MS31-O5 *Ab initio* ^{35}Cl solid state NMR-based crystallography of active pharmaceutical ingredients.

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Active pharmaceutical ingredients (APIs) are commonly commercialised in the form of HCl salts; but, as crystalline solids, they frequently exhibit polymorphism. The polymorphic forms may have different physico-chemical properties and the use of the undesired polymorph in a drug could produce catastrophic consequences, not to mention the economic cost. Therefore, knowledge about API polymorphism and accurate structural determination are of great importance in drug development. Structural resolution of polymorphic structures by X-ray diffraction (XRD) can be challenging, especially if single-crystal samples are not available (*e.g.*, for drugs with an API in an amorphous phase).

In this contribution, we show that experimental –^{35}Cl solid state NMR spectroscopy– and computational –crystal structure prediction and first principles NMR calculations– techniques can be successfully combined to study HCl API polymorphism. We establish a protocol for *ab initio* chlorine-35 solid state NMR crystallography of HCl APIs, see Figure 1. Crystal structure prediction techniques were used to produce a set of computationally generated trial crystal structures for a test set of HCl APIs and to inform about HCl APIs polymorphism trends. First principles ^{35}Cl solid state NMR shielding and quadrupolar tensors were calculated, within the periodic DFT-D/GIPAW framework, on a subset of low energy predicted crystal structures and the deviation of calculated ^{35}Cl NMR tensor parameters from the experimentally determined values allows the selection of a few predicted crystal structures as potential matches to the experimentally known reference structure. The true structure can be selected unambiguously from the set of computationally generated crystal structures when information about DFT-D relative stability is included. Moreover, the reliability of periodic DFT-D calculated dipolar and quadrupolar 35Cl NMR parameters of HCl APIs as well as the potential and limitations of *ab initio* ^{35}Cl solid state NMR crystallography on HCl APIs structure resolution will be discussed.

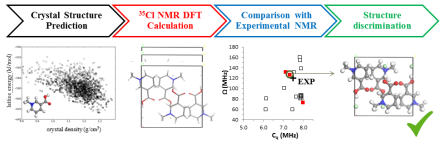

Figure 1. Schematic representation of the protocol for *ab initio* ^{35}Cl solid state NMR crystallography of HCl salts of active pharmaceutical ingredients.

Keywords: Crystal structure prediction, NMR crystallography, 35Cl NMR, DFT calculated 35Cl NMR, Active Pharmaceutical Ingredients.

MS32 Polymorphs, cocrystals, solvates, salts: a jungle for scientists and industries

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MS32-O1 Thymine and Orotic Acid - small molecules with unusual hydrates and intriguing solid state phenomena

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The two structurally related model compounds, thymine [1] and orotic acid [2], show both unique solid state phenomena, with solvate/hydrate formation playing a key role in accessing anhydrous forms and desolvation conditions inducing order-disorder/polytypism and influencing polymorph purity. The solid forms have been studied by a combination of complementary experimental techniques (moisture sorption analysis, thermal analysis, isothermal calorimetry, spectroscopy, X-ray diffractometry) and computational modelling (crystal energy landscape calculations).

Anhydrate polymorphs of thymine (TYM) emerged in an experimental search for solid forms, which was guided by crystal structure prediction studies. The packing mode of three of the four anhydrates, A° – C, only differ in the location of the oxygen and hydrogen atoms and are homeoenergetic. Forms A° and B are ordered phases, whereas C shows disorder (X-ray diffuse scattering). The computationally generated structures provide models for stacking faults, so that intergrowth is likely. Anhydrate A° was identified as the thermodynamically most stable form at ambient conditions. The forms B and C are metastable but show high kinetic stability. The hydrate of thymine is stable only at water activities > 0.95 at temperatures ≤ 25 °C. It was found to be a stoichiometric hydrate despite being a channel hydrate with an unusual water/thymine molar ratio of 0.8. Depending on the dehydration conditions, either anhydrate C or D is obtained. The hydrate is the only known precursor to form D.

The monohydrate of orotic acid (OTA) is a highly stable hydrate, which dissociates above 135 °C and loses only a small part of the water when stored over desiccants (25 °C) for more than one year. Depending on the desolvation conditions of the hydrate or DMSO solvate variability in the crystallinity/ordering of anhydrous OTA is observed, which is also suggested by the computed low energy crystal structures. The variability in anhydrate crystals is of practical concern as it affects the moisture dependent stability of the anhydrate with respect to hydration. These studies highlight the value of