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Solvent-free methods for controllable synthesis of metastable pharmaceutical solids

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Mechanochemistry and vapor-induced transformations of solids have recently drawn attention as green and energy-efficient synthetic alternatives to classic solution procedures. Despite their growing importance and wide application in synthesis and transformation of various materials, from inorganic nanoparticles to soft supramolecular solids, mechanisms and kinetics of these solvent-free reactions are only now becoming unveiled through development of in situ monitoring methods based on powder X-ray diffraction (PXRD) [1] and Raman spectroscopy.[2] These advanced techniques allowed a real-time insight into mechanochemical and vapor-induced reactions without the need to interrupt them, revealing multi-step mechanisms often involving amorphization, recrystallization and various phase transformations.
This talk will focus on the potential of mechanochemical reactions and vapor-induced transformations of solids for rapid, controllable and efficient synthesis of different cocrystal forms of active pharmaceutical ingredients (APIs),[3] presented here on the example of two model APIs, nicotinamide and carbamazepine. In situ monitoring by synchrotron or laboratory PXRD, combined in some instances with Raman spectroscopy, revealed particularly dynamic mechanisms underlying these solvent-free reactions, where different metastable intermediate phases could be detected before formation of the final cocrystal product. We will show here how the correlation between the reaction conditions and the occurrence of particular crystal form could be successfully used for governing the solvent-free reaction and isolation of target metastable forms, some of which are not accessible from solution. Herein presented results demonstrate suitability of mechanochemistry and vapor-induced reactions for controllable synthesis of pharmaceutical materials, and also provide an important contribution to development of new kinetic models of their reactivity.
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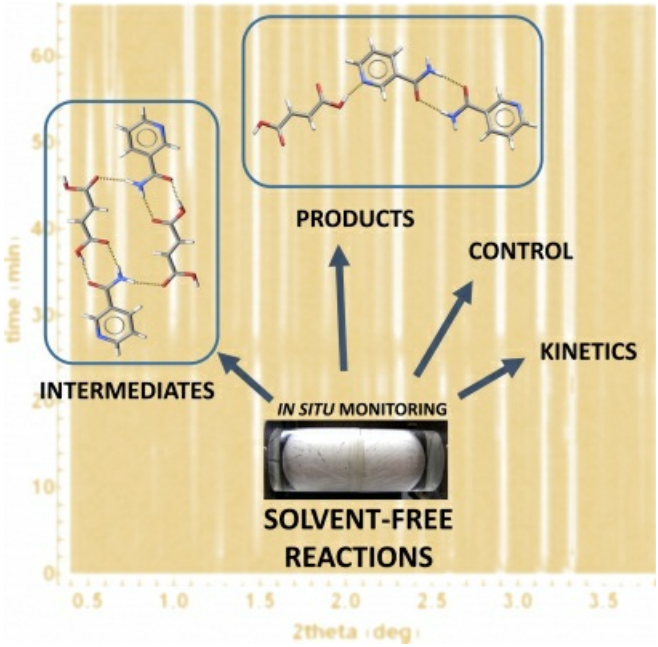

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