Simulating Oral Absorption with PK-Sim®
Methodology and Application Examples

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Presentation Overview

- PK-Sim®’s Absorption Model
- Application Examples
  - Example 1
  - Example 2
  - Example 3
PK-Sim® Model-Structure

Real **Integrated Whole Body Model** comprising:

- Fully integrated GI-tract
- Biliary tract, enables enterohepatic cycling
- Most important organs
- For each organ:
  - metabolizing pathways
  - different active transporter types (influx, efflux, Pgp-like)

**Capability for treating even very sophisticated problems.**

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PK-Sim®‘s Input Parameters

- Lipophilicity (LogMA preferred)
- Plasma Protein Binding (alternatively unbound fraction)
- (effective) Molweight
- pKa values for acids/bases
- Solubility vs. pH table
- Plasma Clearance hepatic/renal (alternatively in vitro metabolism rates, $K_m$ & $V_{max}$, …)

![Compound Data](image)
Simulation of Intestinal Transit & Absorption

Principle

Continuous one-compartment model for small intestine:
• Spatially varying properties (effective surface area, pH)
• GI transit described as *plug-flow with dispersion*

Model for Passive Absorption

- Intestinal permeability is based on an empirical equation:

\[
P_{\text{int}}(\text{MW}, \text{MA}) = A \frac{\text{MW}^{-\alpha - \beta} \text{MA}}{\text{MW}^{-\alpha} + B \text{MW}^{-\beta} \text{MA}} + C \frac{\text{MW}^{-\gamma}}{D^{-\gamma} + \text{MW}^{-\gamma}} \text{[cm/s]}
\]

- Model for the intestinal permeability coefficient was build using a data set of 126 marketed compounds with no solubility limitation at therapeutic doses.

- An excellent fit was obtained.

- All outliers are known to be substrates active transporters.


*Leahy et al. in *Novel Drug Delivery and Its Therapeutic Application* (1989)*
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  - Example 1: Dissolution Limited Absorption
  - Example 2
  - Example 3
Compound X (from ongoing BHC development project)

Properties

- neutral
- medium lipophilicity (LogMA = 2.2)
- MW ~ 450 g/mol
- high permeability (Caco2, animal models)
- low aqueous solubility

- Human study data:
  - single dose under fasted conditions
  - solution: 5 and 10 mg
  - IR tablet: 1.25, 5, 10, 15, 20, 30, 40, 60, and 80 mg
    (mean particle diameter of IR tablet formulation: 3 µm)
Model for Dissolution-Limited Absorption

- Add-on module to dynamically simulate dissolution of polydisperse spherical particles

![Diagram showing dissolution and precipitation processes](image)

**Simulation Parameters: Human**

- **Dissolution Function**: PARTICLE
- **Total amount of drug**: 1.00 mg
- **Density of drug material**: 1 g/cm³
- **Aqueous diffusion coefficient**: 5 x 10⁻⁹ cm²/s
- **Thickness of unstirred water layer**: 20 μm

**Particle size distribution**

- **Particle size distribution**: LogNormal
- **Mean of log distribution**: 10 μm
- **Coefficient of variation**: 2
- **Number of bins**: 10
- **Lower bound of particle radius**: 0.1 μm
- **Upper bound of particle radius**: 100 μm
- **Total precipitated drug as**: Soluble
- **Immediately dissolve particles smaller than**: 10 nm

**Graph showing fraction dissolved over time**

- **3 μm Particles**

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Simulation of Dose Dependent Exposure

- **IR Tablet:** 1.25mg, 5.00mg, 10.0mg, 15.0mg, 20.0mg, 30.0mg, 40.0mg, 60.0mg, 80.0mg
- **Simulation:** Tablet, Solution

**Plasma Concentration**: [µg/L]

**Time [h]**: 0, 2, 4, 6, 8, 10, 12

- **Simulated F_abs**
- **Measured AUC$_{norm}$ [kg h / L]**

**Dose [mg]**: 0, 20, 40, 60, 80, 100

**Plasma Concentration**: [µg/L]

**Time [h]**: 0, 2, 4, 6, 8, 10, 12

- **Solution:** 5.00mg, 10.0mg

- **Simulation**
  - Tablet
  - Solution

- **Experiment**
  - Tablet
  - Solution

*Simulating Drug Absorption*

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  - Example 2: Cimetidine PK Variability
  - Example 3
What About Inter-Individual Variability?
What About Inter-Individual Variability?
Age Dependence and Variability of Physiological and Anatomical Parameters

Data for the age dependence of physiological parameters relevant for PBPK modelling such as

- body weight, body height, body mass index,
- organ weights, blood flow rates,
- tissue composition (water, lipid, and protein content)
- fractions vascular, interstitial and intracellular

and their variability and cross-correlation were collected in a comprehensive literature search.
Modelling Inter-Individual Variability in PK-Sim® with the add-on module “PK-Pop“
Example: Cimetidine

- Available Information:
  - *in vitro* dissolution profiles of IR Tagamet® tablets plus three experimental CR formulations (400 mg cimetidine)
  - *in vivo* data from 12 male volunteers
  - PK profiles after iv admin. in same individuals (clearance distribution !)

- Population Simulation:
  - 100 virtual individuals (age, weight and height matched) with varying gastric emptying time (15–45 min.) and small intestinal transit time (2.5–5.5 h)

Example: Cimetidine

Tagamet® tablets

In vitro release profile:

(unpublished data, Marcus Kleine-Besten, Univ. Frankfurt)
Example: Cimetidine

Eudragit 7,5 %

In vitro release profile:

Plasma Concentration [mg/L]

Time [h]

Mean
5% and 95%
Min/Max

Cimetidine Release

Time [h]

(unpublished data, Marcus Kleine-Besten, Univ. Frankfurt)
Example: Cimetidine

Eudragit 15 %

In vitro release profile:

(unpublished data, Marcus Kleine-Besten, Univ. Frankfurt)
Example: Cimetidine

Eudragit 26%

In vitro release profile:

(unpublished data, Marcus Kleine-Besten, Univ. Frankfurt)
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  - Example 3: Simulations in Children
Special Populations: Children

- Food & Drug Administration (FDA) and European authorities pressuring industry to perform clinical trials in paediatric patients
- Increase access to treatments for children and reduce off-label, unlicensed treatment
- 50% of all drugs administered in hospitals are not properly licensed for use in children*
- Adverse drug reactions due to dosing errors and use in non-labeled ages - from Dec 2001-2004, 820 serious ADRs occurred due to off label use with 130 being fatal (reported)**

Scaling PBPK Models to Children

- PBPK Modelling in children requires knowledge about the physiological and clearance differences relative to adults.
Scaling PBPK Models to Children

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Children are not just small adults!
Scaling PBPK Models to Children

- PBPK Modelling in children requires knowledge about the physiological and clearance differences relative to adults.

-> mechanistic model for clearance scaling

(Edginton et al., Clin. Pharmacokin. (in press 2006))
Simulating Oral Absorption in Children

Example: Oral administration of 10 mg/kg Ciprofloxacin in children
The rate and extent of oral drug absorption can be well simulated based on simple physico-chemical input parameters and a detailed description of the GI physiology.

Physiology-based simulations of drug absorption can be used to make predictions in the early development phase, for hypothesis testing in later development stages, to aid formulation development, and to study sub-populations (e.g. children, elderly, diseases).
The PK-Sim®-Team

- BTS-Systems Biology & Computational Solutions
  - Dr. Andrea Edginton
  - Karsten Höhn
  - Marcus Kleine-Besten
  - Dr. Jörg Lippert
  - Dr. Walter Schmitt
  - Michael Sevestre
  - Juri Solodenko
  - Wolfgang Weiss
  - Dr. Stefan Willmann

- Bayer-internal Cooperations
  - PK groups of BHC-Pharma
    (Dr. G. Ahr, Dr. W. Mück, Dr.H.Stass and colleagues)

- External Cooperations
  - Prof. Jenny Dressman, Uni Frankfurt
  - NIMBUS Biotechnology, Leipzig
  - Physiomics plc, UK
BACKUP SLIDES
Relevant Physiological Parameters: Summary

(Physiological data collected in collaboration with Prof. Dressman, Frankfurt, data for dogs and mice not shown)

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Simulation of Intestinal Transit & Absorption

\[ \frac{d^2 M_{pv}(z, t)}{dz \, dt} = \frac{d}{dz} \left( P_{\text{int}} [C_{\text{lumen}}(z, t) - C_{pv}(t)] A_{\text{eff}}(z) \right) \]

\[ (C_{\text{lumen}}(z, t) \leq S_{\text{int}}) \]

substance-specific properties

physiological properties

Scaling of Intrinsic Clearances

- Hypothetical Compound
  - Renal: 20%
  - CYP 3A4: 30%
  - CYP 1A2: 50%

- Sum:
  - 26%
  - 23%
  - 51%

Bayer Technology Services
Validation of Clearance Scaling

**Observed Clearance vs. Predicted Clearance**

- **One Pathway**
  - Alfentanil
  - Midazolam
  - Gentamicin
  - Isepamicin
  - Caffeine
  - Ropivacaine
  - Morphine
  - Lorazepam

- **Multiple Pathways**
  - Buprenorphine
  - Lidocaine
  - Ciprofloxacin
  - Paracetamol
  - Theophylline
  - Fentanyl

- **R² = 0.91**

- **Using adult clearances would lead to much worse prediction!**

- **R² = 0.61**
Calculation of Partition Coefficients

Steady state organ/plasma partition coefficients

\[ K_{\text{tissue/water}} = f_{\text{lipid}}^{\text{tissue}} \times K_{\text{lipid/water}} + f_{\text{protein}}^{\text{tissue}} \times K_{\text{protein/water}} + f_{\text{water}}^{\text{tissue}} \]

\( K \) = Partition Coefficient (\( K_{\text{protein/water}} \) = HSA binding in case of plasma and calculated from Lipophilicity in all other cases)

\( f \) = Volume fraction

\[ K_{\text{tissue/plasma}} = \frac{C_{\text{tissue}}}{C_{\text{plasma}}} = \frac{K_{\text{tissue/water}}}{K_{\text{plasma/water}}} = K_{\text{tissue/water}} \cdot f_u \]
Calculation of Distribution Dynamic

Permeability x Surface-Area Products

Fick’s First Law:

$$J = K \frac{D}{d} \cdot A \cdot (C_1 - C_2)$$

$$P_{A_{tissue}} \sim \text{Lipophilicity} \cdot MW^{-\alpha} \cdot A_{tissue}$$
Volume of Distribution

The graph shows a scatter plot comparing the measured $V_D_{ss}$ to the calculated $V_D_{ss}$ for different compounds. The x-axis represents the calculated $V_D_{ss}$, while the y-axis represents the measured $V_D_{ss}$. The data points are color-coded to represent different groups, such as Doxorubicin and Beta Blockers. The linearity between the measured and calculated values suggests a good correlation for these compounds.
Prediction of Partition Parameters

Validation

Fraction Unbound in Plasma

Brain/Plasma Partition-Coefficient

Organ/Plasma Partition Coefficients
More Examples

Membrane Affinity

Partitioning into Phospholipid-Membrane

Headgroups

Chains

\[ MA = \frac{C_{\text{membrane}}}{C_{\text{water}}} \]

C_{\text{water}}

C_{\text{membrane}}

Polar compound  Lipophilic compound
Membrane Affinity vs. log\(K_{ow}\)

**Relationship log\(K_{ow}\) / logMA nonlinear**

![Graph showing the relationship between log\(K_{ow}\) and logMA.](image1)

**pH-Dependence different from log\(K_{ow}\)**

*Example*: Basic compound

![Graph showing pH-dependence for a basic compound.](image2)

Gobas et al., J. Pharm. Sci 77, 265 (1988)

Austin et al., Fisons Pharmaceuticals I. logP Symposium, Lausanne 1995
General Model Results

**Assumption:** Dissolution is not the rate limiting step for absorption
General Model Results

Region A: no solubility limitation

Region B: dose-dependent absorption

Region C: $F_{\text{abs}} < 1\%$ (solubility-limited)

Region D: $F_{\text{abs}} < 1\%$ (permeability-limited)

FDA-Suggestion: $(M/S) = 250\text{ ml}$

“Minimum Acceptable Solubility“ *)

*) W. Curatolo (Pfizer)

Example: Cimetidine

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Model Application: Assessment of EHC

Example: Model compound:
weak base with pKa = 8.5, 
LogMA = 4.2, MW = 520, 
Solubility = 250 mg/L at pH 6.5, 
dose = 25 mg, subject to EHC

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- **Population Simulation (N=25)**
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