

The Importance of Crystal Structure Prediction for Developing Drug Molecules.

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The properties of organic solids, including physicochemical stability, solubility, and mechanical behavior, are drastically affected by the way in which molecules arrange themselves. One fundamental component of small-molecule drug development is to determine the crystalline forms (or polymorphs) of the active pharmaceutical ingredient (API), as well as its solvated forms, and choose one that possesses an optimal set of properties as the lead one. Thorough experimental form screens are costly, laborious and yet not guaranteed to find all the important solid phases, leaving the door open for late-appearing, more stable solid forms. Crystal structure prediction (CSP) can be of tremendous value to drug development, as it can help right-size the experimental effort, assess the presence or absence of risks associated with the chosen form and direct experimental work towards the most relevant threats and opportunities. In this presentation, we show how CSP has been used to support industrial drug development projects, including the de-risking of the lead forms of pharmaceutical molecules and key synthetic intermediates, the assessment of the likelihood of hydrate formation, and the study of the effect of configurational disorder on the stability of predicted polymorphs.