MS35-P34 | Controlling the Salt-Cocrystal Continuum and pKa rule: The Multi-Drug Ionic-Cocrystals of Lamatrigine and Valproic Acid

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The rational design of molecular crystals requires that the structure and properties of a crystallization product could be successfully predicted from the knowledge of the structures and properties of its molecular components. Such goal is still to come and synthetic crystallographers must rely to practical rules of thumb to increase chances of success in their endeavours. One of such rule uses the difference in pK_a between interacting molecules to predict whether the product of a cocrysallization forms a salt or a cocrystal. The rule is less reliable for values of ΔpK_a comprised between 0 and 3 and such behaviour is explained by the concept of a continuum between salt and cocrystals.

Here the multi-drug ionic cocrystal between Lamatrigine and Valproic acid is reported. The new form has increased solubility and mechanical properties over the starting materials and a stoichiometry that is indicated in the treatment of epilepsy. Moreover, crystal structure and computational analysis reveal that the ionization of the aminopyridinium-carboxilate synthon depends on ancillary H-bond donors. Ultimately, such multi-molecular synthon explains the salt-cocrystal continuum and the limits of the pK_a rule.