Use of In Silico Mechanistic Models to Support Interspecies Extrapolation of Oral Bioavailability and Formulation Optimization: Model Example Using GastroPlus™

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Outline

• Introduction to GastroPlus PBPK model
• Physiological considerations for interspecies extrapolation of oral absorption and bioavailability

• Examples:
  – Salt selection
    – Animal study was used to verify the in silico model prediction
  – Formulation development
    – Mechanistic model was used to understand the formulation behavior in vivo based on animal study
  – in vitro – in vivo dissolution extrapolation
    – Animal data was used to validate methodology for in vitro - in vivo dissolution extrapolation
  – Interspecies differences
    – Mechanistic model was used to investigate interindividual and interspecies differences in formulation behavior

• Summary
**Discovery PK**

Combine *in silico* technologies to screen compound libraries in animals or humans

- Incorporate preclinical/*in vitro* data to extend FIH simulations to full *in vivo* outcomes (IVIVE)
- Mechanistic predictions of hepatotoxicity through QSP

**Clinical PK/Pharmacology**

Simulate population behaviors (e.g., pediatrics, disease)

- Build population PK/PD models
- Predict DDIs

**Pharmaceutical Development**

Assess various strategies during formulation development

- Assist with Quality by Design (QbD) implementation
- Develop mechanistic *in vitro-in vivo* correlations (IVIVCs)
- Understand food effects

**Discovery**

Preclinical

Clinical
Where are you in the research process?

Save resources and get to market faster with our solutions.
• GastroPlus includes mechanistic absorption models for variety of administration routes

• This presentation focuses on oral administration but similar principles could be applied in development of formulations for non-oral administration routes
Advanced Compartmental Absorption and Transit Model (ACAT™)

Mechanistic Absorption Modeling (MAM)

Physiologically based Pharmacokinetics (PBPK)
Processes Involved in Oral Absorption

These phenomena:
- are happening simultaneously
- are repeated in each of the compartments of the gastrointestinal tract

Transit In
- dose or from previous compartment
- unreleased & undissolved & dissolved

Transit Out
- to next compartment or excretion
- unreleased & undissolved & dissolved

Blood

Enterocytes

Lumen

C\textsubscript{mesentery/portal vein}

C\textsubscript{enterocytes}

C\textsubscript{lumen}

Passive and carrier mediated transport

Gut wall metabolism

Local pH, fluid volume, concentration of bile salts …

Dissolution

Precipitation

Degradation

Drug in solution, C\textsubscript{lumen}
The Big Picture

**Structure → ADMET Pred.**

**In vitro Experiments**

**Formulation - Dose, dosage form, particle size, release profile**

**API:**
- logP/logD
- pKa(s)
- Solubility
- Permeability
- Fup
- B/P ratio
- Clint or Km & Vmax, renal CL
- DDI interaction constants (Ki & kinact, EC50 & Emax)
- .....

**System/Physiology:**
- Body height, weight, BMI
- Tissue sizes & blood flows
- Tissue compositions (water, lipid, protein, acidic phospholipids, etc.)
- Intestinal fluid volume and composition (pH, bile salts, etc.)
- Intestinal transit times
- Enzyme & transporter expression levels
- .....

**PBPK Model**

**Fa%**
Cp-time profile (and F% with PBPK)
Nonlinear kinetics (and DDI)
PK in special populations
System/Physiology Parameters: Built in the Program, Editable by User
Intestinal physiologies for human and variety of animal species
System/Physiology Parameters: Built in the Program, Editable by User

PBPK physiologies for human variety of animal species

Human physiologies for different populations, gender, age (newborns through adults) and health status.

Intestinal physiology scales for given population and age
Species differences: Solubility/Dissolution

Changes in ionization result in changes in solubility in different regions of the intestine

Changes in bile salt concentrations in different regions of the intestine may result in changes in solubility (especially for more lipophilic compounds)

\[ Sol_{\text{bile, pH}} = Sol_{\text{aq, pH}} \left(1 + \frac{MWt_{H_2O}}{\rho_{H_2O}} \times SR \times C_{\text{bile}} \right) \]

Species differences: Absorption

The model accounts for:

- Difference in pH
- Difference in absorptive surface area
- Difference in pore sizes (tight junctions) and porosities
- Difference in distribution of transporter and enzyme expression levels (where known)

Example of interspecies differences in paracellular absorption

Species differences: Absorption

The model accounts for:

- Difference in pH
- Difference in absorptive surface area
- Difference in pore sizes (tight junctions) and porosities
- Difference in distribution of transporter and enzyme expression levels (where known)

Example of interspecies differences in transporter distributions (mRNA)

![Example of interspecies differences in transporter distributions (mRNA)](image)

Herrera-Ruiz AAPS PharmSciTech 2001, 3(1) article 9
Examples
Salt Selection I

- Mechanistic absorption model was used for sensitivity analysis to determine solubility requirements for the select salt form
- Animal PK study (rat) was conducted to verify the predictions
Salt Selection II

PBPK model was developed and verified by predicting the exposure after administration of phenytoin free acid administration.

Sensitivity analysis showed significantly increased absorption for even the lowest salt solubility.

in vivo study in rat confirmed the results of sensitivity analysis.

Table II. In Vivo Pharmacokinetics of Phenytoin Following Administration of a 100 mg/kg Oral Dose to Rats in the Form of the Free Acid or Salts (n=3 per Dose Group)

<table>
<thead>
<tr>
<th>Group</th>
<th>Form dosed</th>
<th>Precipitation inhibitor</th>
<th>AUC (µM*h)</th>
<th>C_max (µM)</th>
<th>%F</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Free acid</td>
<td>No</td>
<td>155±61</td>
<td>18±1</td>
<td>34±8</td>
</tr>
<tr>
<td>2</td>
<td>Na salt</td>
<td>No</td>
<td>444±96*</td>
<td>36±6*</td>
<td>97±22*</td>
</tr>
<tr>
<td>4</td>
<td>Piperazine salt</td>
<td>No</td>
<td>493±159*</td>
<td>36±12*</td>
<td>107±40*</td>
</tr>
<tr>
<td>3</td>
<td>Na salt</td>
<td>Yes</td>
<td>405±168*</td>
<td>35±15*</td>
<td>88±36*</td>
</tr>
<tr>
<td>5</td>
<td>Piperazine salt</td>
<td>Yes</td>
<td>405±74*</td>
<td>30±4*</td>
<td>88±19*</td>
</tr>
</tbody>
</table>

AUC area under the concentration-time profile, C_max, maximum observed concentration
*p<0.05; significantly different than group 1 using ANOVA followed by the least significant difference (LSD) post-hoc test
Select Formulation to Mitigate Food Effect I

NVS123

- weak base with pH-dependent and limited solubility
- when administered as dry filled capsules displayed positive food effect
- *in vitro, in vivo* preclinical (F1-F4) and/or clinical (F1-F3) studies and PBPK modeling was used to evaluate formulation strategies to mitigate the food effect.
Select Formulation to Mitigate Food Effect II

- *In vivo data* from animal (dog) study was used to analyze formulation behavior and determine the most likely cause of observed food effect.
- Differences in precipitation rates explained differences between fasted and fed state for the four formulations; these differences were supported also by *in vitro* experiments where precipitation was fasted in FaSSIF than in FeSSIF media for F1-F3.
Select Formulation to Mitigate Food Effect III

- *In vivo* data for the F1-F3 formulations in human was used to confirm that the fitted precipitation rates in dog translated to human and to evaluate relationship between *in vitro* and *in vivo* dissolution.
- The methodology was applied to predict behavior F4 in fasted and fed condition in human.
Select the Most Relevant *in vitro* Assay I

Lacidipine

- Rat and Dog data after IV and PO suspension administration were used to validate prediction of systemic distribution, elimination and intestinal absorption
- Dog PO data was used to select the most predictive *in vitro* dissolution experiment and validate methodology for *in vitro – in vivo* dissolution extrapolation
Select the Most Relevant *in vitro* Assay II

Dog data after PO administration of different formulations was used to select the most predictive *in vitro* dissolution experiment and test the methodology for prediction of *in vivo* dissolution.
Select the Most Relevant *in vitro* Assay III

The data from most predictive *in vitro* dissolution experiment was used to predict human PK.

**Fig. 8** The simulated and observed human *in vivo* PK profiles for the three lacidipine formulations using the Z-factor form FaSSIF-V2 dissolution media.
Ciprofloxacin:

- Mechanistic absorption/pharmacokinetic models for ciprofloxacin were used to deconvolute dissolution and absorption behavior after oral administration (solution and two table formulations) in human and dog.
- Deconvoluted dissolution and absorption profiles provided insights into causes of intersubject variability and interspecies differences in ciprofloxacin behavior in vivo.
Explore Interspecies Differences in Oral Absorption II

**in vivo dissolution and absorption in human**

Table II. The ADMET predictor-generated ciprofloxacin physicochemical characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight (g/mol)</td>
<td>331.35</td>
</tr>
<tr>
<td>pKa</td>
<td></td>
</tr>
<tr>
<td>Acid</td>
<td>5.75</td>
</tr>
<tr>
<td>Base</td>
<td>8.9</td>
</tr>
<tr>
<td>Aqueous solubility</td>
<td></td>
</tr>
<tr>
<td>pH 7.32</td>
<td>0.0266</td>
</tr>
<tr>
<td>Simulated gastric fluid pH 7.32</td>
<td>5.34</td>
</tr>
<tr>
<td>Fed simulated small intestinal fluid pH 6.5</td>
<td>0.76</td>
</tr>
<tr>
<td>Bile salt concentration = 3 mM</td>
<td></td>
</tr>
<tr>
<td>Fed simulated small intestinal fluid pH 5.0</td>
<td>0.73</td>
</tr>
<tr>
<td>Bile salt concentration = 15 mM</td>
<td></td>
</tr>
<tr>
<td>Solubilization ratio</td>
<td>2.30E+05</td>
</tr>
<tr>
<td>Log P</td>
<td>0.81</td>
</tr>
<tr>
<td>Log D</td>
<td></td>
</tr>
<tr>
<td>pH 1.2</td>
<td>-1.9</td>
</tr>
<tr>
<td>pH 4.6</td>
<td>-1.67</td>
</tr>
<tr>
<td>pH 6.8</td>
<td>-0.85</td>
</tr>
<tr>
<td>pH 7.4</td>
<td>-0.83</td>
</tr>
<tr>
<td>Diffusion coefficient (cm²/s × 10⁸)</td>
<td>0.76</td>
</tr>
<tr>
<td>Pept (cm²/s × 10⁸)</td>
<td>0.56</td>
</tr>
</tbody>
</table>

**in vivo dissolution and absorption in dog**

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25
Explore Interspecies Differences in Oral Absorption III

**Fig. 2.** Comparison of observed ciprofloxacin absolute bioavailability in the three formulations: dogs (n = 5) versus human (n = 10).

**Fig. 5.** Mean fraction (±dev) of administered dose absorbed as a function of formulation across the intestinal segments of dogs (a) and humans (b).
Summary

• PBPK models provide unique platform to combine information from *in vitro, in silico* and animal assays for accurate prediction of complex drug behavior *in vivo*

• These models are now routinely used to predict first-in-human exposure, and applications in the area of formulation design and development have also been increasing in last few years

• The models are useful not only for prediction of drug exposure before an *in vivo* study, but are invaluable tool in investigation of complex drug/formulation behaviors observed *in vivo*

• There are still gaps in characterization of physiologies (especially in animals), closing these gaps will further increase accuracy and utility of these models
GastroPlus Development Team

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With support from:
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Consulting Studies
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Discovery Cheminformatics
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