

Using charge density to understand structure-property relationships in pharmaceutical co-crystals

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Co-crystals have emerged over recent years as a promising way to modify the properties of a compound through judicious selection of a co-former molecule. Hence they provide attractive new and alternative solid forms particularly in pharmaceutical applications, using active pharmaceutical ingredients (APIs). Traditional design strategies utilise supramolecular synthons facilitated by strong hydrogen bonding interactions, chosen depending upon the functional groups present in the molecule of interest. If no, minimal, or only restricted (through sterics) functional groups are present on a molecule the design is more challenging. Studies on such molecules are limited and primarily use trial and error-based methods for co-former selection hence, an alternative method is required.

Two contrasting APIs have been studied. One, lisdexamfetamine, contains a typical hydrogen bonding functional group (carboxylic acid) for which a supramolecular synthon approach is appropriate, whilst the second, propyphenazone, contains only a single, sterically hindered, hydrogen bond acceptor group (carbonyl) and no donor groups. Co-former selection for propyphenazone required an alternative prediction methodology and a knowledge-based design strategy was designed and implemented.¹

Both systems resulted in a number of new multicomponent materials including co-crystals, salts and solvated forms. All were characterised using X-ray diffraction techniques with physicochemical properties measured, thus allowing comparisons between the different materials to be realised and structure-property relationships to be analysed.

Charge density studies allow analysis at the electronic level, particularly regarding the nature of the interactions occurring between the different molecules through property calculations at bond critical points (BCPs). A systematic approach has been taken with the two systems, applying small changes to the co-former structure and investigating its effect via the resulting electronic distribution. Using a series of related structures, trends can be identified and thus rules for co-former selection / physicochemical property modification learnt.

[1] Mapp, L.K., Coles, S.J. Aitipamula, S. (2017). *Crystal Growth & Design*, 17, 163-174.

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