

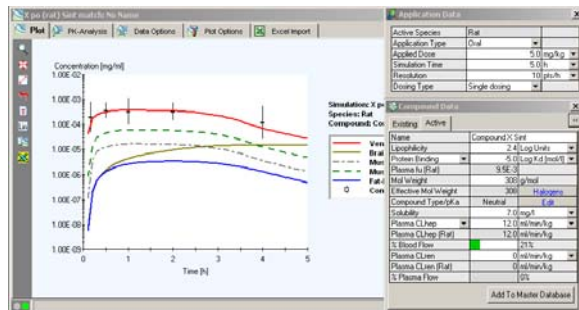
PK-SIM®

The solution for Physiology Based Pharmacokinetic Simulations

Whole-body physiology-based pharmacokinetic (PBPK) simulation is a technique that has been in use for many years. It offers a unique opportunity to investigate the fate of xenobiotics, particularly drugs, in the human body using a mathematical description of the underlying physiological, biochemical and physical processes. Compared to other pharmacokinetic modelling techniques PBPK-modelling has a much lower demand for in-vivo data with concomitantly higher predictive power in extrapolating simulations to new scenarios not covered by experimental data.

Our Product

PK-Sim® simulates the processes responsible for absorption, distribution, metabolism and excretion (ADME) in the body. The whole-body model underlying PK-Sim® is universally applicable such that any compound of interest can be simulated virtually only by setting compound parameters without any modification of the model itself.



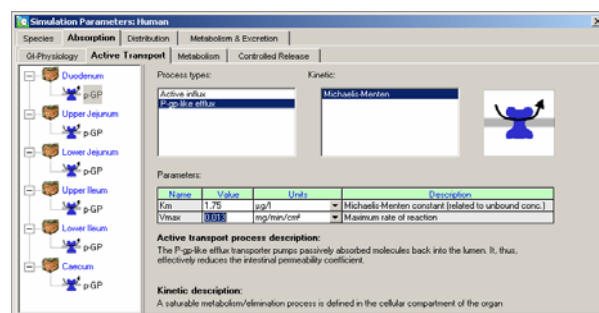
PK-Sim® allows the analysis of mammalian pharmacokinetics following single or multiple intravenous and oral administrations as well as user defined administrations in various organs. The primary result of a simulation run is a set of concentration time curves illustrating the temporal behaviour of a drug in the blood and in various relevant organs. PK-Sim® also calculates automatically all major pharmacokinetic parameters. The tool's high flexibility enables specific user defined simulations, sensitivity analyses and detailed 'what-if' studies.

PK-Sim® offers the possibility to create and adjust putative substance specific transport processes with saturable kinetics, in all ADME phases. This is essential for many substances, especially for their distribution in the elimination organs and for intestinal uptake.

For example, with the help of active transporters one can realize intestinal uptake and hepatobiliary excretion.

Furthermore, metabolism reactions can be introduced in any organ to represent organ specific intrinsic clearances.

Especially, if the simulated plasma curve does not agree with the experimental data, alternative mechanisms for the metabolism reactions and transport processes may be assumed. Thus, PK-Sim® contributes plausibly to the generation of hypotheses and the testing of new mechanisms, such as enterohepatic circulation and organ specific drug metabolism.



PK-Sim® comprises literature values for all accessible physiological parameters needed for whole body simulations. Substance specific parameters such as permeabilities and partition coefficients are calculated internally from the physico-chemical properties of the substance. Values for renal and hepatic clearances must be determined a priori and given by the user. Nevertheless, the number of obligatory parameters to be provided by the user is reduced to a minimum. However, if supplementary data are available, it can be directly entered into PK-Sim® bypassing the calculation.

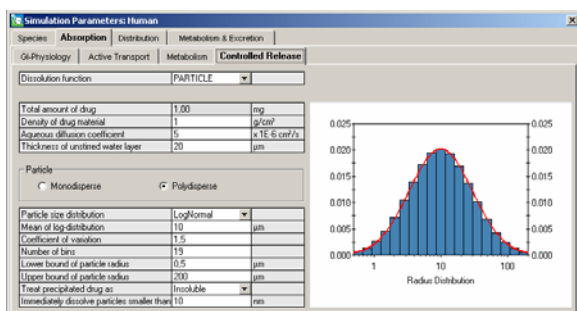
Physiology-Based Absorption Model

The PK-Sim® Absorption model enables simulations of the gastro-intestinal transit and absorption processes of orally administered dosage forms.

Different solution dynamics of solid acids and bases can be handled using an internal solubility versus pH relationship which is automatically created based on user input of one single solubility value at a certain pH.

Even modified release formulations can be modelled. If experimental data of the dissolution process are not available for a direct input, predefined or user defined dissolution functions can be used. The other possibility is to simulate the process itself with a given particle size distribution and the physical properties of the dosage form.

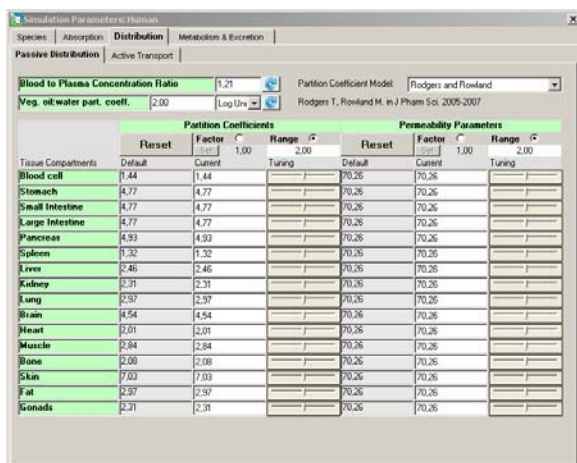




Physiology-Based Distribution Model

A major advantage of PK-Sim® resides in the fact that due to the inclusion of permeability and tissue composition, organs are not generally subjected to the 'well stirred' assumption. In fact during the distribution phase, perfusion limitation as well as permeability limitation may occur, distinguishing the distribution behaviour for example in the liver from that in the brain, which enhances by far the reliability of the simulations.

The distribution of a drug into the peripheral organs, especially in the target organ and in other affected organs, can be easily observed from the corresponding concentration versus time curves.



Physiology-Based Elimination Model

Renal and hepatic eliminations are determined by the user defined clearance parameters and occur automatically when a drug distributes through these organs. However, if the interest focuses on metabolism, PK-Sim® allows to model explicit metabolism reac-

tions in the corresponding organs. This is especially useful for the analysis of drug interactions in the liver or in the gut wall.

These features make PK-Sim® a valuable tool for researchers involved in drug discovery, particularly in biopharmaceuticals and formulation development. An extension of PK-Sim® namely PK-Sim® Clinical additionally allows the consideration of subject populations in clinical trials, especially the consideration of infant populations with adapted physiological parameters.

Key Features

- ✓ Completely integrated PBPK model describing the key processes in Absorption, Distribution, Metabolization and Excretion.
- ✓ Physiology-based simulation of gastro-intestinal transit and absorption
- ✓ Generation of pH versus solubility tables
- ✓ Simulation of the dissolution dynamic of a solid particle formulation with predefined particle size distribution
- ✓ Simulation of saturable active uptake and efflux processes as well as luminal degradation and gut wall metabolism
- ✓ Permeation limited distribution model.
- ✓ Minimized requirements for compound specific input data
- ✓ Population database providing physiological information that mainly depend on age, gender and BMI for different races
- ✓ Species database providing physiological data for different animal models
- ✓ Graphical user interface for convenient control of simulation parameters.
- ✓ Calculation of pharmacokinetic data
- ✓ Integrated project database for management and storage of data and results.
- ✓ Import of experimental PK data for convenient and easy comparison with simulation results.

System Requirements

- OS: Windows XP, Windows 2000
- Processor: Pentium III, 500 MHz or better
- Memory: 256 MB RAM
- Disk Space: 40 MB

Integrated Solutions and Services

BTS offers an integrated suite of products including:

- PK-Sim
- MoBi

These tools build the platform for our services in the field of mechanistic modeling and simulation:

- ADME Simulation
- Biological Network Modeling
- Evaluation of Drug and Licensing Candidates
- Drug Response Prediction

Contact

Sales Bayer Technology Services GmbH
 Business Management • D-51368 Leverkusen
 E-Mail: info@bayertechnology.com
 Fax: +49 / (0) 214 / 30 - 62 530