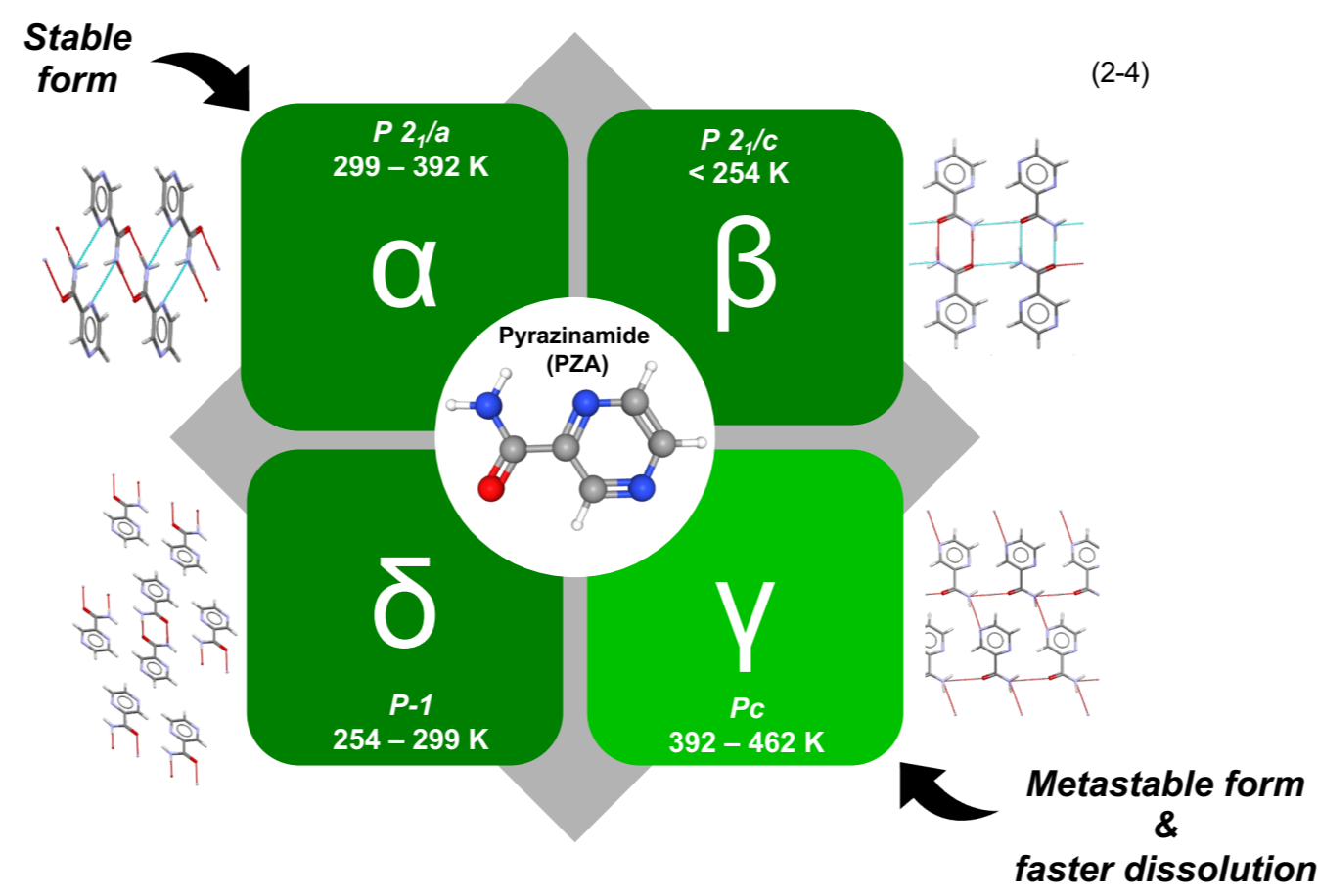


Fig. 3 Polymorphs of pyrazinamide.

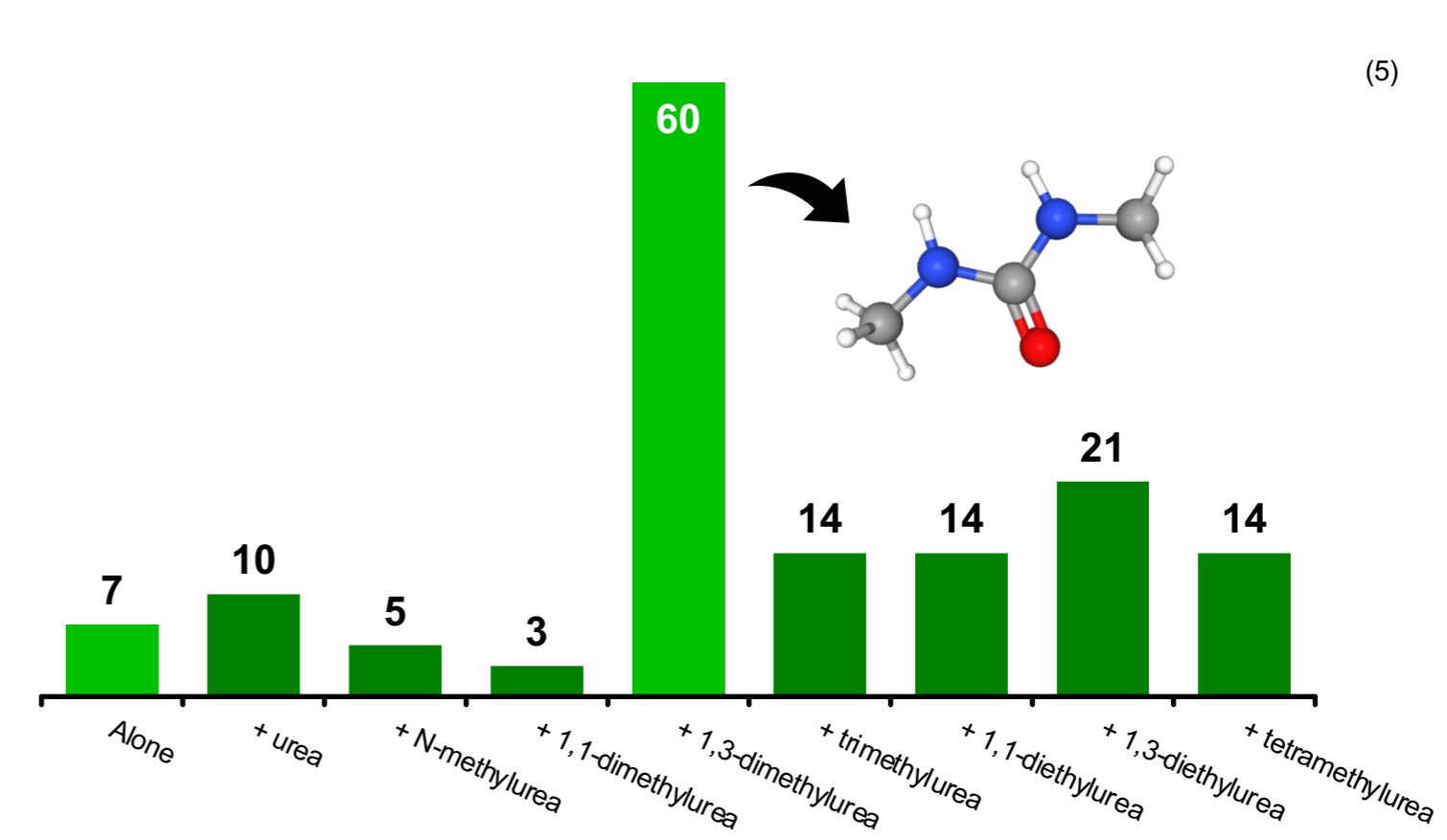


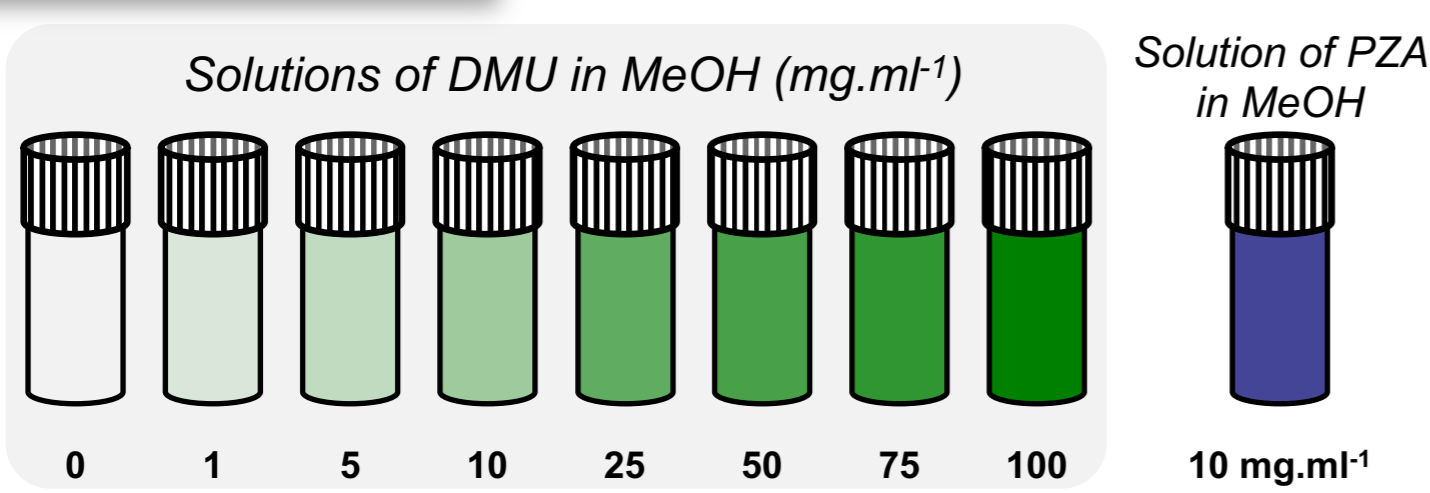
Fig. 4 Transition time of  $\gamma$ -PZA in days alone and with urea derivatives.

## HOW CAN WE DESIGN AN INTERFACE TO EXPLORE STABILISATION OF $\gamma$ -PYRAZINAMIDE POLYMORPHISM BY 1,3-DIMETHYLUREA ?

## MATERIALS

API	Additive	Solvent	Substrate
Pyrazinamide (PZA)	1,3-dimethylurea (DMU)	Methanol (MeOH)	Glass slide (18 x 18 x 0,13 mm)

## METHODS



### 1 Dropcasting (1/2)

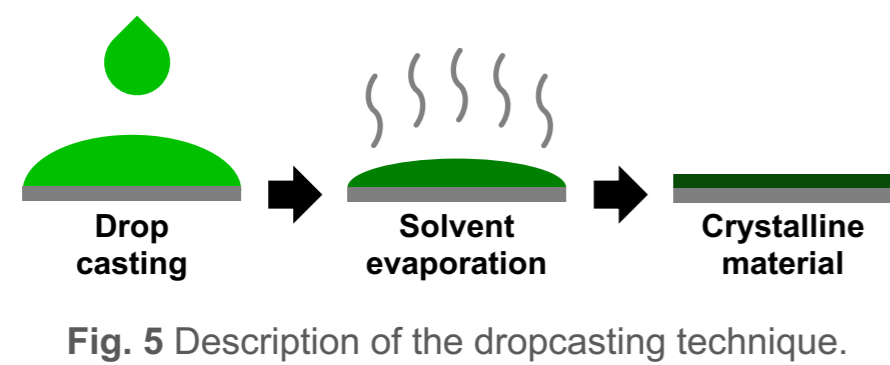


Fig. 5 Description of the dropcasting technique.

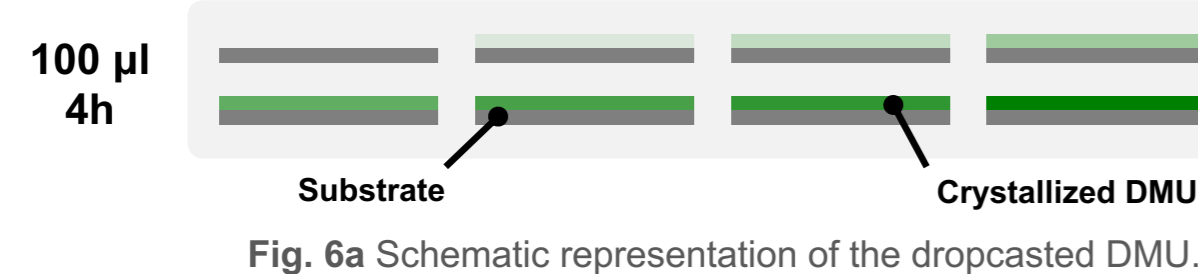


Fig. 6a Schematic representation of the dropcasted DMU.

### 2 Dropcasting (2/2)

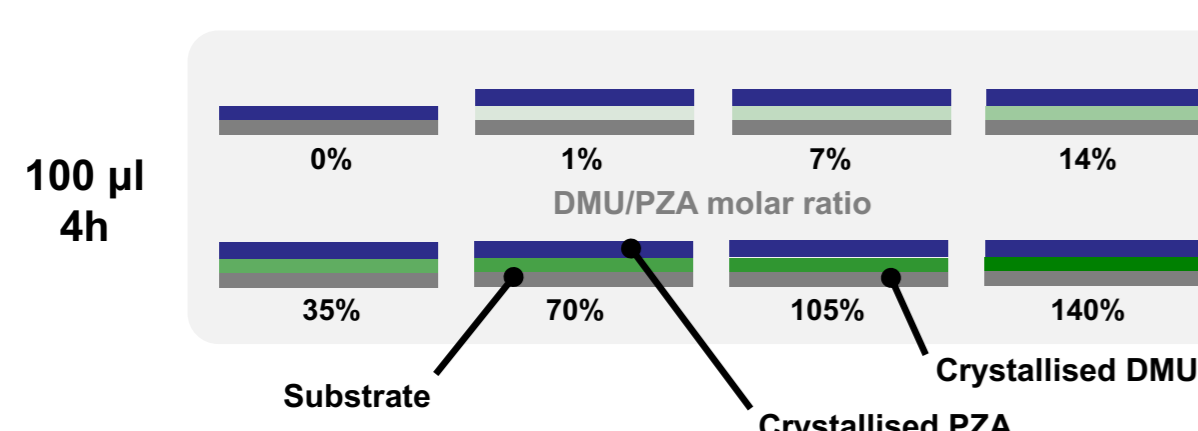


Fig. 6b Schematic representation of the dropcasted PZA onto DMU.

- X-ray diffraction, infrared and polarized light microscopy analysis are performed on dry layer (DMU & DMU + PZA).

## RESULTS

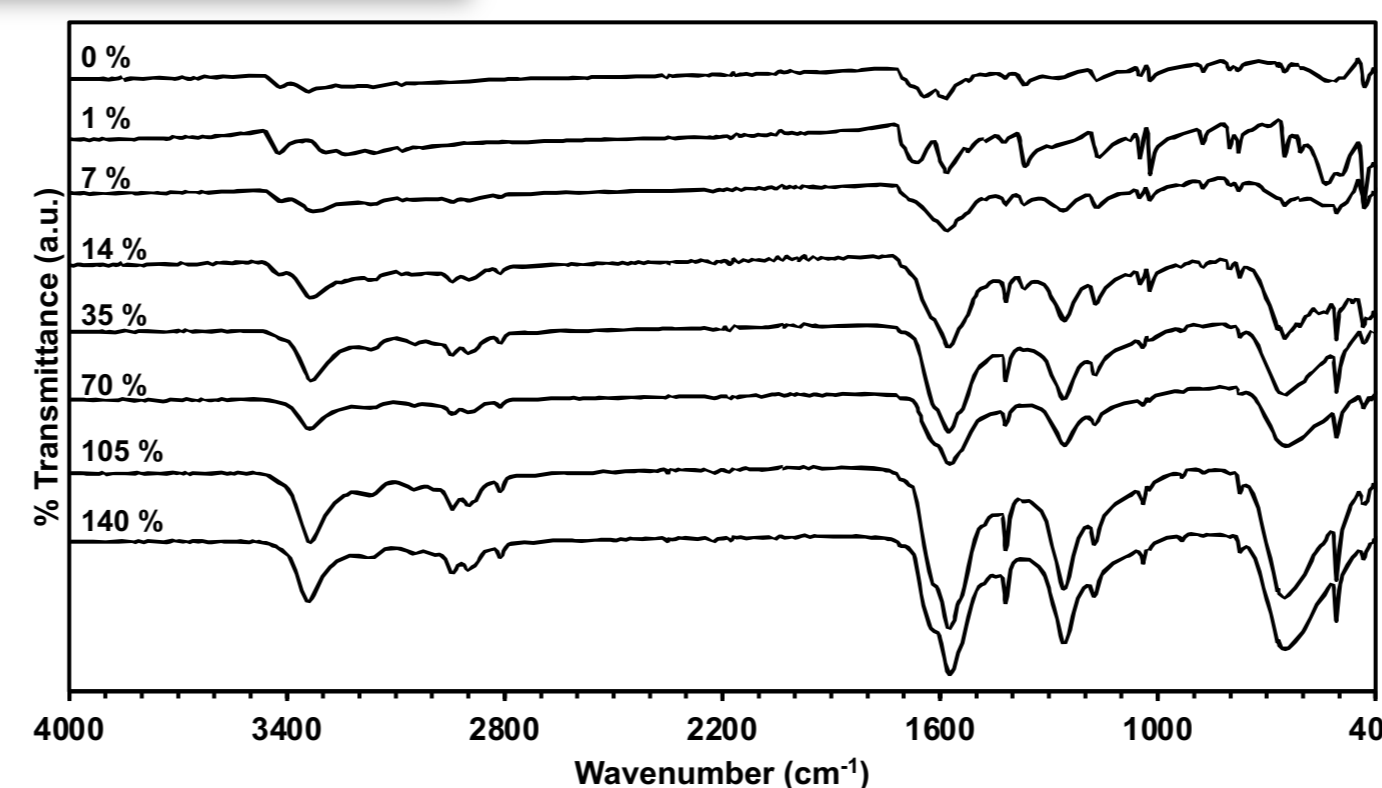
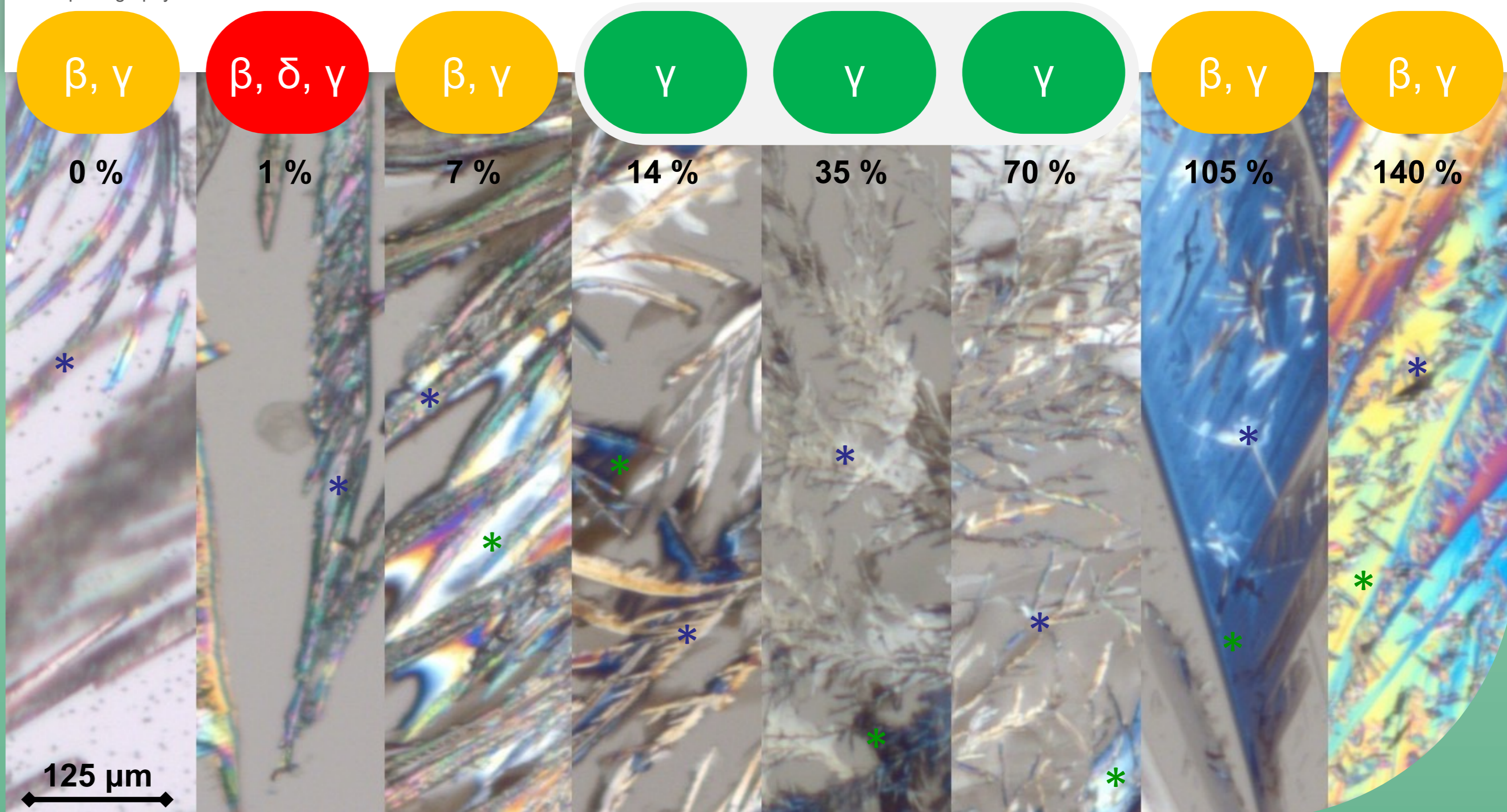


Fig. 7 FT-IR spectra. Left: Dropcasted samples (DMU/PZA molar fraction indicated); right: comparison between  $\gamma$ -PZA, dropcasted DMU/PZA and DMU form I.

- Pyrazinamide crystallises onto DMU with an observed  $\gamma$ -PZA range.
- Dilution effect of DMU.
- Any clear interaction observed.

- Functional region: 105% got spectrum of DMU.
- Fingerprint region (stabilised liaisons): amide, ring vibration,  $\text{NH}_2$  rocking, ring torsion and bending.

Fig. 8 Polarized light microphotography of crystalline PZA over DMU by double dropcasting deposition method. PZA phase and DMU/PZA molar ratio are indicated in % on the top of the photography.



Tentative assignment: \*Pyrazinamide, \*1,3-dimethylurea.

## CONCLUSION

- Pyrazinamide easily crystallises with the desired  $\gamma$  form as thin layer onto a 1,3-dimethylurea layer using dropcasting.
- Polymorphic phase of pyrazinamide appears to depend on the amount of 1,3-dimethylurea underneath.
- FT-IR helped in understand how could interact DMU and PZA (probably hydrogen liaisons and  $\pi$ -stacking).
- Interface sensitive methods (AFM, GIXRD, Raman) must be explored to understand interactions and molecular packing.

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