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BEYOND MOLECULES: HOW ELECTRON DENSITY GUIDES PHARMACEUTICAL SOLID DESIGN FOR BETTER THERAPEUTICS

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Developing solid-state modifications is a robust method to improve the physicochemical properties of active pharmaceutical ingredients. Deeply understanding the particularities of the target molecule is key to rationally planning which modification will enhance those properties. As an example, we present the design, development, structural characterization and electron density distribution study of several new solid forms of Rilpivirine (RPV), a diarylpyrimidine derivative antiretroviral drug with high conformational flexibility belonging to a group of second-generation non-nucleoside reverse transcriptase inhibitors (NNRTIs) used in the treatment of HIV. The role of Artificial Intelligence (AI) and Machine Learning (ML) methods in the development of tailor-made materials is hard to overstate. The application of deep learning models to materials design has boosted the discovery of new functional materials in the recent years. In a direct partnership with the Cambridge Crystallographic Data Centre (CCDC), we applied new computational screening tools as a starting point for the application of innovative 3D vortex-slurry mechanochemical supramolecular synthesis methods resulting in several new solid forms of RPV, including organic and inorganic salts as wells as cocrystals. This approach integrates the benefits of slurry and mechanochemistry within a unique 3D thermodynamic environment not achieved by traditional 1D or 2D milling. The structures of these solid were analyzes by In-house Single Crystal X-ray diffraction methods as well as studies at Manacá Beamline at the Brazilian synchrotron facility and Micro Electron Diffraction. Since the rational design of pharmaceutical solid forms depends on a detailed understanding of the intermolecular interactions, analysis of electronic distribution emerges as a central tool in this process, allowing for the precise characterization of the covalent and non-covalent interactions that govern its formation and stability. Such analyses are crucial for correlating the electronic structure with its physical properties. As such Hirshfeld Atom Refinement (HAR) methods were applied to improve the refinement parameters within the NoSpherA2 module of Olex2 [1]. To recover the physical meaning of the charge density model in the wavefunction generated by HAR, X-ray Constrained Wavefunction refinement techniques (XWR) were applied. These results show that quantum crystallography, combined with solid-state design of solid forms, could be a useful approach for understanding the nature of the intermolecular interactions. This approach provides valuable information that could eventually be fed back into the ML methods to improve the prediction of solid-state interactions and, consequently, the design of novel materials.

References:

[1] Kleemiss, F. Dolomanov, O. V.; Bodensteiner, M. et al., *Chem. Sci.,* **2021,** 12, 1675-1692.