

Identifying mistakes in cocrystal structures

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Pharmaceutical solid-state forms, such as salts and cocrystals, play a crucial role in drug development due to their impact on bioavailability, stability or dissolution rates. The difference between salts and cocrystals is primarily given by the position of a single hydrogen atom [1]. Regulatory agencies, such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA), have established guidelines that emphasise the importance of accurately identifying and characterising the pharmaceutical phase to ensure consistency in quality, efficacy, and safety [2,3].

In our previous work, we partially tested a density functional theory (DFT)-based method for salt–cocrystal differentiation. However, this earlier study was limited only to 95 structures and used the PBE functional, which exhibited limitations in cases of strong hydrogen bonds [4]. In our present work, we significantly expanded the dataset to 404 cocrystal models and improved the computational methodology by employing the rSCAN functional for the primary screening. We confirmed that 301 structures were indeed cocrystals. For 87 structures we had identified that the phase determination is suspicious, and the structures probably create a salt-cocrystal continuous phase. Additionally, 16 structures were identified as salts, in disagreement with original experimental data interpretation. These problematic cases were further investigated through experimental methods, including collection of data using single-crystal X-ray diffraction (SCXRD). To get the best possible hydrogens positions, we used Hirshfeld Atom Refinement (HAR) as implemented in Olex2 software and NoSpherA2 [5-8]. Crystallization experiments were successfully reproduced for 7 of these cases, while complete experimental datasets from the original authors were available for 2 additional structures, allowing data re-interpretation. We also evaluated whether in these problematic cases, more advanced functionals (r2SCAN, PBE0, PBE50) could provide results consistent with experimental data.

The findings revealed that rSCAN occasionally provided unreliable results for strong hydrogen bonds; however, the discrepancies were often corrected by using better-renormalized or hybrid functionals, such as r2SCAN, PBE0, and PBE50. Among the structures exhibiting salt-like behavior, five were confirmed as salts. Our results suggest that the r2SCAN functional offers a reliable balance between accuracy and computational efficiency, particularly for O–H···N bonds longer than 2.554(5) Å [9].

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