Mechanistic Absorption/PBPK Modeling to Predict Positive/Negative Food Effects: Approaches and Special Considerations

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Presentation Outline

• Early examples and proposed approach
• Fasted vs. fed state model descriptions – where are we today?
• Case study: positive food effect predictions – input review
• Case study: negative food effect predictions – *in vitro* considerations
• Future directions and conclusions
EARLY EXAMPLES AND PROPOSED APPROACHES
BCS* Predicts Likelihood and Direction of Food Effect 60 – 70% of the Time

<table>
<thead>
<tr>
<th>Food Effect/BCS</th>
<th>Class I</th>
<th>Class 2</th>
<th>Class 3</th>
<th>Class 4</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Negative</td>
<td>9 (30%)</td>
<td>0 (0%)</td>
<td>14 (61%)</td>
<td>1 (9%)</td>
<td>24</td>
</tr>
<tr>
<td>No effect</td>
<td>20 (67%)</td>
<td>8 (29%)</td>
<td>7 (30%)</td>
<td>2 (18%)</td>
<td>37</td>
</tr>
<tr>
<td>Positive</td>
<td>1 (3%)</td>
<td>20 (71%)</td>
<td>2 (9%)</td>
<td>8 (73%)</td>
<td>31</td>
</tr>
<tr>
<td>Total</td>
<td>30</td>
<td>28</td>
<td>23</td>
<td>11</td>
<td>92</td>
</tr>
</tbody>
</table>

The number of compounds in each BCS class for a specific food effect category is listed and the percentage is provided in the parentheses.

- 67% of Class I drugs had **no** food effect.
- 71% of Class II drugs had a **positive** effect.
- 61% of Class III drugs had a **negative** effect.
- 73% of Class IV drugs had a **positive** effect.

* Based on maximum absorbable dose (MAD), dose number, and logD(7.4)
Early Mechanistic ‘Food’ Predictions – Grapefruit Juice

First ACAT™ model simulations of gut and liver first pass extraction & grapefruit (GFJ) effect

→ Build/validate baseline models across several doses w/o GFJ

← Predict PK w/ GFJ

PO Midazolam: 7.5, 15, 30 mg solution

PO Midazolam: 15 mg w/ and w/o GFJ

Biorelevant Solubility Data – Inform Food Effect Predictions

1.5- to 2.4-fold increase in AUC under fed conditions due to increased solubility at higher bile salt concentrations
Utility of Physiologically Based Absorption Modeling in Implementing Quality by Design in Drug Development

Xinyuan Zhang,1 Robert A. Lionberger,1,2 Barbara M. Davit,1 and Lawrence X. Yu1

Table III. Comparison of Predicted vs. Observed Mean Plasma PK Parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Suspension</th>
<th>IR tablet</th>
<th>XR tablet</th>
<th>XR capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dose (mg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>400</td>
<td>400</td>
<td>300</td>
</tr>
<tr>
<td>Cmax (ng/mL)</td>
<td>Fasted</td>
<td>3066.7</td>
<td>3610.1</td>
<td>3015.2</td>
</tr>
<tr>
<td></td>
<td>Fed</td>
<td>2580.0</td>
<td>3713.7</td>
<td>3105.2</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2914.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC0-t (µg·h/mL)</td>
<td>Fasted</td>
<td>5920.0</td>
<td>3239.9</td>
<td>3786.6</td>
</tr>
<tr>
<td></td>
<td>Fed</td>
<td>5501.2</td>
<td>3878.6</td>
<td>2798.5</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUCinf (µg·h/mL)</td>
<td>Fasted</td>
<td>279.8</td>
<td>297.0</td>
<td>270.4</td>
</tr>
<tr>
<td></td>
<td>Fed</td>
<td>301.6</td>
<td>263.7</td>
<td>286.1</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tmax (hr)</td>
<td>Fasted</td>
<td>40.3</td>
<td>38.6</td>
<td>265.6</td>
</tr>
<tr>
<td></td>
<td>Fed</td>
<td>34.8</td>
<td>27.2</td>
<td>236.7</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>POT30 (hr)</td>
<td>Fasted</td>
<td>[0.6,8.5]</td>
<td>[3.7,41]</td>
<td>[10.42]</td>
</tr>
<tr>
<td></td>
<td>Fed</td>
<td>[1.1,16]</td>
<td>[2.3,19]</td>
<td>[8.1,42]</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fa (%)</td>
<td>Fasted</td>
<td>99.9</td>
<td>93.0</td>
<td>71.6</td>
</tr>
<tr>
<td></td>
<td>Fed</td>
<td>99.9</td>
<td>99.8</td>
<td>78.2</td>
</tr>
<tr>
<td>Correlation coeff. (r²)</td>
<td>Fasted</td>
<td>0.956</td>
<td>0.975</td>
<td>0.974</td>
</tr>
<tr>
<td></td>
<td>Fed</td>
<td>0.940</td>
<td>0.954</td>
<td>0.954</td>
</tr>
</tbody>
</table>

POT30 peak occupancy time, time span over which the concentration is within 20% of Cmax; Fa, fraction absorbed; N.A. not available.

Fig. 7. PK profiles sensitivity to the mean particle radius is different under fasted and fed state. a IR suspension, fasted state; b IR suspension, fed state. Legend in (b) is also applied to (a).
Proposed Flow Diagram for Simulation Studies in Quality by Design (QbD)

- **Build/validate models under fasted conditions**
  - Construct the PK model: (1) If human PK data are available, deconvolute PK data from i.v. administration (ideally) and/or p.o. administration of the fastest dissolving formulation to obtain disposition model; (2) If no human data, predicted from in vitro or animal data.
  - Collect drug information: formulation information, physicochemical properties, gut and liver extraction ratio, and etc.
  - Fix the parameters with high confidence in the ACAT model and optimize the parameters with high uncertainty to fit PK data obtained from another formulation.
  - Validate the model with different PK data set(s): different dosing regimens, different formulations, and different food conditions, etc.
  - Does the model predict the trend? Do we have enough confidence about the model?
  - No
  - Yes

- **Predict absorption/PK exposure under fed conditions**
  - Model exploration: (1) perform PSA to identify the key parameters in the formulation under different conditions to guide the next formulation design to achieve the target PK profile; (2) deconvolution of PK data to obtain in vivo dissolution profile and to identify biorelevant dissolution conditions by comparing with in vitro dissolution profiles; (3) simulate different dosing regimens; (4) conduct virtual BE study; (5) connect the PK model with a PD model; etc.

Fig. 1. The flow diagram shows a general process of using a physiologically based absorption model in QbD-based drug development.
FASTED VS. FED STATE MODEL DESCRIPTIONS – WHERE ARE WE TODAY?
What is ‘MAM’? What is ‘PBPK’?

MAM = Mechanistic Absorption Model

Physiological:
- pH gradients
- Dynamic fluid volumes
- Bile salt distributions
- Residence times
- Microvilli SAE
- Paracellular pore sizes
- Enzyme/transporter expressions

Drug Specific:
- pKa(s)
- Solubility vs. pH
- logD vs. pH
- Permeability
- Formulation properties

PBPK = Physiologically-Based Pharmacokinetic Model

Tissue properties:
- Specific volume(s)
- Blood perfusion rate
- Enzyme/transporter expression levels
- Volume fractions of lipids & proteins
- Tissue:plasma partition coefficient ($K_{p}$)

Drug Specific:
- Clearance
- Uptake
- Plasma protein binding
- Blood:plasma ratio
Main changes between Fasted and Fed state (default = moderate-fat meal):
- Higher stomach volume
- Changes in pH (stomach and upper SI)
- Longer gastric emptying
- Higher bile salt concentrations
- Increased liver blood flows
Fed State – Light and High-Fat/Caloric Meals

Gastric emptying is expected to vary between high-fat, high-caloric, and light meals.

The fat in high-fat meal may aid in dissolution of highly lipophilic compounds.
Food Effect Predictions – Select References

Evaluating impact of gastric pH, volume, and emptying of food effect (Sutton et al., 2017)

Bottom-up + Top-down approaches to assess food effect (Lu et al., 2017)

Applying PBPK modeling to inform clinical development and assess food effects (Chung et al., 2015)

Identification of food effect for MR dosage forms (Ilic et al., 2015)
POSITIVE FOOD EFFECT PREDICTIONS – INPUT REVIEW
Food Effect Modeling – Class II/IV Compound ‘X’

- Compound X (BCS Class II/IV)
- Lipophilic (log P > 4) and moderate base (pKa 3.2 and 6.2)
- Low (0.001 mg/mL), pH dependent aqueous solubility
- Moderate intestinal permeability (1.48 x 10^{-4} cm/s)
- Estimated bioavailability of compound is ~30%

Are the different (fitted) precipitation and gastric emptying times under fasted & fed conditions masking something else in the model?
Lysosomal Trapping of Lipophilic Cations

**Table:**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Log P</th>
<th>Basic pKa</th>
<th>$T_{max}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Propranolol</td>
<td>4.69</td>
<td>10.0</td>
<td>27</td>
</tr>
<tr>
<td>Maprotiline</td>
<td>4.7</td>
<td>10.1</td>
<td>16</td>
</tr>
<tr>
<td>Metaproline</td>
<td>3.81</td>
<td>8.52</td>
<td>15</td>
</tr>
<tr>
<td>Norpropoline</td>
<td>4.46</td>
<td>9.65</td>
<td>7.8</td>
</tr>
<tr>
<td>Fluoxetine</td>
<td>4.39</td>
<td>9.82</td>
<td>7</td>
</tr>
<tr>
<td>Chloroquine</td>
<td>5.11</td>
<td>9.86</td>
<td>6</td>
</tr>
</tbody>
</table>

**Diagram:**
- Hepatocyte
- Lysosome pH 4 - 5
- Cytosol pH ~7.2
- Plasma pH ~7.4

Lipophilic Amines
- LogP > 1
- pKa > 6

**Equation:**

The basis of pH partitioning of lipophilic amines into lysosomes. The diagram illustrates the mechanism by which lipophilic amines (i.e., CADs) accumulate in lysosomes. From plasma (pH 7.4) and cytosal (~7.2), a lipophilic amine (logP > 1, pKa > 6.5) will readily diffuse across membranes in its unionized form ($\text{RNH}_2$) while maintaining Henderson-Hasselbach equilibrium with its unionized form ($\text{RNH}_3^+$), which cannot readily diffuse across membranes. After diffusion into the acidic environment of the lysosome (pH 4-5), the equilibrium between charged and uncharged species shifts in favor of the unionized form of the lipophilic amine, limiting diffusion of the drug back into the cytosal and, in effect, trapping the drug in lysosomes. For highly permeable lipophilic amines, the concentration of unionized drug ($\text{RNH}_2$) at equilibrium is assumed to be the same in all three compartments (lysosomes, cytosal, and plasma). The figure is not to scale; lysosomes may be as much as 1% of the hepatocyte volume.

**References:**
- Kazmi F., Drug Metab. Disp. 41(3):897 (2013)
- PBPK Symposium 2018 – April 4th, 2018
Compound ‘X’ – Fasted State Model Development

Measured & ACAT™ Default Model Parameters

- Default precipitation
- Optimized precipitation

- Precipitation can’t account for delayed onset alone
- Hence, need to optimize gastric emptying time

![Graphs showing concentration vs. simulation time for different states of absorption and circulation.]

Hum 200 mg IR Cap - Fasted

- Dissolved
- Absorbed Enterocyte
- Portal Vein
- Systemic Circulation
Compound ‘X’ – PSA Around Fu, Enterocyte

Baseline fasted state model w/optimized precipitation

Fu, Enterocyte ~3.6% necessary to predict observed Tmax
Compound X: MembranePlus™ Fu, Enterocyte Prediction

Mechanistic simulated Fu, Enterocyte = 3.47% matches close to the value determined from the GastroPlus™ PSA predictions.
Compound ‘X’: GastroPlus™ Simulations with MembranePlus™ Fu, Enterocyte = 3.47%

- The lag between absorption into enterocyte and basolateral clearance into portal vein captures the extended Tmax
- No changes to default GI physiology required

Optimized precipitation & simulated Fu, Enterocyte

Dissolved
Absorbed Enterocyte
Portal Vein
Systemic Circulation
Compound ‘X’ – Food Effect Predictions Across Doses

- Optimized precipitation from low dose/fasted state PK data + simulated MembranePlus™ Fu, Enterocyte input
- Default ACAT™ fasted/fed physiology parameters

200 mg dose

400 mg dose
Mitigating Food Effect: Design of Experiments (DoE) Approach

- Is there an optimal combination of formulation parameters that allow us to reach our target endpoint (e.g., Fa%, Cmax, AUC)?
- Can we “design out” the food effect?
Parameter sensitivity analysis was run across dose and particle size together

- API particle size reduction may be useful to mitigate the food effect
  - But, only if nanoparticle formulations are options
Virtual BE Trial Simulation: Fasted vs. Fed Crossover – 25 Subjects

PBPK Population Simulation Approach:
1. Run ‘x’ subject population simulation applying systemic PK variability only
2. Load subjects from trial #1 and apply variability to fasted state ACAT™ model
3. Load subjects from trial #1 and apply variability to fed state ACAT™ model
4. Calculate virtual BE

PBPK Population Simulation: Hum 200 mg IR Cap - Fasted

Population Simulation: Hum 200 mg IR Cap - Fasted

200 mg IR capsules: d(50) PSD = 10 nm
Yellow = FASTED
Green = FED
NEGATIVE FOOD EFFECT PREDICTIONS – 
IN VITRO CONSIDERATIONS
Food Effect Modeling – Class III Charged Compound

Trospium HCl

- BCS Class III
- Hydrophilic (log P = -1.22)
- High (~700 mg/mL)
- Low intestinal permeability (0.07 x 10^-4 cm/s)
- Not Metabolized
- Estimated bioavailability of compound is ~10%

Mechanistic investigation of food effect on disintegration and dissolution of BCS class III compound solid formulations: the importance of viscosity

Asma Radwan⁶, Gordon L. Amidon⁎, and Peter Langguth⁎⁻⁸

⁎Institute of Pharmacy and Biochemistry, Johannes Gutenberg University, Mainz, Germany
⁎College of Pharmacy, The University of Michigan, Ann Arbor, MI 48109-1065, USA

PBPK Symposium 2018 – April 4th, 2018
Trospium Solution Viscosity

Table 2. Physicochemical properties of trospium chloride products in different disintegration media.

<table>
<thead>
<tr>
<th>Media</th>
<th>Disintegration time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIF</td>
<td></td>
</tr>
<tr>
<td>0.1 N HCl</td>
<td></td>
</tr>
<tr>
<td>0.5% HPMC (pH = 6.8)</td>
<td></td>
</tr>
<tr>
<td>1% HPMC (pH = 6.8)</td>
<td></td>
</tr>
<tr>
<td>2% HPMC (pH = 6.8)</td>
<td></td>
</tr>
<tr>
<td>Acetate buffer</td>
<td></td>
</tr>
<tr>
<td>0.5% HPMC (pH = 4.6)</td>
<td></td>
</tr>
<tr>
<td>1% HPMC (pH = 4.6)</td>
<td></td>
</tr>
<tr>
<td>2% HPMC (pH = 4.6)</td>
<td></td>
</tr>
<tr>
<td>0.25% guar (pH = 6.8)</td>
<td></td>
</tr>
<tr>
<td>0.5% guar (pH = 6.8)</td>
<td></td>
</tr>
<tr>
<td>0.75% guar (pH = 6.8)</td>
<td></td>
</tr>
</tbody>
</table>

ND, not determined.

Figure 3. Disintegration times of various trospium chloride products in different disintegration media. The effects of increasing media viscosity on disintegration times were in all cases significant (p < 0.05), whereas the effect of change of pH for HPMC solutions at the same concentrations of VEA was insignificant (p > 0.05). *pH 6.8; **pH 4.6

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Reference:

DOI: 10.1002/bdd
Trospium *in vitro* Dissolution

Figure 5. (a) Dissolution profiles for Spasmolyt® in viscous HPMC and guar solutions at pH 6.8, 50 rpm in USP-2 apparatus. In all cases values for $f_2$ were < 50. Mean ± SD, $n = 3$. (b) Dissolution profiles for Spasmex® in viscous HPMC and guar solutions at pH 6.8, 50 rpm in USP-2 apparatus. In all cases values for $f_2$ were < 50. Mean ± SD, $n = 3$. (c) Dissolution profiles for Trospil® in viscous HPMC and guar solution at pH 6.8, 50 rpm in USP-2 apparatus. In all cases values for $f_2$ were < 50. Mean ± SD, $n = 3$
Negative Food Effect – Predictions

Model building steps:
1. Create virtual human physiology
2. Incorporate in silico/in vitro property data
3. Utilize in vitro dissolution data from ‘fasted’ method to fit Z-Factor
4. Build MAM/PBPK model under fasted conditions
5. Utilize in vitro dissolution data from ‘fed’ method (high viscosity) to fit Z-Factor
6. Apply baseline MAM/PBPK model to predict PK profiles under fed conditions

Model results:
1. Capture fasted state PK profile well
2. Predict trend, but not magnitude, of negative food effect

Figure 8. Simulated and predicted plasma concentration–time profiles for trospium in fasted and fed states in humans
Ion pairing with bile salts modulates intestinal permeability and contributes to food-drug interaction of BCS class III compound trospium chloride.
Novartis Negative Food Effect: Caco-2 Experiment in FeSSIF Buffer
FUTURE DIRECTIONS AND CONCLUSIONS
Improved *In Vitro* Tools: Example – Biphasic Dissolution Experiment

**Aqueous Layer**

![Aqueous Layer Diagram]

**Organic Layer**

![Organic Layer Diagram]

**Fitted Mechanistic Nucleation Model Parameters using DDDPlus™**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exp. Correction</td>
<td>0.152</td>
</tr>
<tr>
<td>Lindfors Param (um)</td>
<td>0.330</td>
</tr>
</tbody>
</table>

**IVIVE for precipitation kinetics**

- PO-200mg fasted-Barone
- PO-200mg fed-Barone

**In vivo fit for precipitation kinetics**

- PO-200mg fasted-Barone
- PO-200mg fed-Barone

**Itraconazole**

![Itraconazole Molecule]

**Clinical Data:** Barone JA, Pharmacotherapy 1998; 18(2):295-301

**Modeling:** Szeto, Poster W5237 AAPS Annual Meeting Nov., 2015

33 Modeling: Szeto, Poster W5237 AAPS Annual Meeting Nov., 2015

Improved *In Vitro* Tools: Example – Biorelevant Permeability

**Biorelevant Permeability**


<table>
<thead>
<tr>
<th>HBSS</th>
<th>FaSSIF</th>
<th>FeSSIF</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.1% HSA</td>
<td>0.1% HSA</td>
<td>0.1% HSA</td>
</tr>
</tbody>
</table>

Control | FaSSIF | FeSSIF

| pH 6.5 Apical/pH 7.4 Basolateral |

Incubation at 37°C, 3 hours

Absorptive permeability estimated as indicated below:

\[ P_{\text{app}} = \frac{J}{C_{\text{ap}} \cdot \text{Area}} \]

HBSS: Hank’s-buffered salt solution

HSA: human serum albumin (non-specific binding reduction)

SIF: simulated gastric fluid (lectin, taurocholate, others)

**Compounds in Biorelevant Permeability Assay**

Assessment for micellar complexation

**PBPK simulations food effect for Compound X**

Using permeability difference of ~4-6 (FaSSIF vs. FeSSIF) in C2BBe1 cells

TODAY: Attempt to create absorptive flux vs. Peff correlations

FUTURE: Allow for flux input into models (dependent on method that combines system + drug-specific parameters)
What About Non-Oral Administration Sites?

Midazolam SubQ Dosing

Default IVIVE

With 45% SubQ Blood Flow Increase

Conclusions & General Observations

• Mechanistic modeling and simulation approaches are predictive and play an important role in QbD for drug development and regulatory interactions

• Need to better understand impact of fruit juices/nutritional supplements on metabolic and transporter processes

• Focus on building baseline models under fasted conditions first
  – Important to consider all mechanisms of your drug before predicting food effect

• Continued collaborations will lead to:
  – Advanced understanding of GI (and other administration site) physiology
  – Improved *in vitro* methods for defining model inputs (e.g., precipitation kinetics)
Acknowledgements

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  – Michael Bolger: Chief Scientist
  – Viera Lukacova: Director – Simulation Sciences
  – Jim Mullin: Team Leader – Simulation Technology
  – Grace Fraczkiewicz: Team Leader – Simulation Studies
  – Members of the Simulation Technologies team
  – Members of the Simulation Studies team
  – Members of the ADMET Cheminformatics team
Thank you for your kind attention!
Questions?