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Milling for better pharmaceuticals: green synthesis, phase transformations and reaction kinetics of vitamin B_3:C cocrystal polymorphs studied in situ

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The use of mechanochemistry continues to grow due to its efficiency, selectivity and greener way in obtaining desired products. Inability to directly and in real-time monitor reaction progress of milling reactions, without the need to obstruct the milling process, was historically considered as a main drawback of mechanochemistry. This has been recently addressed by advanced synchrotron powder X-ray diffraction[1] and laboratory Raman spectroscopy[2] in situ monitoring methods which provided a direct insight into physical and chemical changes in reaction mixtures. Utilization of mechanochemistry in pharmaceutical industry is driven primarily by increasing need to create more sustainable drug manufacturing processes. Here we present mechanistic study of mechanochemical cocrystal synthesis of nicotinamide (vitamin B_3) and L-ascorbic acid (vitamin C).

Using ethanol and methanol as additives in milling 1:1 reaction mixture we have obtained two vitamin B_3:C cocrystal polymorphs. Kinetically favored polymorph I is known from the literature[3] and is in fact intermediate in the formation of previously unknown polymorph II which is thermodynamically more stable. We have successfully solved crystal structure of B_3:C cocrystal polymorph II from synchrotron powder X-ray diffraction data.

Both polymorphs remained in their respective solid forms even after 6 months of shelf life. Thermodynamic relationship of cocrystal polymorphs was determined by competitive slurry experiment which resulted in pure cocrystal polymorph II. Scaling up manufacturing process for both cocrystal polymorphs up to 10 grams and 100 grams has been achieved using planetary mill and twin screw extruder, respectively. Mechanochemically obtained cocrystal polymorphs exhibit excellent tableting properties compared to their reactants. This is important since L-ascorbic acid is famous for having poor compactible properties. Solution cocrystalization experiments resulted always in kinetically favored polymorph I, whereas the thermodynamically more stable polymorph II is available exclusively by mechanochemical milling.

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References:

[1] T. Friščić, I. Halasz, P. J. Beldon, A. M. Belenguer, F. Adams, S. A. J. Kimber, V. Honkimaki, R. E. Dinnebier, Nature Chemistry 2013, 5, 66–73.
[2] D. Gracin, V. Štrukil, T. Friščić, I. Halasz, K. Užarević, Angew. Chem. Int. Ed. 2014, 53, 6193−6197.
[3] X. Mei et al., Chem. Commun. 2016, 52, 13452-13455.

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