Lessons Learned from 30 Commercial Pharmaceutical Crystal Structure Prediction Studies

Jacco van de Streek
Marcus A. Neumann
Crystal Structure Prediction (CSP)
Crystal Structure Prediction

Also called “polymorph prediction”

*In silico* polymorph screening

Does not suffer from kinetics

The calculations take several months…
Crystal Structure Prediction

Compound → Trial structures → Predicted structures

- Structure generation
- Energy ranking

lattice energy

Compound

Trial structures

Predicted structures

Avant-garde Materials Simulation
Example: CSP of Dalcetrapib
Energy Landscape of Dalcetrapib

The graph shows the energy landscape of Dalcetrapib with energy in kcal/mol on the y-axis and density in g/cm³ on the x-axis. The graph includes predictions represented by blue dots and an experimentally determined point marked with a red circle. The area with disorder is indicated by a bracket. The graph also includes a legend identifying 'Predictions' and 'Exp.'
CSP of Dalcetrapib

Predicted #2

Experiment
Energy Landscape of Dalcetrapib

Energy / kcal/mol

Density / g/cm³

higher density

Predictions
Exp.
Pressure Scan of Dalcetrapib
High-Pressure Crystallisation

Francesca Fabbiani crystallised Dalcetrapib at “high pressure” and found the new form (which turned out to be less stable at ambient pressure).

CCDC Blind Test Statistics
CSP Blind Tests

Crystal-structure Prediction Blind Tests: Organised by CCDC and Dr Graeme Day


CSP Blind Tests

Commercial CSP Statistics
The 30 Compounds

On average:

30 non-H atoms
23 H atoms
3 trivial flexible torsion angles (e.g. CH₃)
6 non-trivial flexible torsion angles
1 flexible ring

4 hydrates
2 zwitterions
20 chiral

Bicalutamide
Energy Gap (Exp. - #1)

- 15 x rank 1
- 30 commercial CSP studies
- 18 x safe
- 9 x grey area
- 3 x missing stable form
Energy Gap (Exp. - #1)

30 commercial CSP studies

10 – 40% of thermodynamically stable forms missing!

15 x rank 1

18 x safe

9 x grey area

3 x missing stable form
Matching XRPD Patterns

31 powder patterns made available
(including duplicates,
possible solvates,
sometimes very poor quality)

14 new crystal structures solved by
matching against predicted structures

Resources

On 384 cores (an average laptop has about 2 cores)
So roughly the equivalent of 200 laptops

Parameterising the tailor-made force field
Average: 2 weeks
Min: < 1 week
Max: > 1 month

CSP, Z’=1
Average: 2 weeks
Min: < 1 day
Max: > 2 months
Conclusions

At least 10% of all small-molecule drugs on the market have an as yet unknown significantly more stable polymorph.

Crystal structure prediction can be used as a last resort method for crystal structure solution from powder diffraction data.