Harnessing the structural diversity of multicomponent crystals: strategies from synthesis to functional properties

M. Lopresti[1], A. Mirocki[2], L. Palin[1], M. Milanesio[1], A. Sikorski[2]

[1]Department of Science and Technological Innovation. University of studies of the Eastern Piedmont "Amedeo Avogadro",Viale Teresa Michel 11, 15121 Alessandria, Italy. [2] Faculty of Chemistry, University of Gdańsk, W. Stwosza 63, 80-308 Gdańsk, Poland.

mattia.lopresti@uniupo.it

The realm of multicomponent crystals, encompassing cocrystals, salts, and salt cocrystals, represents a frontier in crystal engineering for both materials science and pharmaceutical development, offering profound opportunities to tailor material properties and enhance drug efficacy. The complexity of these systems arises from the intricate interplay of molecular interactions, stoichiometry, polymorphism, and solvent effects, which collectively influence their structural landscape and functional characteristics. This contribute aims to illuminate the multifaceted world of multicomponent crystals, integrating recent advances in synthesis, structural analysis, and property modulation, as exemplified by recent research articles.

A significant focus is placed on mechanochemical approaches, including liquid-assisted grinding and dry grinding, which have demonstrated high yields and efficiency in producing targeted multicomponent forms such as drug-drug salts and cocrystals [1]. These methods enable access to otherwise elusive polymorphs and solvates, emphasizing the role of physical parameters, like stoichiometry and reaction environment, in directing crystallization pathways [1]. For instance, studies on the formation of double-drug salts involving ethacridine with salicylic and acetylsalicylic acids highlight how controlled synthesis conditions can stabilize specific hydration states and molecular arrangements.

Structural elucidation remains pivotal in understanding the nature of these materials. Techniques such as single-crystal and powder X-ray diffraction are employed to determine precise molecular packing, identify intermolecular synthons [2], and assess polymorphic variability. Complementary analyses, including Hirshfeld surface analysis and energy framework calculations [3], have provided deeper insights into packing motifs, interaction strengths, and the stability of different crystalline forms. These tools contribute not only to our fundamental understanding but also to the predictive capacity for designing new multicomponent materials.

Furthermore, the properties of these crystals, such as solubility, bioavailability, and stability, are intricately linked to their structural features. The ability to modify these properties through strategic co-former selection and stoichiometric adjustments paves the way for optimized drug formulations with enhanced therapeutic profiles. The examined systems, such as naproxen-acridine complexes, exemplify how molecular design combined with comprehensive structural analysis informs property tuning.

Ultimately, the integration of synthetic strategies, advanced characterization, and property evaluation encapsulates the multifaceted nature of multicomponent crystals for innovative applications. These efforts collectively advance our understanding of the complex crystallization landscape and open new avenues for tailored material design in materials science, pharmaceuticals and beyond. This presentation underscores the importance of an interdisciplinary approach, harnessing both classical and modern techniques, to explore and exploit the rich structural diversity inherent in multicomponent crystalline systems.

[1] Mirocki A., Lopresti M., Palin L., Conterosito E., Sikorska E., Sikorski A. & Milanesio M. (2024). *Sci. Rep.* **14**, 1834.

[2] Bombicz P., Gruber T., Fischer C., Weber E. & Kálmán A. (2013). *CrystEngComm.*, **16**, 3646.

[3] Mirocki A., Conterosito E., Palin L., Sikorski A., Milanesio M., Lopresti M. (2022). *Crystals*. **12**, 1573.

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