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BOOK OF ABSTRACTS

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Beyond Molecules: How Electron Density Guides Cocrystal Design for Better Therapeutics

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Analysing the electron density distribution of pharmaceutical co-crystals provides detailed information on the bonding and non-bonding interactions between molecules, which are crucial for understanding its stability, solubility, and bioavailability properties. Examining how electrons are distributed and how they influence intermolecular interactions is an important step towards the optimization of the physical properties of the cocrystal, leading to better drug design and performance. These applications could lead to more effective and reliable treatments for patients, especially in regions where drug stability is a significant concern due to environmental factors. As a case of application we will discuss the application of the experimental and theoretical electron density distribution analyses for the design of robust combination therapies involving the drug-drug cocrystal of the antifungal prodrug 5-Fluorocytosine and the tuberculostatic drug Isoniazid. This Drug-drug cocrystal was design for the treatment of cases of coexistence of invasive fungal infections and tuberculosis, mainly in immunocompromised patients. It shows superior phase stability properties against moisture which is beneficial for storage and transportation in tropical climates, extending in this way its shelf life so it could be considered as a potential candidate for the treatment of concomitant fungal infections, tuberculosis, and cancer.

The recognition and manipulation of the supramolecular synthons are the key aspects to successfully design these kinds of solid forms. However, only few cases of drug-drug cocrystals have been reported in the literature because drug-drug cocrystals are considered as fixed-dose combination products, and hence, the active pharmaceutical ingredients involved need to be those which are usually co-administered, also presenting proper dosage.

Topological analyses of the charge density of this cocrystal were performed for both experimental and theoretical data (periodic and gas phase calculations), indicating good agreement between experiment and theory. The comparison with gas phase calculations enabled the evaluation of the charge redistribution upon cocrystallization as well as the effect of the intermolecular interactions. In this manner, it was possible to evaluate the variations in bond distances and electron density at the bonds involved in the intermolecular heterosynthon. Through the analysis of the laplacian of the electron density it was also possible to have insights on the charge redistribution when both molecules crystallize together. Electrostatic potential maps calculations will also be discussed. HAR partition model for 5FC:INH were also calculated using ORCA 5.0, at the M062-X/def2-TZVP level of theory, assuming two asymmetric units in the refinement as means to take into account the F...F and F...H contacts.

[1] C. B. Pinto *et al.* Cryst. Growth Des. ***2024***, [***https://doi.org/10.1021/acs.cgd.4c00401***](https://doi.org/10.1021/acs.cgd.4c00401)

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