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# MECHANOCHEMICALLY INITIATED ISONIAZID–BENZOIC ACID COCRYSTAL FORMATION UNDER ACCELERATED CONDITIONS

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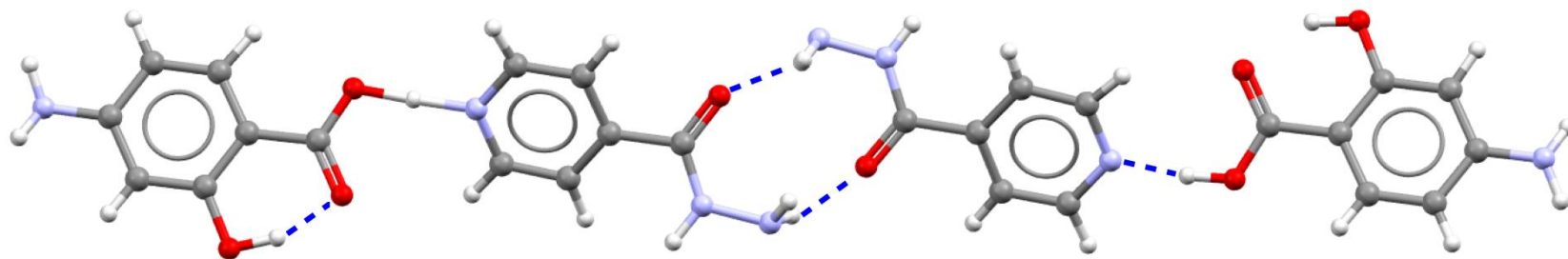
# Overview

- Background
- Isoniazid cocrystal screening
- Crystal structure of isoniazid cocrystals and isoniazid – benzoic acid cocrystal
- Physicochemical properties of isoniazid cocrystals
- Kinetics of isoniazid cocrystal mechanochemical formation

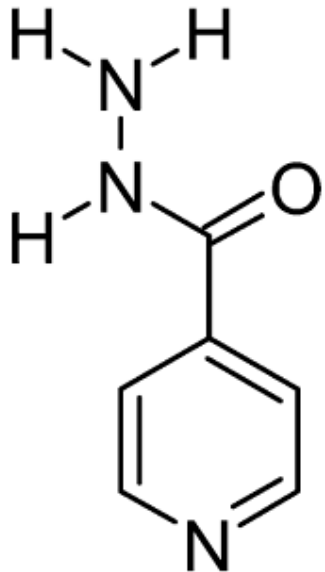
# Background

**Cocrystals** are crystalline single phase materials that:

- Are composed from two or more molecular components
- May have enhanced properties
- Contain several compounds in one crystal structure



# Background



isoniazid

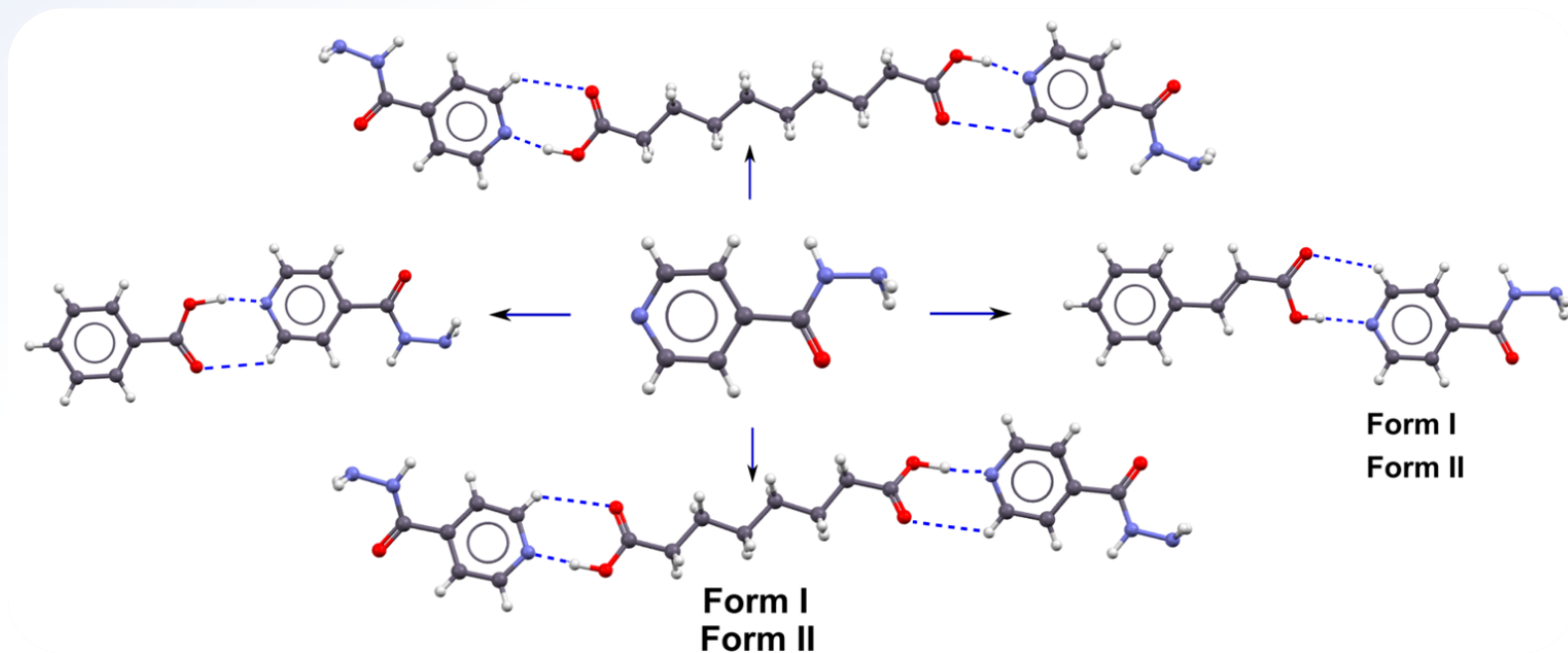
## Isoniazid

- antitubercular drug to treat the *Mycobacterium tuberculosis* bacterial infection
- exhibits synergistic activity with the cinnamic acid
- isoniazid tablet formulations undergo degradation

# Isoniazid cocrystal screening

## Screening strategy:

- Isoniazid – a pyridine and hydrazide group containing compound
- Forms a persistent pyridine – carboxyl synthon





# Mechanochemical cocrystal screening

- ✓ Polymorph control
- ✓ Result - pure crystalline form
- ✓ Fast

## Aspects to consider:

Milling time

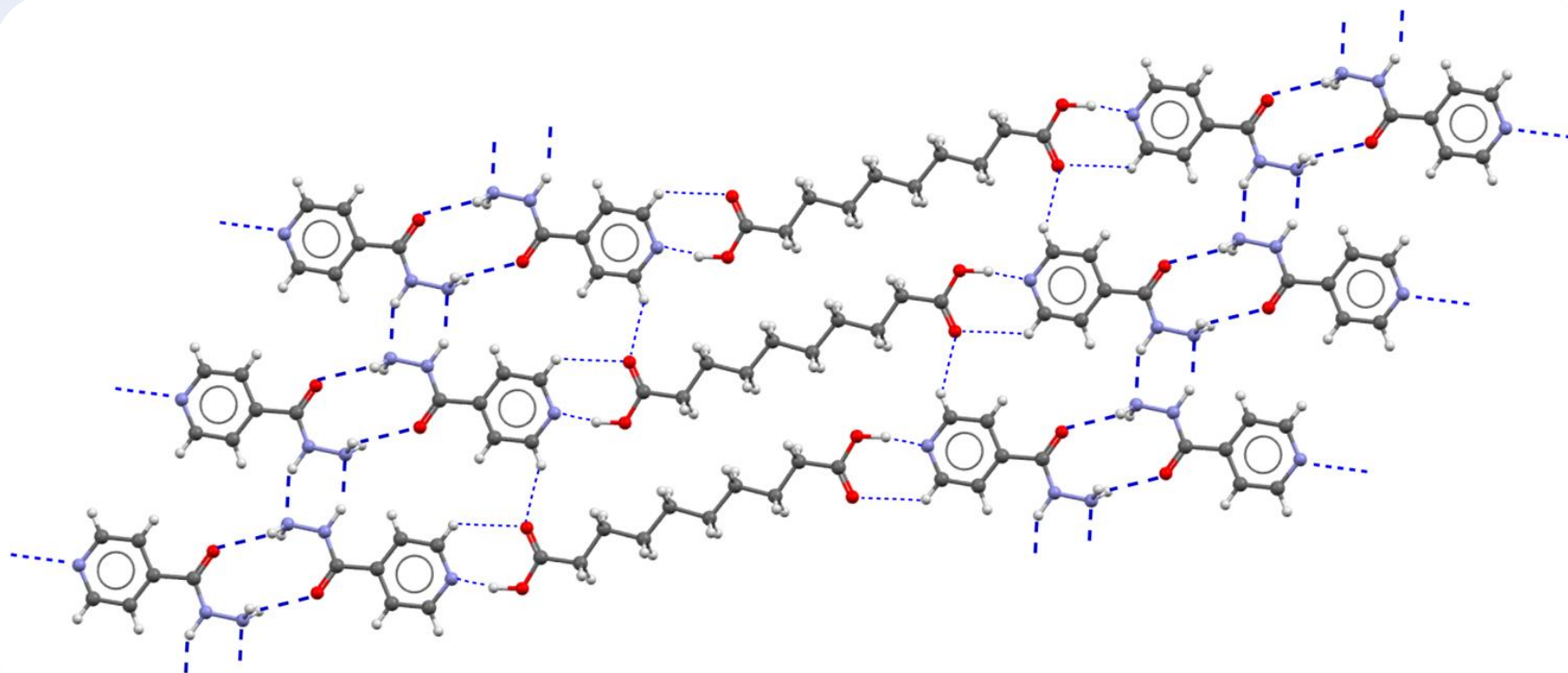
Milling frequency

Solvent choice



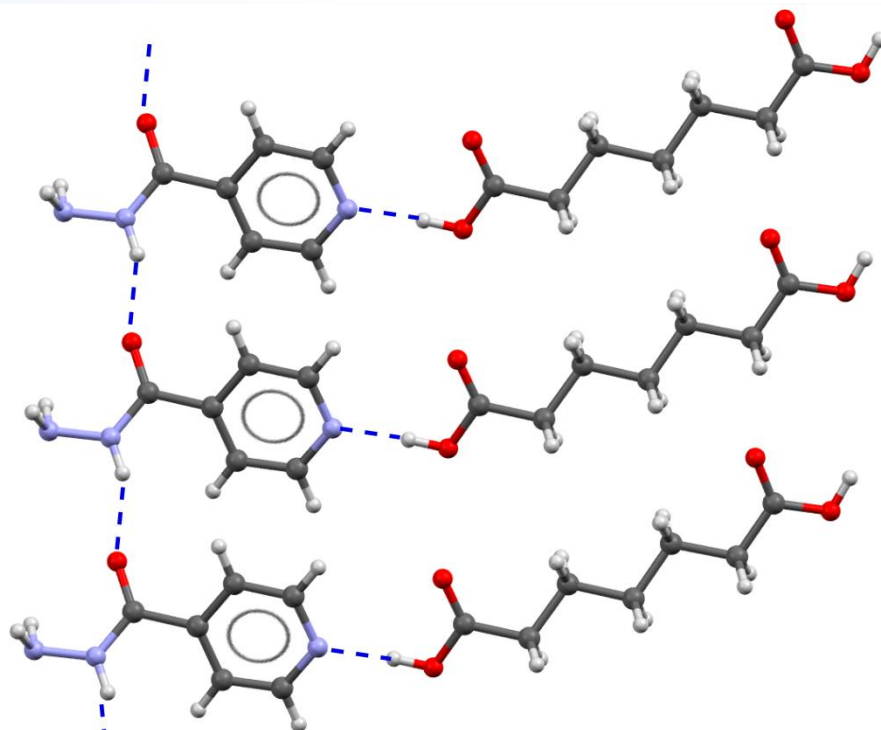
# Crystal structures of isoniazid cocrystals with even chain diacids

- Cyclic homosynthons formed by hydrazide groups
- 2:1 stoichiometry

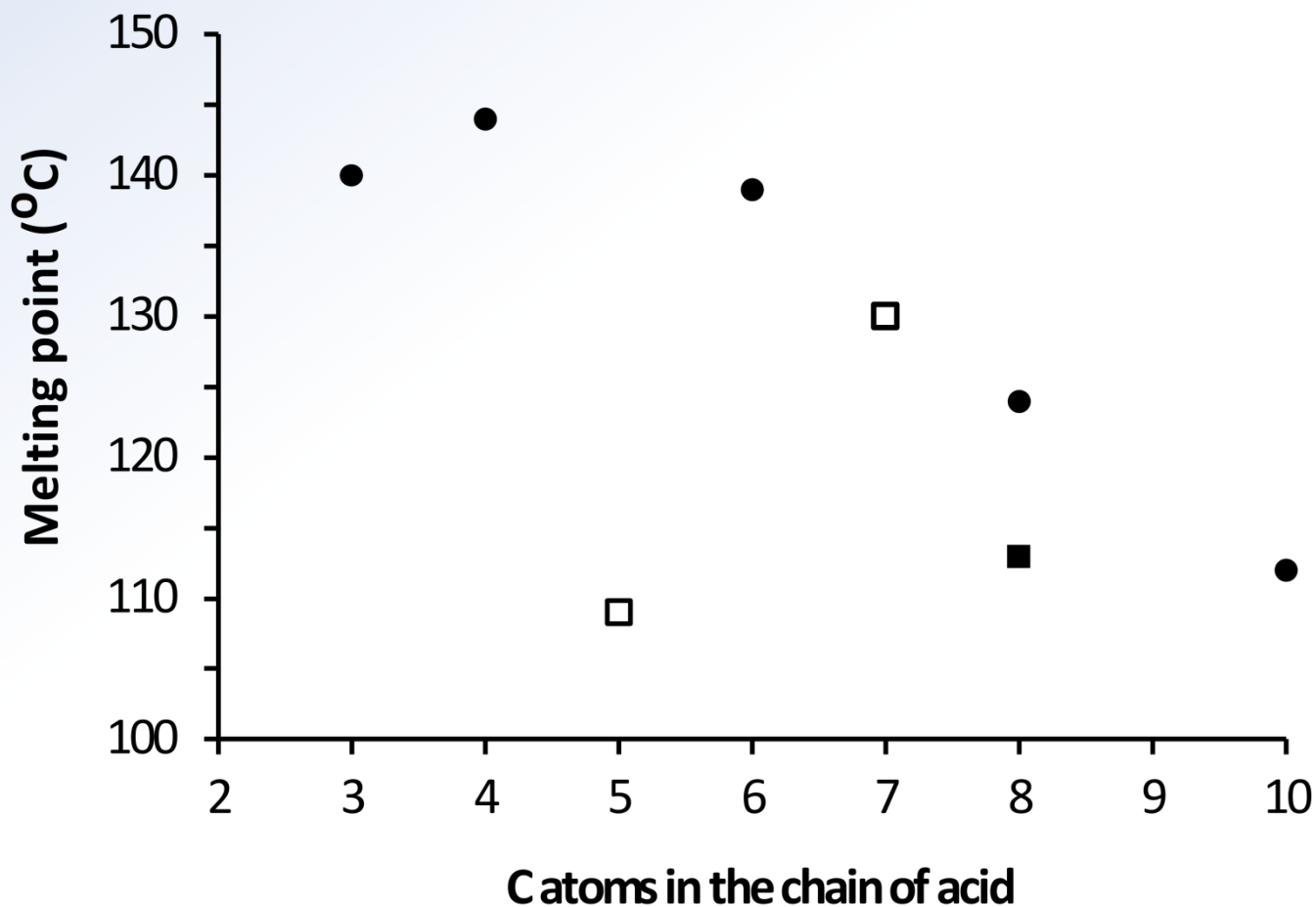


# Crystal structures of isoniazid cocrystals with odd chain diacids

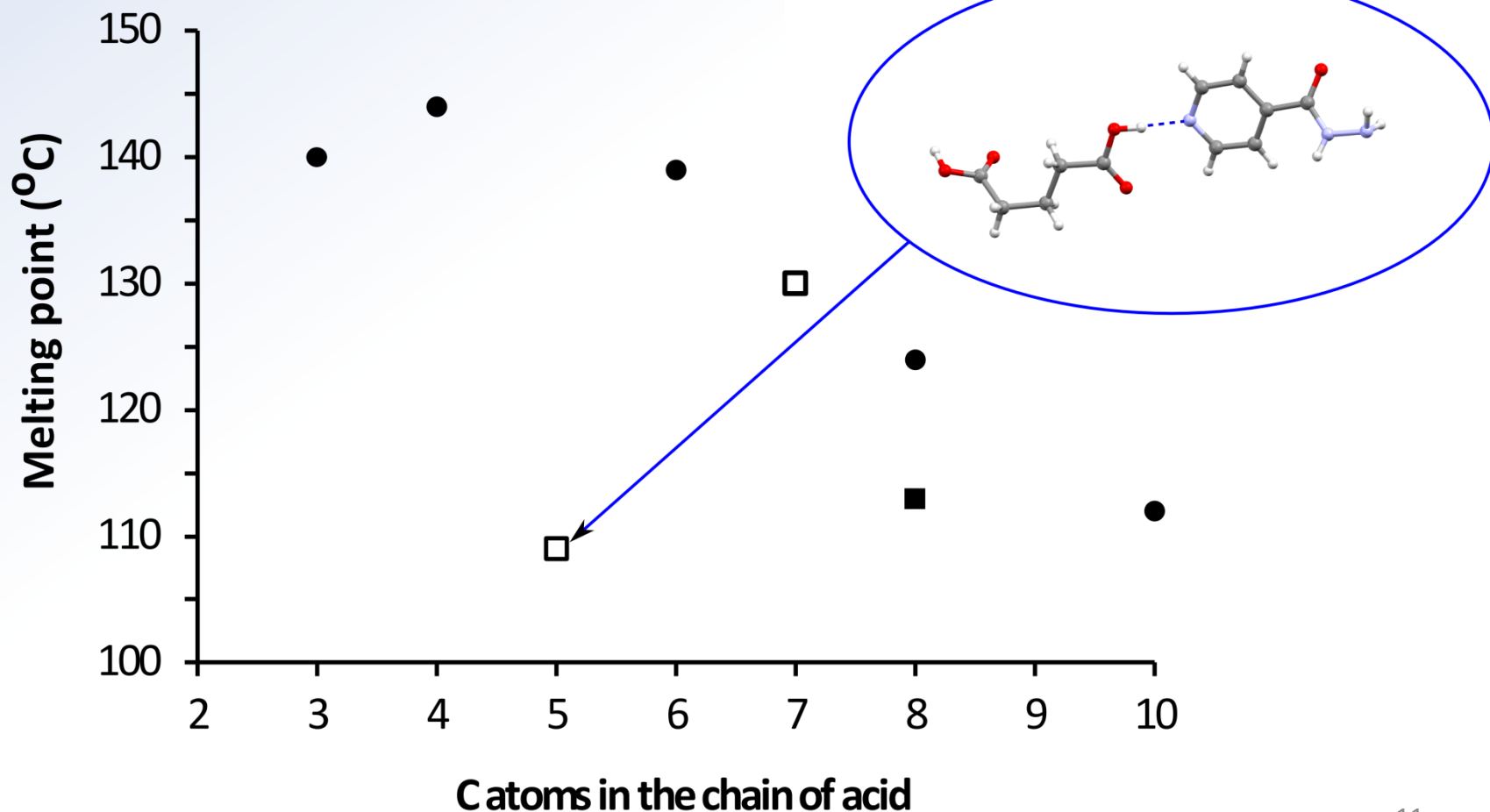
- Chain synthons in cocrystals with odd chain acids
- 1:1 stoichiometry  
(isoniazid – malonic acid cocrystal has 2:1 stoichiometry)



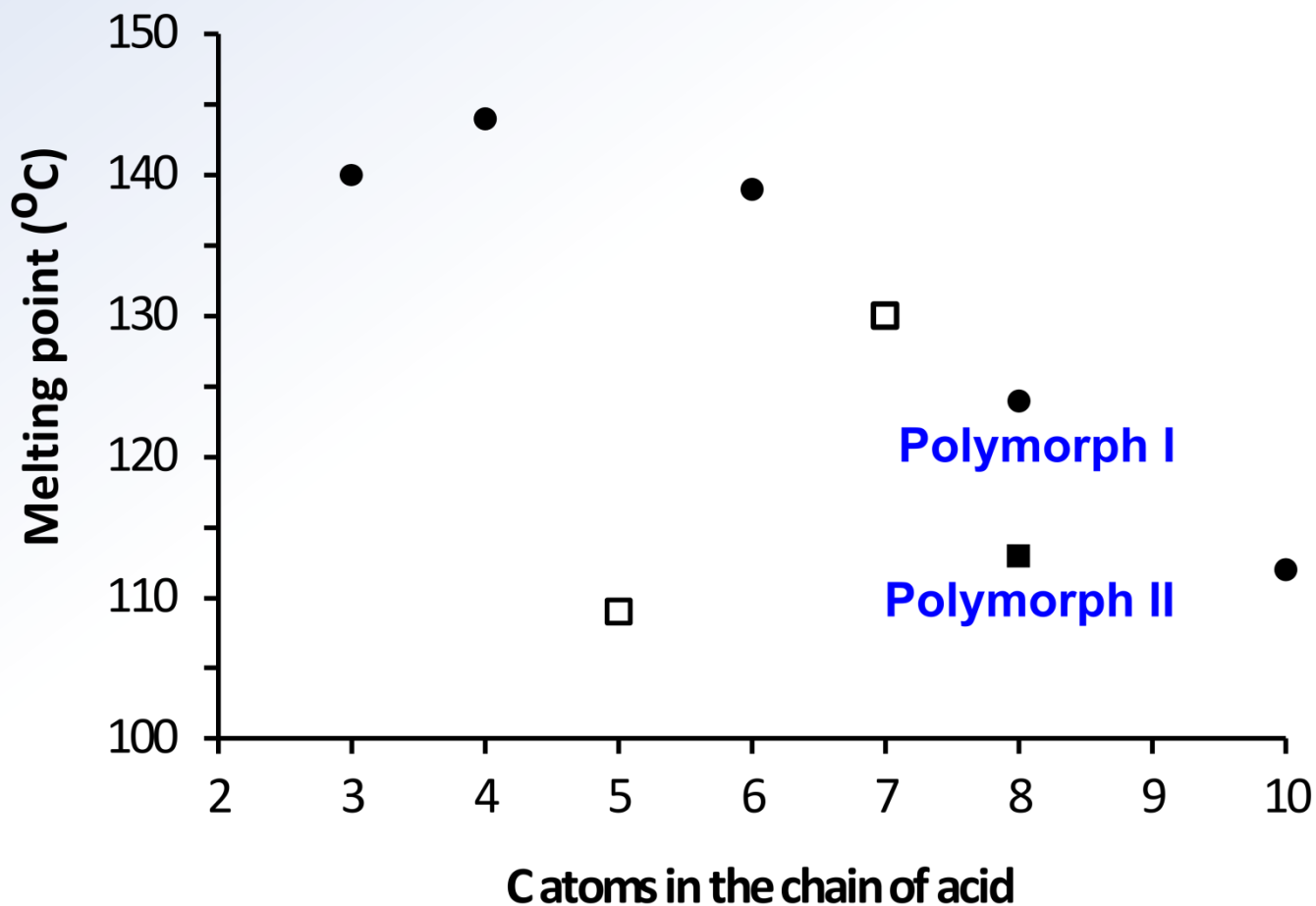
# Physicochemical properties of isoniazid cococrystals: melting points



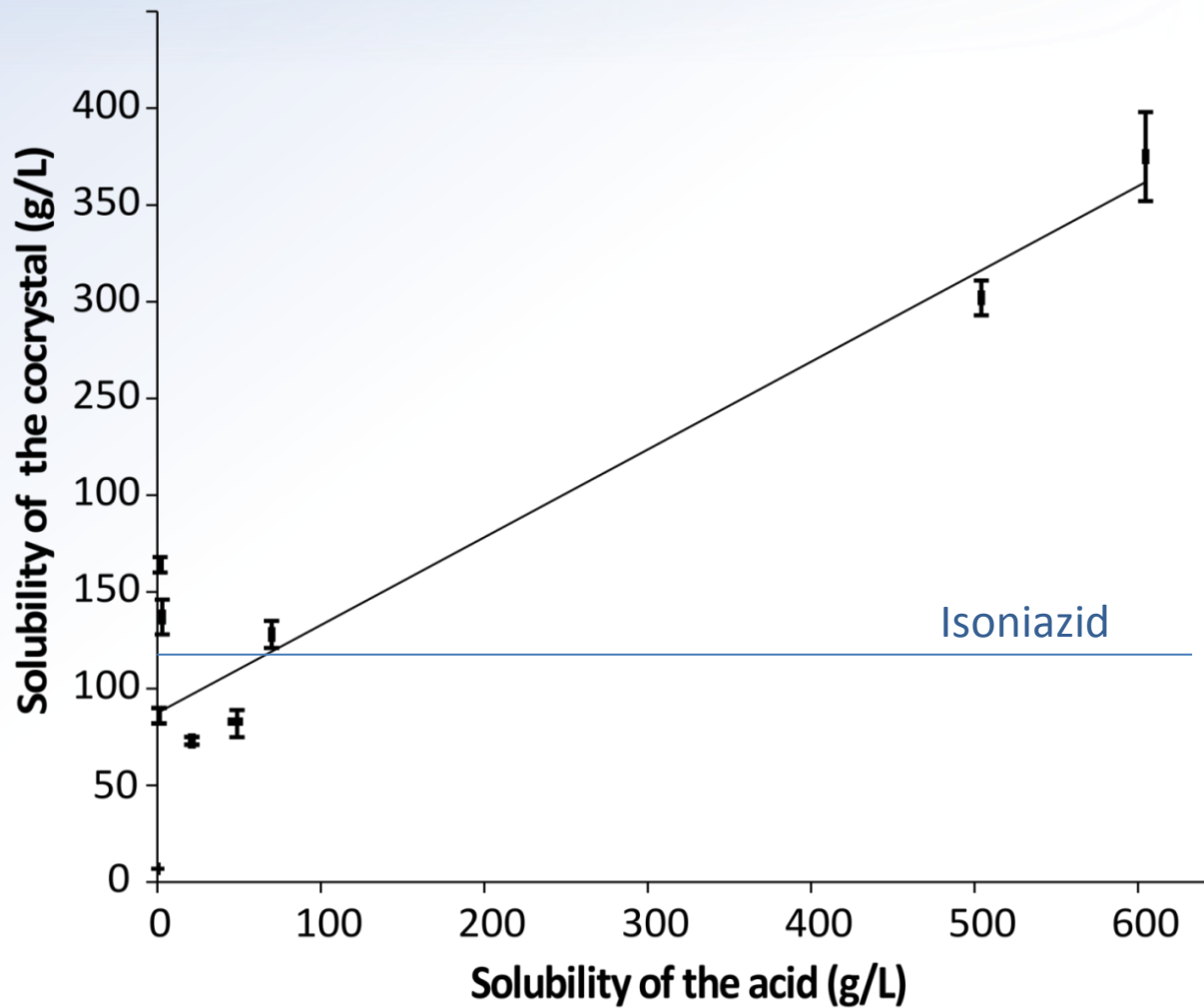
# Physicochemical properties of isoniazid cococrystals: melting points



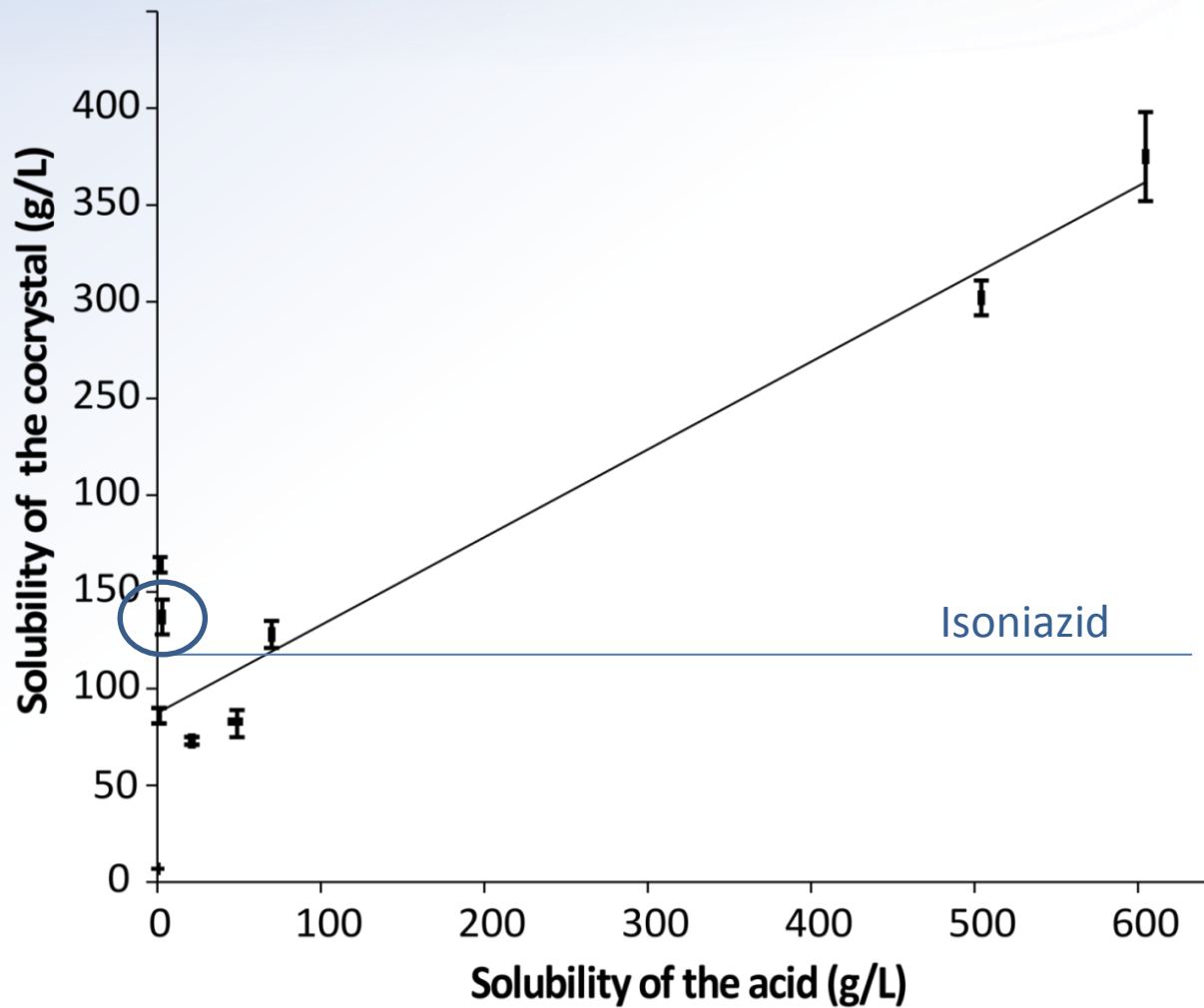
# Physicochemical properties of isoniazid cocryystals: melting points



# Physicochemical properties of isoniazid cococrystals: solubility

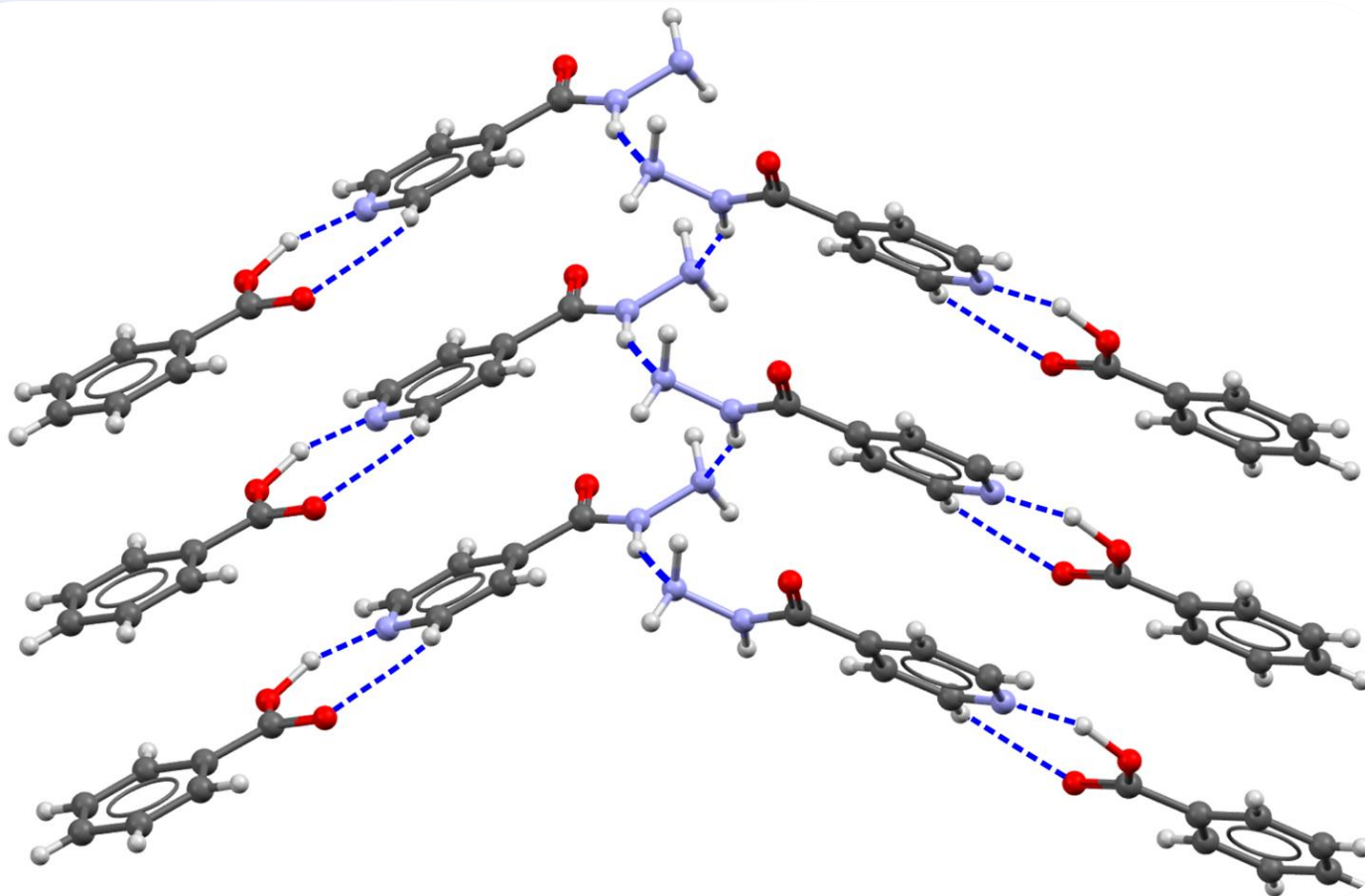


# Physicochemical properties of isoniazid cocrystals: solubility



# Crystal structure of isoniazid – benzoic acid cocrystal

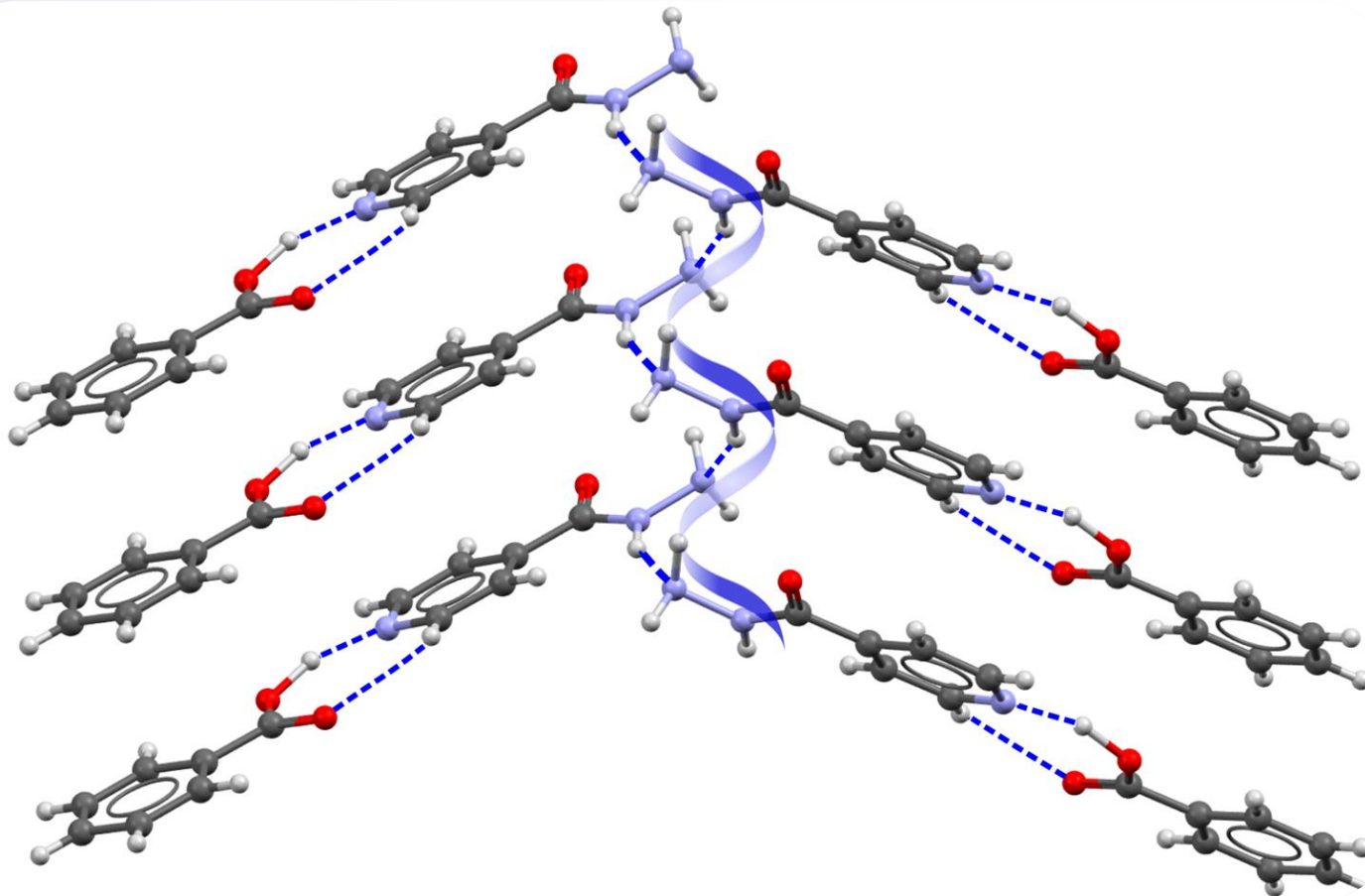
- Similarity to isoniazid crystal structure
- Chirality of the crystal structure





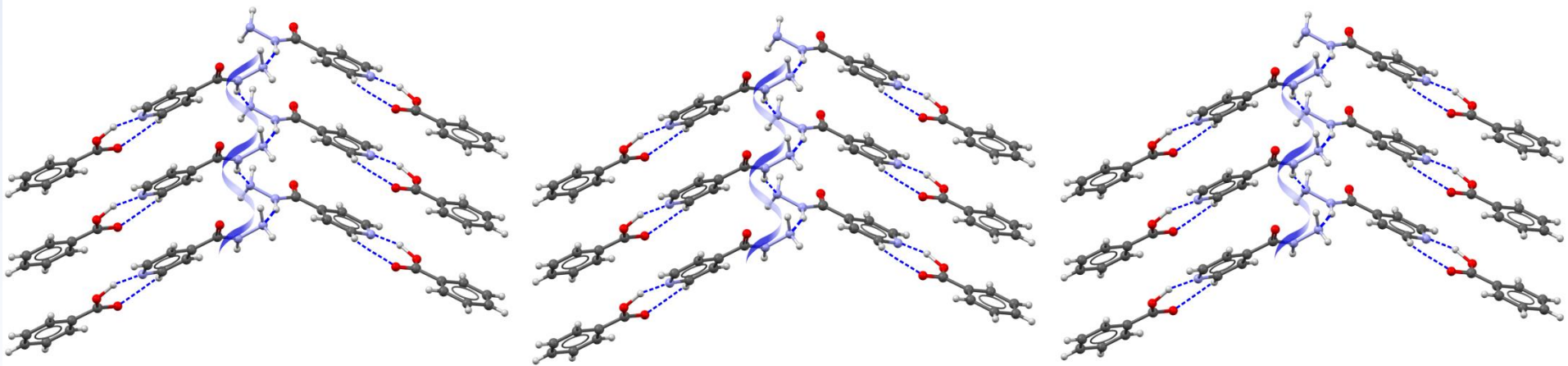
# Crystal structure of isoniazid – benzoic acid cocrystal

- Chirality of the crystal structure



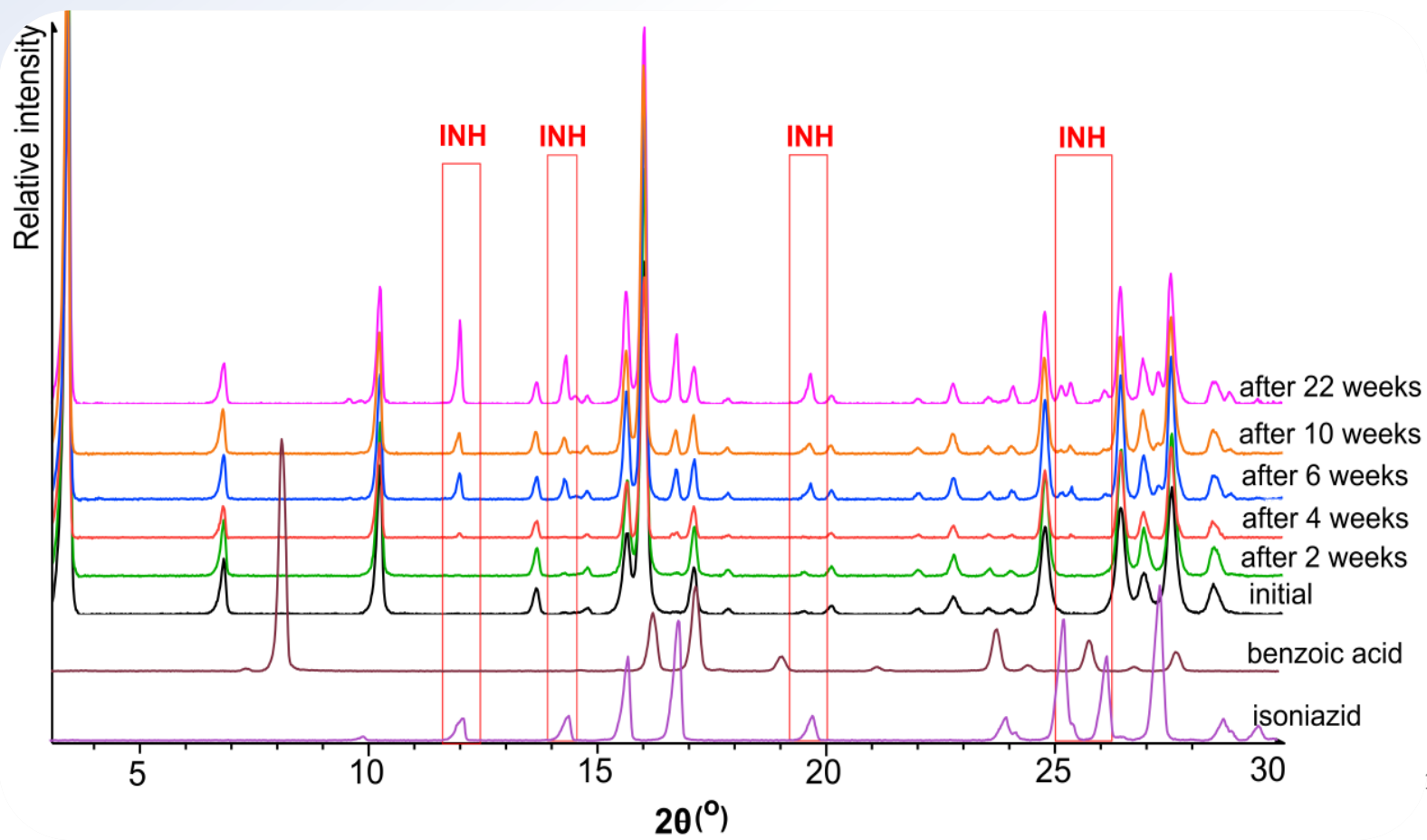
# Crystal structure of isoniazid – benzoic acid cocrystal

- Chirality of the crystal structure



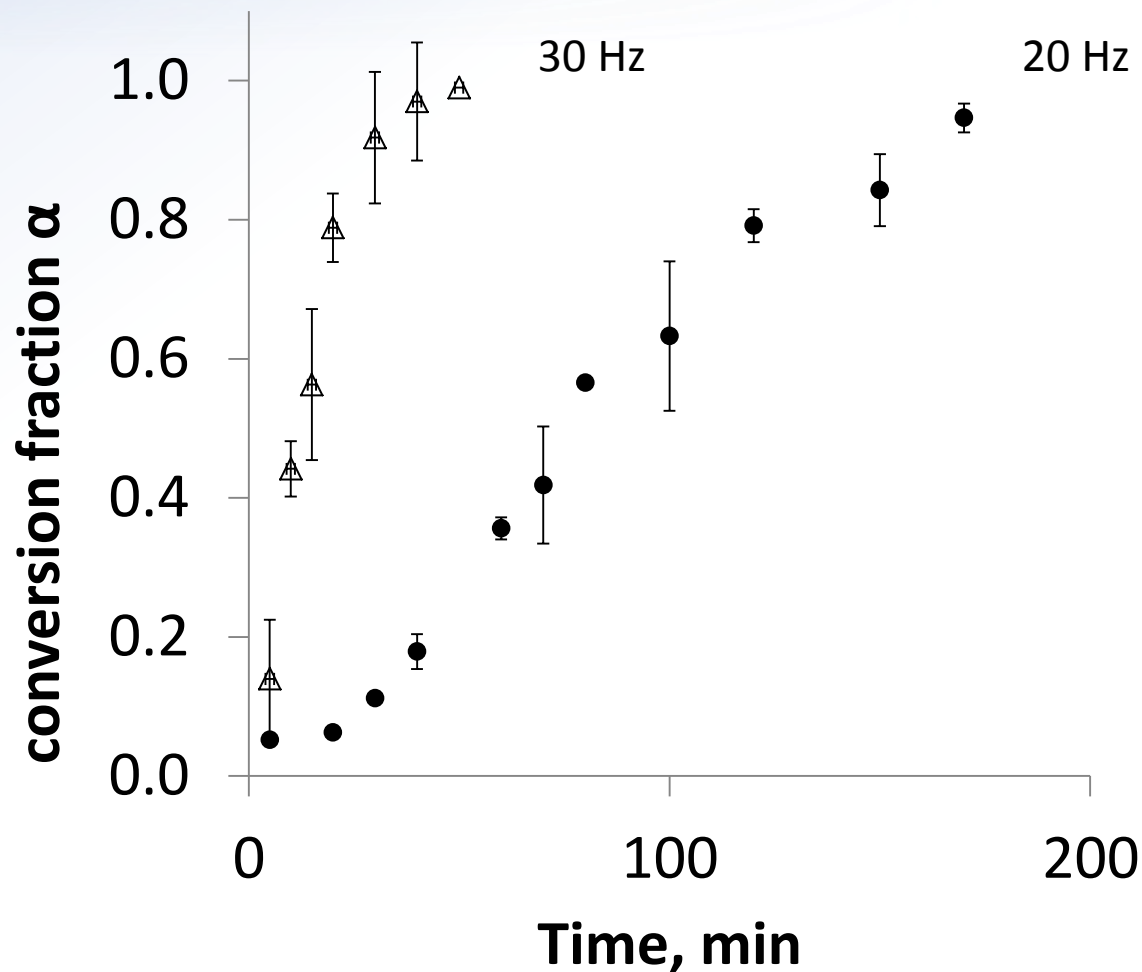
# Stability of isoniazid – benzoic acid cocrystal

Decomposition of isoniazid – benzoic acid cocrystal at  
75% RH, 30 °C:



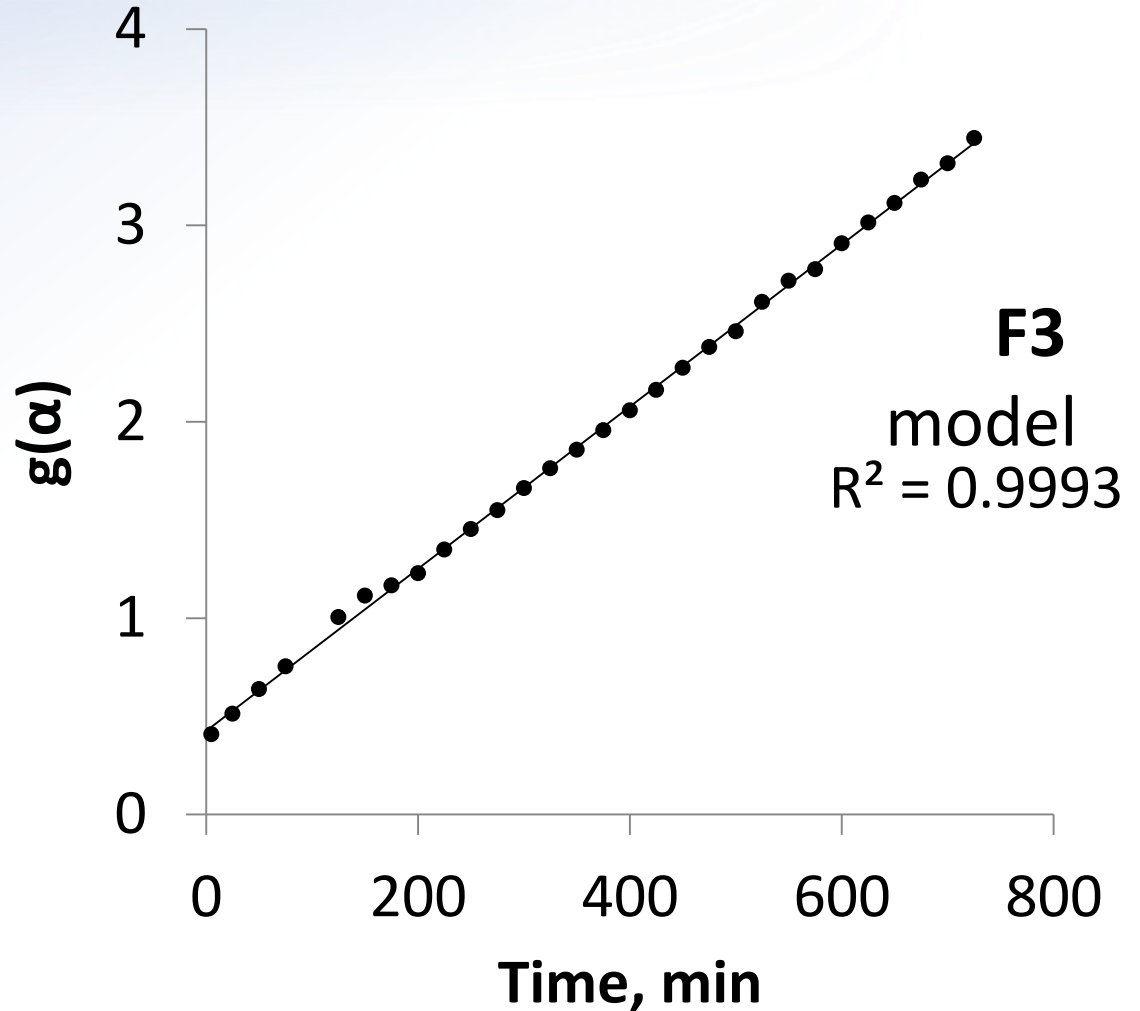
# Kinetics of isoniazid – benzoic acid cocrystal mechanochemical formation

- Without solvent addition
- 2 mmol isoniazid + 2 mmol benzoic acid
- 5 ml grinding jars



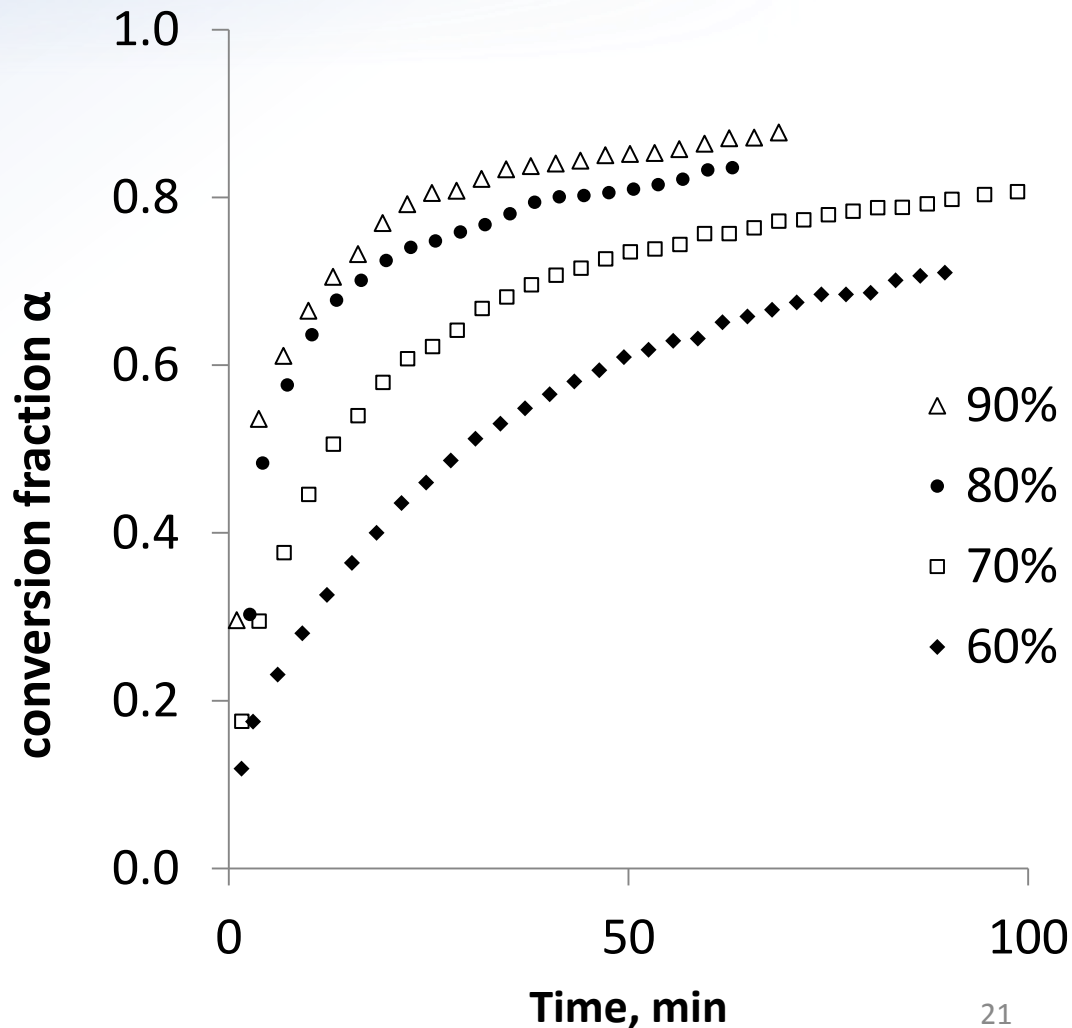
# Formation of the cocrystal after milling

- Sample: 20 Hz, 60 min, no solvent
- Ambient conditions (20% RH, 22°C)

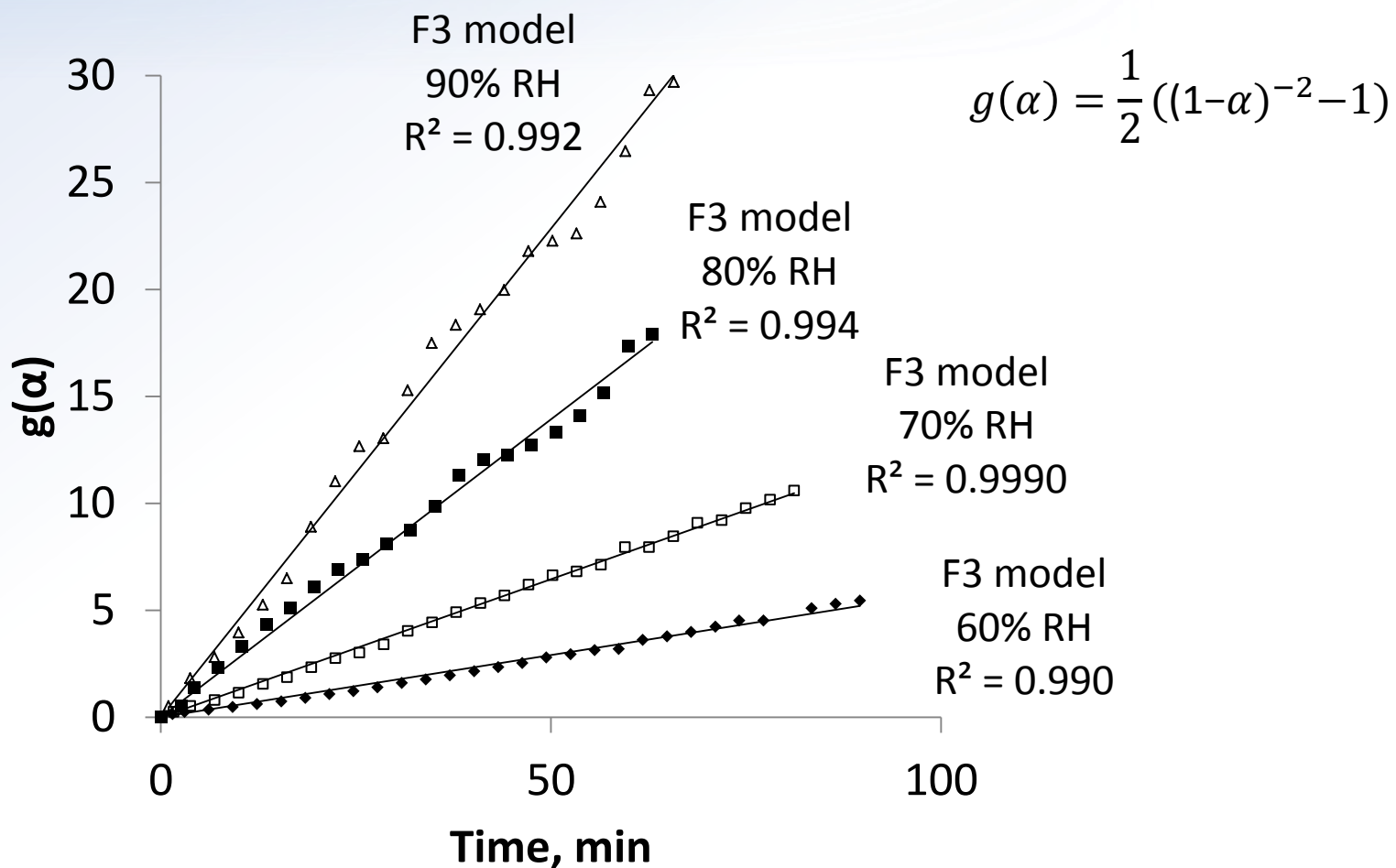


# Mechanochemically initiated formation of the cocrystal at elevated humidity

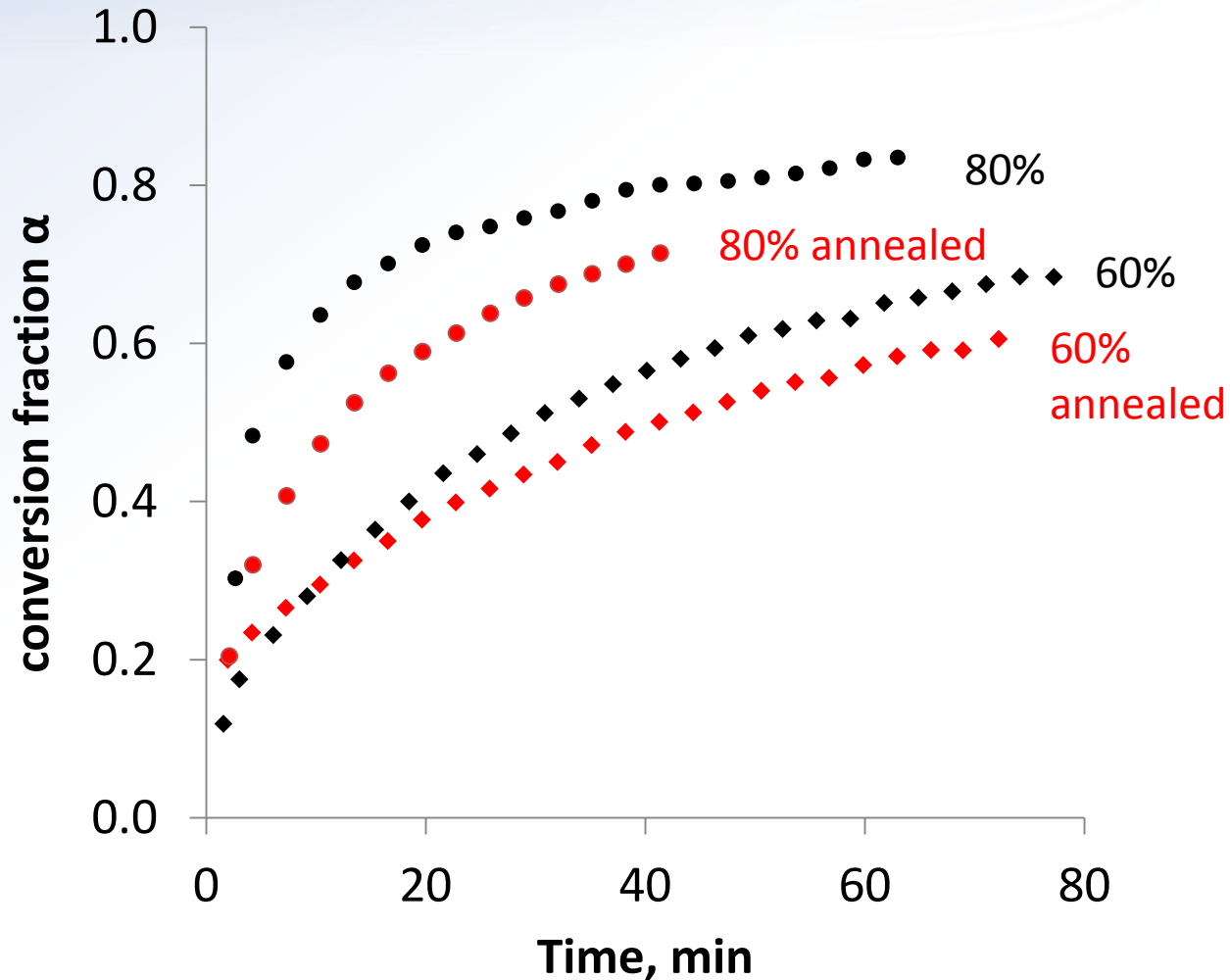
- Sample: 30 Hz, 5 min, no solvent
- 30°C, different RH (60%, 70%, 80% and 90%)



# Mechanochemically initiated formation of the cocrystal at elevated humidity



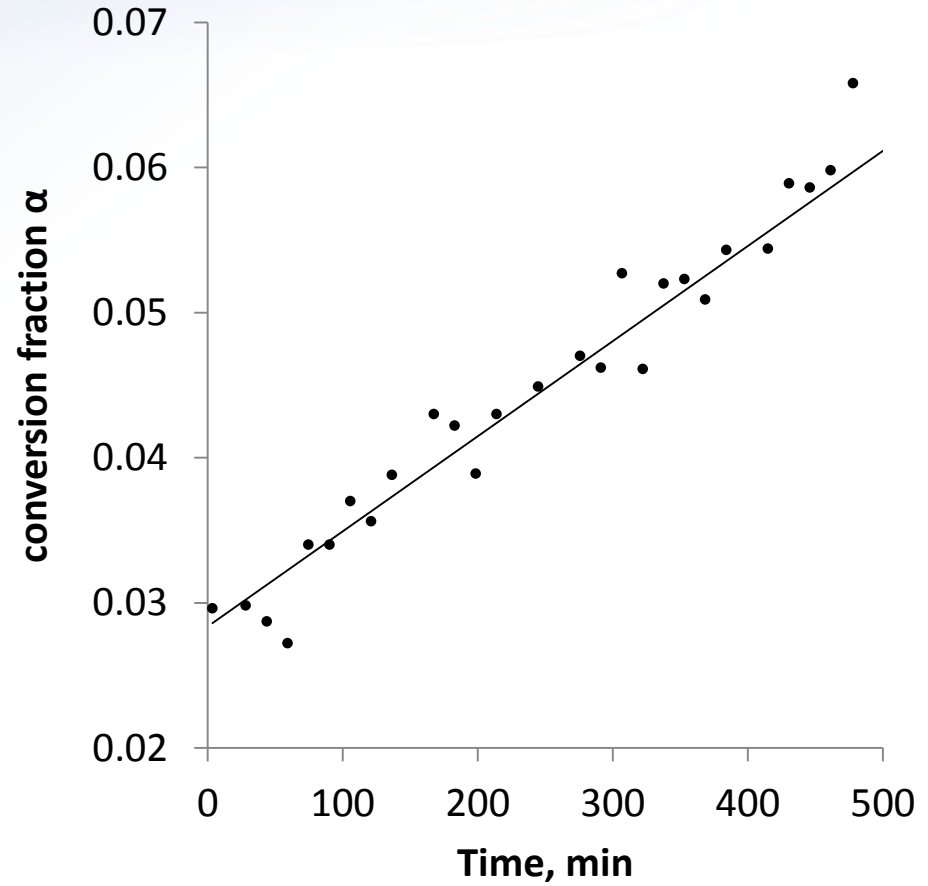
# Mechanochemically initiated formation of the cocrystal at elevated humidity: effect of annealing





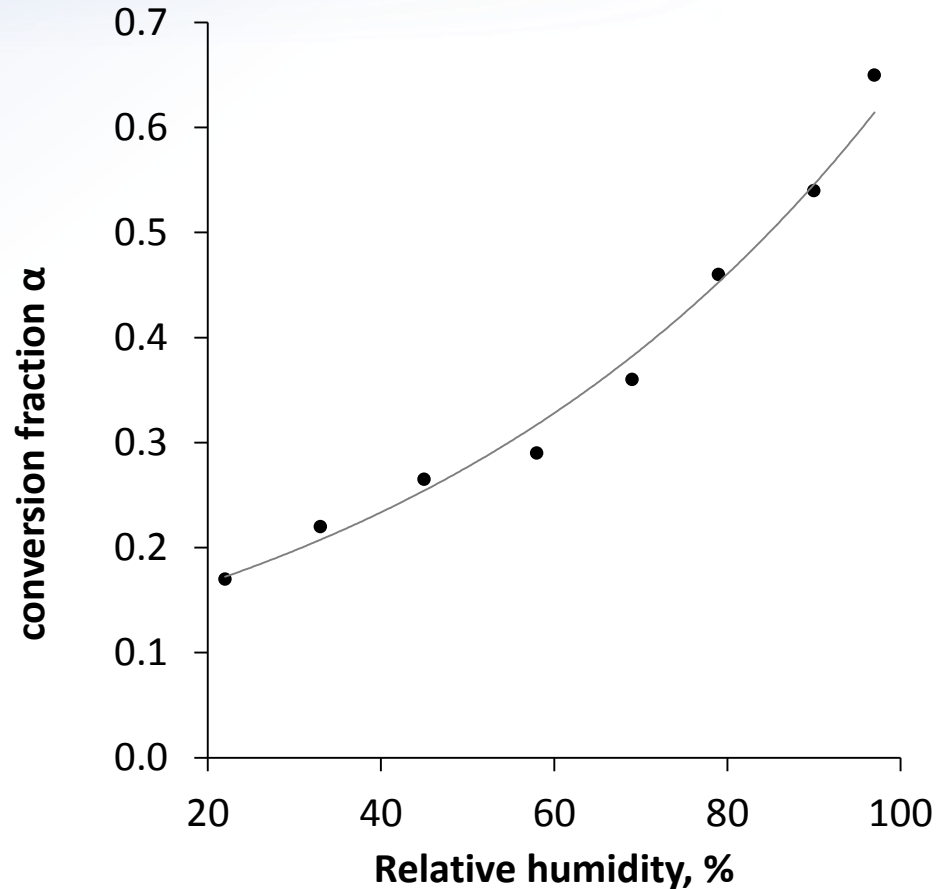
# Formation of the cocrystal at elevated humidity (90% RH)

- Sample:  
no milling
- 30°C, 90% RH



# Formation of the cocrystal at elevated humidity

- Sample:  
no milling
- 30°C, RH: 22%-97%





# Summary

- Cocrystallization of isoniazid with carboxylic acids results in pyridine-carboxyl synthon containing cocrystals.
- Physicochemical properties depend on hydrogen bonds and molecular structures of both components in the cocrystal.
- Similar hydrogen bonding motifs in crystalline isoniazid and isoniazid – benzoic acid cocrystal affects the stability of this cocrystal.



# Summary

- The rate of mechanochemical cocrystallization of isoniazid with benzoic acid is a function of milling frequency.
- Isoniazid – benzoic acid cocrystal forms at elevated humidity and the formation kinetics depend on RH.
- The annealing of a cocrystal reduces the rate of cocrystallization.

# Acknowledgements

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