Oral solid dose

Improving bioavailability through predictive modeling of solubility enhancement strategies

In silico modeling helped narrow formulation options and accelerate early development.

Development challenge

Poor aqueous solubility continues to limit the development potential of many small-molecule drug candidates. When solubility is extremely low, identifying an effective formulation approach can require extensive screening of excipients and technologies—often resulting in long timelines and high material consumption during early development.

A development program involving a poorly soluble compound (approximately 0.015 mg/mL solubility in FaSSIF media) faced exactly this challenge. The sponsor initially considered evaluating multiple formulation technologies experimentally to identify a path forward. While feasible, that approach would have required significant trial-and-error experimentation and extended development timelines.

Applying predictive modeling to formulation design

To reduce experimental trial and error, predictive modeling tools from the OSD Predict™ framework were used to guide formulation design earlier in the process.

The Quadrant 2™ predictive platform was applied to evaluate potential solubility enhancement strategies before laboratory testing began.

The approach combined calculated molecular descriptors, experimental physicochemical data, and computational modeling of drug–excipient interactions. Quantum mechanics and molecular dynamics simulations were used to evaluate interactions between the drug molecule and potential polymers, enabling broad screening of excipients in silico before narrowing the list for experimental validation.

Selecting and scaling the formulation strategy

Modeling identified several promising polymers for amorphous solid dispersion development, including HPMCAS-M, PVAP, Soluplus®, HPMCP-HP55, and PVPVA-64. These candidates were then evaluated experimentally to confirm modeling predictions and refine formulation parameters.

Based on pharmacokinetic performance in animal studies, HPMCAS-M and PVAP were selected as the lead polymers.

The development strategy focused on producing an amorphous solid dispersion using spray drying. Thermodynamic modeling and targeted design-of-experiments studies supported scale-up of the process to pilot-scale spray drying using an MS-150 spray dryer.

At a glance

Program focus
Solubility enhancement of a poorly soluble small-molecule drug candidate with limited bioavailability.

Methods used
AI/ML-driven predictive modeling using the Quadrant 2™ platform, combined with quantum mechanics (QM) and molecular dynamics (MD) simulations.

Formulation strategy evaluated
Amorphous solid dispersion development using candidate polymers including HPMCAS-M, PVAP, Soluplus®, HPMCP-HP55, and PVPVA-64.

Key technical finding
Computational screening identified polymer systems capable of stabilizing drug–polymer interactions and improving dissolution prior to experimental testing.

Development impact
The optimized formulation improved exposure (~8× Cmax and ~5× AUC vs. crystalline drug) and enabled progression to Phase I clinical studies.

Development outcome

The optimized HPMCAS-M formulation significantly improved systemic exposure compared with the crystalline drug form. Clinical data showed approximately eight-fold improvement in Cmax and five-fold improvement in AUC.

By using predictive modeling to narrow formulation options early in development, the team focused experimental work on the most promising strategies and reduced the need for extensive technology screening.