Oral presentation

Decocrystallization as a new route to elusive polymorphs

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Many polymorphic forms of organic compounds, in particular of drug molecules, are notoriously difficult to crystallize. This often hinders their crystal structure characterization and hence also our understanding of polymorphism and crystallization phenomena. We have recently developed a protocol for reliable crystallization of three elusive polymorphs of meloxicam (MLX), an anti-inflammatory drug [1], which led to their crystal structure determination [2]. All of these forms, MLX-II, III and V were accessible in pure forms only through desolvation of the parent solvates, which is not uncommon, and has been also observed for example for a number of polymorphs of galunisertib [3]. In the search for new crystallization routes, inspired by desolvation experiments, we envisaged that elusive polymorphs (and possibly yet undiscovered crystal forms) can be accessed through cocrystals of a parent drug with easily sublimating coformers, a process we called decocrystallization. Having obtained several new binary systems of MLX with pyrazole (POL), pyrazine (PNA) and imidazole (IMI), we report here our first discoveries from the performed decocrystallization experiments.

The most interesting results were obtained for two polymorphic forms of MLX:POL 1:1 cocrystals. Decocrystallization of CC1 (cocrystal form I) led to MLX-I, which is the most thermodynamically stable form of MLX, even at relatively mild conditions (heating at 90°C for 30 minutes). However, upon decocrystallization of CC2 (cocrystal form 2), elusive MLX-V could be obtained (**figure 1**), provided that a sample of high crystallinity was taken for the experiments. The CC2 form can be obtained either *via* mechanochemical grinding of 1:1 molar ratio of components in a ball mill (sample MM200) or *via* melting of MLX with an excessive amount of POL (sample MELT). Although both preparation methods led to the same crystal phase, the PXRD reflexes for the MM200 sample were much broader, with significantly lower number of counts and somewhat higher background than for the MELT sample. Upon decocrystallization at the same conditions the MM200 sample converted quickly to MLX-I, while the MELT sample converted to MLX-V. This can be explained by a certain degree of amorphization of the ground sample, with an amorphous phase easily recrystallizing to the most thermodynamically stable MLX-I and driving any further transformation of MLX crystals to this very form.

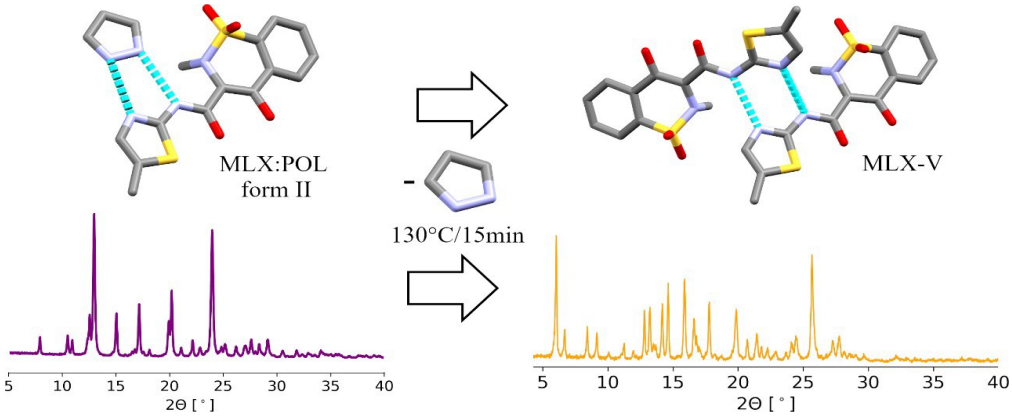

Figure 1. PXRD patterns and main hydrogen bond interactions in MLX:POL CC2 and MLX-V.

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[2] Jeziorna, A., Malinska, M., Sugden, I., Paluch, P., Dolot, R. & Dudek, M. K. (2024). *submitted*

[3] Bhardwaj, R. M., McMahon, J. A., Nyman, J., Price, L. S., Konar, S., Oswald, I. D. H., Pulham, C. R., Price S. L. & Reutzel-Edens, S. M. (2019).*J. Am. Chem. Soc.*, **141**, 13887.

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