Mechanochemical Syntheses of Nicorandil Cocrystals and Characterization by ^{14}N SSNMR

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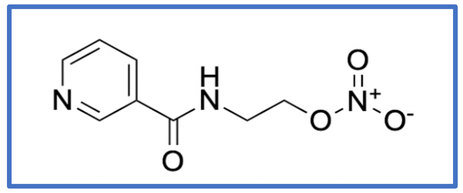
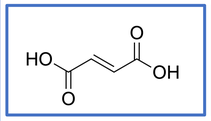
Introduction

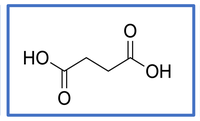
- Previous research identified four cocrystals of nicorandil (Ncr), with dicarboxylic acids: oxalic acid (Oxa), fumaric acid (Fum), succinic acid (Suc), and suberic acid (Sub).[1-2]
- Nicorandil ($C_8H_9N_3O_4$) is a drug used to treat angina pectoris.



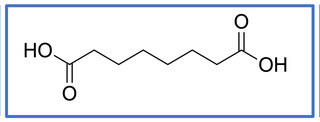
Nicorandil



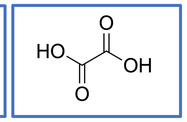
Fumaric Acid



Succinic Acid



Suberic Acid



Oxalic Acid

Methods

- Nicorandil was ball milled with different dicarboxylic acids in stoichiometric molar ratios (*e.g.*, 1:1, 1:2, *etc.*), using a small amount of solvent (*i.e.* 20 μL) to facilitate the reaction (*i.e.*, liquid assisted grinding or LAG).[3-5]
- Resulting microcrystalline powders were collected and analyzed using powder X-ray diffraction (PXRD) to confirm cocrystal formation.
- Samples that were identified as API cocrystals were characterized using ^{14}N SSNMR experiments at the National High Field Magnetic Laboratory.[6]

Retsch Mixer Mill MM 500 Vario

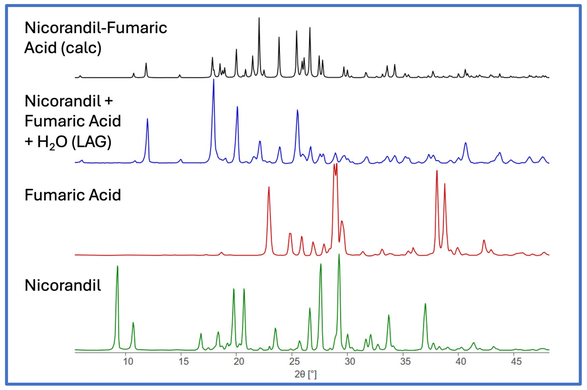
Objectives

- To investigate if nicorandil cocrystals can be made in high yields and purity using mechanochemical synthesis.
- To characterize the cocrystals with PXRD and solid-state nuclear magnetic resonance (SSNMR) techniques.
- To expand these methods to the synthesis of cocrystals covering a wider range of APIs and coformers.

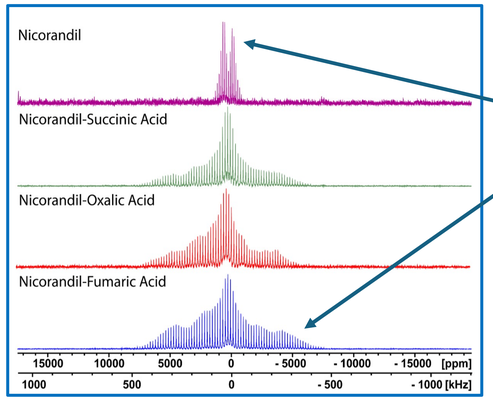
Mechanochemical Synthesis

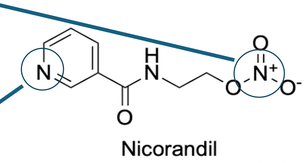
- Mechanochemistry is a beneficial method for synthesizing cocrystals.[7]
- It can be easily upscaled for manufacturing of pharmaceuticals and is more efficient than alternative slow evaporation methods, which can take days or weeks whereas milling takes minutes.
- Cocrystal synthetic parameters:
  - Teflon milling jars
  - 1 Teflon 12 mm ball bearing
  - Reactants placed in jars with 20 μL of each solvent
  - Milled at 35 Hz for 30 min for NcrOxa, NcrFum, & NcrSuc
  - Milled at 30 Hz for 30 min for Ncr_2Sub

PXRD and ^{14}N SSNMR Results



Rigaku MiniFlex





Nicorandil

The pyridine forms a hydrogen bond with the acidic proton of the coformer, resulting in a narrower ^{14}N powder pattern that can be easily acquired.

Conclusions

- Four reported cocrystals, NcrOxa (1:1), NcrFum (1:1), NcrSuc (1:1), Ncr_2Sub (2:1) were synthesized with mechanochemistry.
- A hemihydronitrate salt ($NcrH:Ncr:NO_3$) was also formed with nicorandil and HNO_3.

Future Directions

- Try to synthesize other cocrystals of APIs using mechanochemistry.
- Further explore the utility of ^{13}C, ^{14}N, ^{15}N, and ^{17}O SSNMR for other solid forms of other APIs.

References and Acknowledgements

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