Mechanistic Modeling and Simulation of Oral Drug Absorption: Opportunities and Challenges

Masoud Jamei
VP of R&D, Simcyp

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Outline

IVIV_E-Linked PBPK absorption modelling

Physiologically-based IVIVC (PB-IVIVC)

Bioequivalence and PBPK modelling
Physiologically Based Pharmacokinetics (PBPK) models are very limited in prediction/extrapolation.

Without IVIVE, PBPK models are very limited in prediction/extrapolation!
Systems pharmacology paradigm – Separation of system/drug data

Trial Design

Dose
Administration route
Frequency
Co-administered drugs
Populations
No of male/female

Mechanistic IVIVE linked PBPK models

Prediction of drug PK (PD) in population of interest

Jamei, Current Pharmacology Reports, (in press)
A mechanistic absorption framework (ADAM model)

Jamei et al., AAPSJ, 2009
Monte Carlo (MC) vs. Correlated Monte Carlo (CMC)

Are there any relationships between the stomach emptying (pH) and duodenum motility (pH)?

A randomly generated subject using MC sampling

Randomly generated subjects using CMC sampling
Gastric emptying changes with age?

Bonner et al., BDD, 2015

aq: aqueous solution
bm: breast milk
fm: formula
ss: semi-solid meal
sol: solid meal

Age was not a significant covariate for gastric emptying but meal type was. Aqueous solutions were associated with the fastest emptying time (mean simulated gastric residence time of 45min) and solid food was associated with the slowest (98 min).
Luminal fluid volumes and dynamics from MRI studies

Total Small Bowel Water Volumes

Imaging 1 hr after 150 mL Water Drink

1 hr Mean ~80 mL

(Excl. outlier)

Imaging at Intervals after 240 mL Water Drink (Fasted)

1 hr Mean ~85 mL

* Schiller, Weitschies et al. 2005

* Mudie, Marciani et al. 2014 with permission
Luminal water fluid dynamics

- In reality luminal water fluid is dynamically changing

- Considering this dynamic assists with:
  - Handling variability in water taken with dose
  - Dynamic dilution of food and viscosity
  - Accounting for molecular/micellar diffusivity
  - Particle dissolution
  - Disintegration
  - Supersaturation / Precipitation
Embracing Variability: Gut Wall Permeability

Exp. Loc-l-gut Human Jejunal $P_{eff}$ ($10^{-4}$ cm/s)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Obs Fold (Max / Min)</th>
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<tbody>
<tr>
<td>Antipyrine</td>
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<tr>
<td>Fluvastatin</td>
<td>9.6</td>
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<tr>
<td>Atenolol</td>
<td>11.4</td>
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<tr>
<td>Metoprolol</td>
<td>5.4</td>
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<tr>
<td>Study Means</td>
<td>5.0</td>
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Individual measurements in 9 subjects*

MechPeff Model Predicted 1,000 simulated individuals

*Lindahl *et al.* 1996 CPT
In vitro in vivo extrapolation (IVIV_E) – clinically relevant specifications

**In vitro** dissolution

\[
(D(t)) = -NS \frac{D_{\text{eff}}}{h_{\text{eff}}(t)} 4\pi a(t)(a(t) + h_{\text{eff}}(t))(S_{\text{surf}}(t) - C_b(t))
\]

**API Parameters**
- \(S_0\), pKa, SR, PRC
- Log\(K_{m:w}\)
- Particle size *etc.*
- DLM scalar \((S)\)

**In vitro System parameters**
- RPM (Fluid velocity)
- Buffer (e.g., Phosphate)
- Media (pH, [Bile Salts] …)

**In vivo** dissolution

*Ind 1*

**In vivo System parameters + variability**
- Fluid dynamics
- Luminal fluid velocities
- Buffer (bicarbonate)
- Luminal pH, [Bile Salts]
- …

*Ind. x etc.*
Summary of Sequential Modelling Approach

Aqueous Solubility Modelling

\[ S_{(BS)Tot} = \left( [BS] \cdot \frac{S_0}{C_{H_2O}} \cdot K_{mww,unionized} + S_0 \right) + \left( [BS] \cdot \frac{S_i}{C_{H_2O}} \cdot K_{mww,ionized} + S_i \right) \]

Biorelevant Solubility Modelling

\[ S_{(BS)Tot} = \left( [BS] \cdot \frac{S_0}{C_{H_2O}} \cdot K_{mww,unionized} + S_0 \right) + \left( [BS] \cdot \frac{S_i}{C_{H_2O}} \cdot K_{mww,ionized} + S_i \right) \]

USP-2 Dissolution Modelling

\[ DR(t) = -NS \frac{D_{eff}}{h_{eff}(t)} 4\pi a(t) \left( a(t) + h_{eff}(t) \right) \left( S_{surface}(t) - C_{bulk}(t) \right) \]

Transfer Experiment Modelling

Confirmed Intrinsic Solubility & Solubility Factors

Confirmed Bile Micelle Partition Coefficients

Confirmed Disintegration & other Parameters

Confirmed Precipitation Parameters
Simulating \textit{in vivo} dissolution using \textit{analysed} \textit{in vitro} dissolution data

Solubility, DLM and Precipitation Parameters from \textit{in vitro} experiments

Virtual Population
Simulating Clinical Trial as in Psachoulias et al. 2011

Duodenal Precipitation

\textbf{Ketoconazole Duodenal Dissolved concentration}

DLM: Diffusion Layer Model

Pathak et al. 2016 PBP Meeting

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Luminal Data- Psachoulias et al. 2011
Physiologically-based IVIVC

Mechanistic Deconvolution

Simple IVIVC Function

Conventional Deconvolution

Complex IVIVC Function

Dissolution  Permeation  Systemic Input
PB-IVIVC deconvolutes to dissolution rather than absorption

IVIVC of Metoprolol CR products

A. Physiologically based Method (%Dissolved)

\[ y = 0.95x + 2.7809 \]
\[ R^2 = 0.9883 \]

B. FPE method Sirisuth&Eddington 2002

\[ y = 1.1579x - 0.2493 \]
\[ R^2 = 0.9244 \]

C. ND Method Eddington et al. 1998

\[ y = 1.1402x - 0.201 \]
\[ R^2 = 0.9592 \]

D. ND method Rivivc package

\[ y = 1.112x - 12.231 \]
\[ R^2 = 0.9691 \]
PB-IVIVC for metoprolol was established and the consequences of following were explored:

1) method of fitting a Weibull function to the in vivo dissolution;
2) selection of optimization and weighting schemes;
3) the impact of applying a fixed versus fitted gastric emptying time;
4) The importance of factoring population variability into the IVIVC estimation and profile re-convolution.

Model then applied to predict formulation performance in CYP2D6 PM subjects.
A virtual bioequivalence workflow

1. Develop a robust PBPK Model
2. Using clinical observations assess the model performance
3. Develop and assess PB-IVIVC
4. Determine inter-occasion variability and incorporate those
5. Conduct virtual BE studies
6. Determine dissolution limit specification and construct the safe space design
Determining dissolution specifications for a Tramadol ER

Dissolution profiles obtained using optimum $\alpha$ and $\beta$ Weibull parameters and used to define upper and lower bounds of dissolution specifications.

Pathak et al., CRS meeting, UK, 2015
Fitting/assuming model parameters

Some absorption processes are poorly understood or are yet to be fully characterised.

Hence, the “bottom-up” approach may not work well and observed data may be used to improve predictions.

When fitting/assuming parameters then assumptions should be clearly stated.

Sensitivity Analysis can help to assess/justify assumptions.
Therapeutic Equivalence Assessment using PBPK Simulations

Ibuprofen IR products PK and PD differences with dose

Cristoforetti & Dressman 2014, J Pharm Sci, 103 (10), 3263-75
Extrapolating Formulation Assessment from Adult to Paediatric

Exploratory Investigation of the Limiting Steps of Oral Absorption of Fluconazole and Ketoconazole in Children Using an *In Silico* Pediatric Absorption Model

Rodrigo Cristofoletti¹,², Naseem A. Charoo³,⁴, Jennifer B. Dressman²,*

Using Physiologically Based Pharmacokinetic (PBPK) Modelling to Gain Insights into the Effect of Physiological Factors on Oral Absorption in Paediatric Populations

Angela Villiger¹,³, Cordula Stillhart¹, Neil Parrott², and Martin Kuentz³,⁴

Development of physiologically based pharmacokinetic model to evaluate the relative systemic exposure to quetiapine after administration of IR and XR formulations to adults, children and adolescents

Trevor N. Johnson⁵, Diansong Zhou⁶, and Khanh H. Bui⁶,*
PBPK models are used to predict/understand food effects

**Differences in Food Effects for 2 Weak Bases With Similar BCS Drug-Related Properties: What Is Happening in the Intestinal Lumen?**

Rodrigo Cristofoletti\(^1,2\), Nikunjkumar Patel\(^3\), Jennifer B. Dressman\(^2,\ast\) 2016

Quantitative prediction of formulation-specific food effects and their population variability from *in vitro* data with the physiologically-based ADAM model: A case study using the BCS/BDDCS Class II drug nifedipine 2014

Nikunjkumar Patel\(^a,\ast\), Sebastian Polak\(^a,b\), Masoud Jamei\(^a\), Amin Rostami-Hodjegan\(^a,c\), David B. Turner\(^a\)

**Case Studies for Practical Food Effect Assessments across BCS/BDDCS Class Compounds using *In Silico*, *In Vitro*, and Preclinical *In Vivo* Data**

Tycho Heimbach\(^1,2\), Binfeng Xia\(^1\), Tsu-han Lin\(^1\), and Handan He\(^1\) 2013
Opportunities and Challenges!

• Extrapolation (e.g. patient/special populations)
• Better understanding of formulation performance in vivo
• Determining the product critical quality attributes and clinically relevant specifications
• Prediction of food effects
• PB-IVIVC
• Virtual bioequivalence studies
  • Knowledge gaps in both systems data and absorption mechanisms
  • Advancing our knowledge of inter-occasion variability (BE)
• A collective and multi-disciplinary paradigm
• Education, Education, Education
• Colonic absorption
## Acknowledgements

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<tr>
<th>Simcyp Team</th>
<th>Academic/Regulatory</th>
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<tr>
<td>Nikunj Patel</td>
<td>Luca Marciani (University of Nottingham, UK)</td>
</tr>
<tr>
<td>David Turner</td>
<td>Deanna Mudie, Gordon Amidon &amp; colleagues (Michigan)</td>
</tr>
<tr>
<td>Bo Liu</td>
<td>Dimitrios Psachoulias, Christos Reppas, Maria Vertzoni &amp; colleagues</td>
</tr>
<tr>
<td>Shriram Pathak</td>
<td>(National and Kapodistrian University of Athens, Greece)</td>
</tr>
<tr>
<td>Amin Rostami</td>
<td>Jennifer Dressman, Edmund Kostewicz &amp; Aaron Ruff (Goethe University)</td>
</tr>
<tr>
<td>Deven Pade</td>
<td>B Mistry, M Martinez (FDA)</td>
</tr>
<tr>
<td>Sibylle Neuhoff</td>
<td>R Cristofoletti (ANVISA)</td>
</tr>
<tr>
<td>Matt Harwood</td>
<td>Shinji Yamashita (Setsunan)</td>
</tr>
<tr>
<td>Helen Musther</td>
<td><strong>Orbito Project</strong></td>
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<td>Anette Mullertz, Christel Bergstrom, Xavier Pepin, Christos Reppas, Maria Vertzoni and colleagues</td>
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Backup Slides
Simcyp Dynamic vs. GastroPlus and GI-SIM Static Volumes

G+ - Babiskin 2015 FDA; Sjogren et al 2016
40% of anatomical cylindrical volume

GI-SIM - Sjogren et al 2016

Total FASTED SI Volumes
- Simcyp (v15) Baseline 140 mL Peak 200 mL (240 mL with dose)
- G+ 607 mL
- GI-SIM 527 mL
Simcyp Dynamic vs. GastroPlus and GI-SIM Static Volumes

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Total FASTED SI Volumes
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Luminal Fluid Volume Jejunum I vs. Time (Representative HV)
- Dose 1 240 mL drink
- Dose 2 88 mL drink