**The synergy of computational modeling, machine learning, and experiments in pharmaceutical solid-state research and development**

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**Purpose:**

Computational modeling and machine learning (ML) have achieved recognition as vital technologies in drug discovery. Using these technologies, XtalPi has developed a series of methods to guide and enhance experimental workflows for drug development.

**Methods:**

• Virtual multicomponent screening to predict the likely salts, cocrystals, and solvates of a compound and recommend solvents for formation experiments. These virtual screenings can be used to reduce the number of wet-lab experiments performed and increase the likelihood of generating the desired result.

• AI-enhanced crystallization (Xtal2) is a machine learning model—constructed from more than 100k virtual and 10k experimental data—used to recommend crystallization strategies based on molecular structure information. Combining Xtal2 with autonomous workstations allows intelligently designed experiments to be run 24x7.

• Morphology prediction calculations reveal how variables like solvent and additives affect the particle shape of a crystallized compound. These calculations reveal if an undesirable morphology (e.g. needles) is expected and can be avoided by crystallization conditions, or if engineering solutions (e.g. milling) will be required.

• Crystal structure prediction (CSP) predicts all possible polymorphs of a compound and ranks them by thermodynamic stability. The CSP structure-energy landscape can reveal if the most stable polymorph has been discovered and complements experimental XRPD, SC-XRD, and MicroED techniques for crystal structure determination.

**Results:**

• Higher hit rates, lower material requirements, faster timelines

• Alleviate unfavourable morphologies without extensive material DOE studies

• Elimination of late-stage polymorph surprises and enhanced IP protection

**Conclusions:**

XtalPi’s complete solid form screening platform represents a paradigm shift from art to science, reducing the resource and time costs for confident drug substance solid form selection.

**Keywords:**

CSP, ML, solid form screening, electron diffraction, predictive simulation