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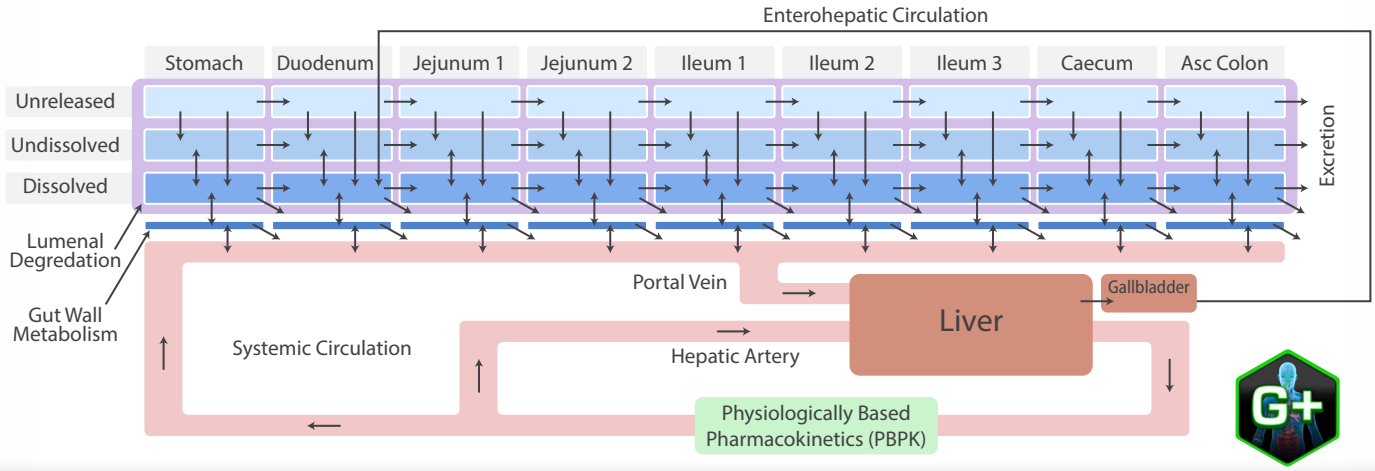
ADME Predictions with GastroPlus® for Small Molecule R&D

How you can leverage insights into bioavailability and pharmacokinetics to help guide preclinical and clinical decisions

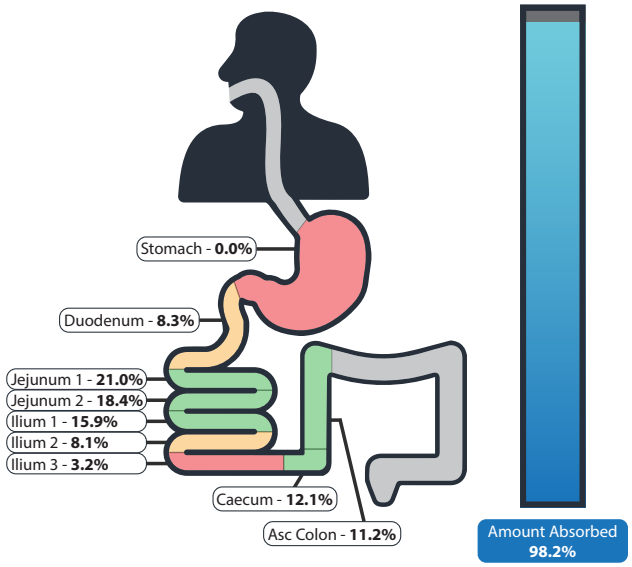


The GastroPlus absorption model considers pH based in-vivo solubility at the tissue level and the intestines

GastroPlus is an advanced software tool used in pharmaceutical development for physiologically-based pharmacokinetic (PBPK) modeling.

This tool incorporates in-vivo and in-vitro data to simulate the ADME profile of drug candidates in animal and human models.

These predictions provide valuable insights at all stages across preclinical and clinical development.



GastroPlus simulates partitioning and absorption for 9 different segments of the gastrointestinal tract

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Building Animal Models

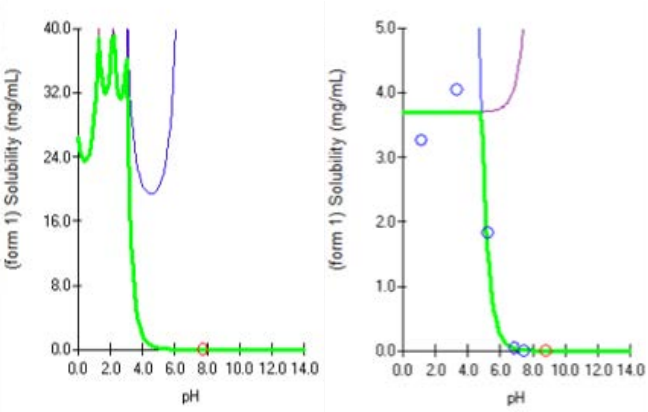
Experts evaluate the available in-vitro and in-vivo data including:

- Physicochemical properties
- Dose, dosage form, dose frequency
- IV data
- PO data

In this case, the in-silico prediction is more representative of amorphous solubility, while the in-vitro data measures the crystal lattice strength.

The in-vitro data establishes the lower limit for solubility, serving as the strongest starting point for all subsequent predictions.

In-Silico vs In-Vitro Measurements



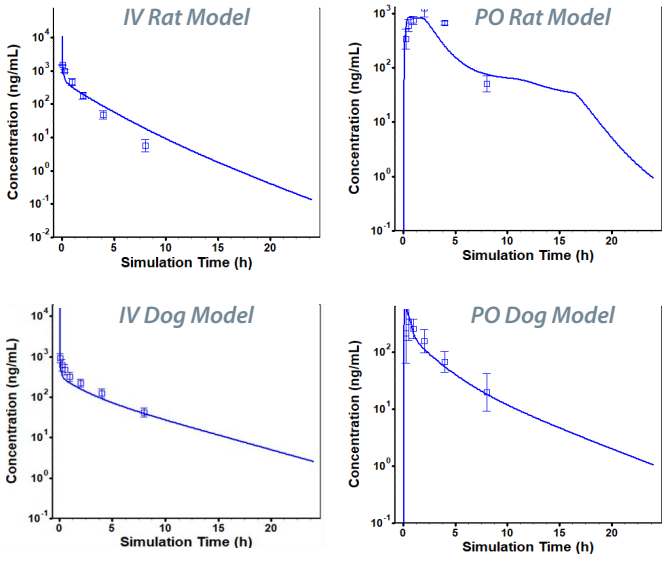
In-silico predicted solubility (left). In-vitro crystalline solubility with a curve fitted by GastroPlus (right).

In-vivo data is individually inputted, analyzed, and fitted to the model.

The IV model provides the baseline clearance which is then used for the PO model.

The species with the best fit and lowest standard deviation are used for the human models.

PBPK Models



Semi-log plots for IV and PO models of Rats and Dogs

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Scaling to Human Models

The best fitting models are scaled to humans. Multiple species are used to enable comparisons across multiple physiological variables.

Similar results from different species provided confidence in the accuracy of the human model.

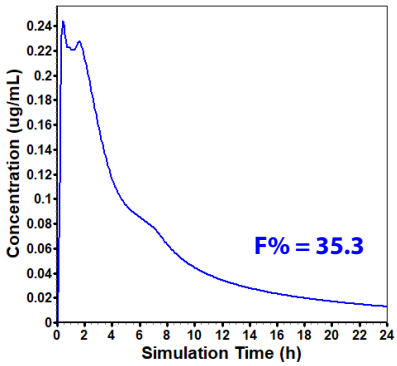
If there are differences between models, it would require investigation to determine which model is most accurate.

Significant liver metabolism resulted in decreased bioavailability despite a high fraction absorbed.

The models can be used to evaluate parameter sensitivity including:

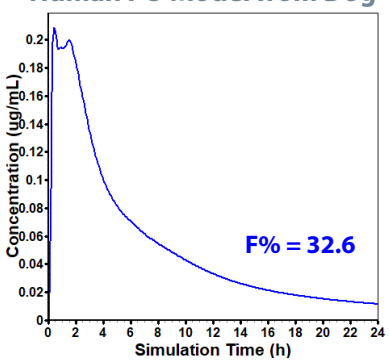
- Food effect
- Varying dose
- Dosage form
- Increasing solubility
- Particle size

Human PO Model from Rat



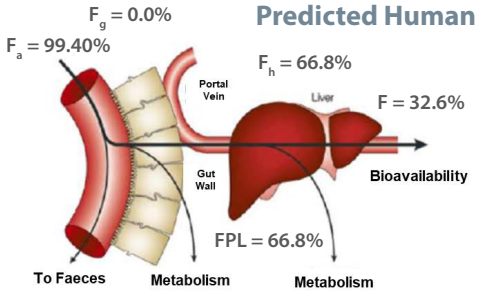
Fasted plasma concentration vs time. Human PBPK model scaled from rat

Human PO Model from Dog



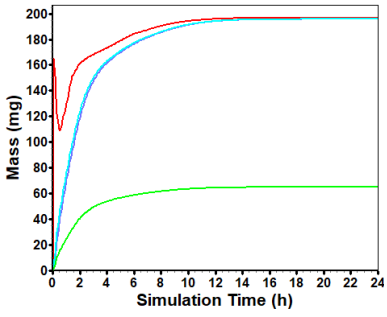
Fasted plasma concentration vs time. Human PBPK model scaled from dog

Predicted Human Metabolism

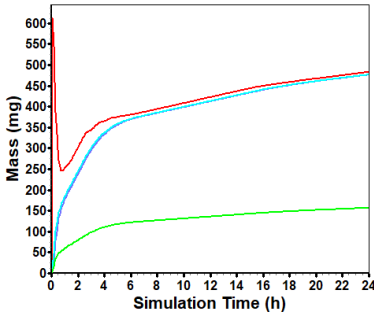


Fa = Fraction absorbed
Fg = Fraction available over gut wall
Fh = Fraction available over liver
FPL = First pass loss
F = Bioavailability

PBPK Model at 200mg Dose



PBPK Model at 800mg Dose



Red: Amount dissolved
Cyan: Amount absorbed into enterocytes
Blue: Amount reaching portal vein
Green: Amount reaching systemic circulation

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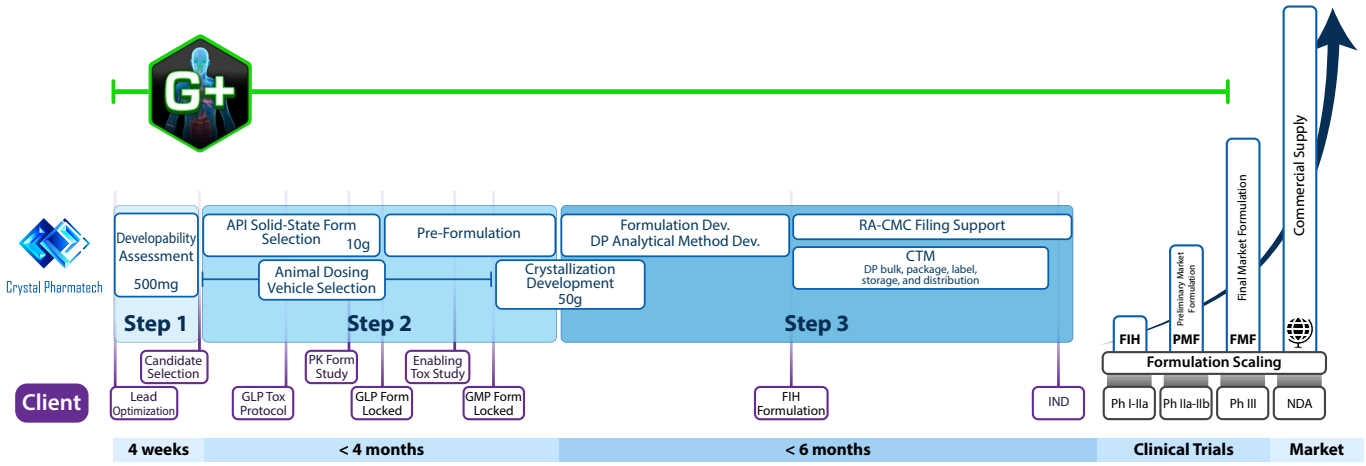
Incorporating PBPK Modeling into Your Program

Because models are consistently updated as new in-vivo and in-vitro data become available, PBPK models can help guide decisions from lead optimization to clinical development.



Crystal Pharmatech incorporates GastroPlus as a vital component of its Developability Assessment with continued use through formulation development.

GastroPlus, combined with experienced solid-state chemists and formulators, can provide invaluable insights for **lead candidate selection** and the optimal **GLP Tox and FIH formulation** approaches.

Crystal Pharmatech has in-house experts in GastroPlus PBPK modeling and regularly helps innovators incorporate PBPK modeling into their programs for more efficient and effective development.

If you would like to learn more about how this powerful tool can benefit your program, please reach out to BD_Global@CrystalPharmatech.com.