Case Studies of Mechanistic Absorption Modelling and IVIVC

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A Case Study in Avoiding Relative Bioavailability Studies for a BCS2 Drug

Neil Parrott

Background to the case study

- In 2010, a drug being developed for treatment of schizophrenia, is entering Ph 3 trials
- Roche held an EOP2 meeting with the FDA and requested waiver of an absolute bioavailability study for registration
- FDA agreed but requested a relative bioavailability study comparing the market formulation with a solution or suspension
- In 2011 Roche submitted a PBPK modelling report arguing that the relative BA study could be avoided
## Biopharmaceutical properties

<table>
<thead>
<tr>
<th>Property</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipophilicity logD at pH 7.4</td>
<td>3.0</td>
</tr>
<tr>
<td>Ionization constant</td>
<td>Neutral</td>
</tr>
<tr>
<td>Caco2 permeability scaled to HPeff</td>
<td>3.5 *10^{-4} cm/s</td>
</tr>
<tr>
<td><strong>Solubility</strong></td>
<td><strong>µg/mL</strong></td>
</tr>
<tr>
<td>Aqueous buffer pH 7</td>
<td>5</td>
</tr>
<tr>
<td>FaSSIF</td>
<td>25</td>
</tr>
<tr>
<td>FeSSIF</td>
<td>100</td>
</tr>
<tr>
<td>SGF</td>
<td>25</td>
</tr>
<tr>
<td>Clinical dose</td>
<td>~20 mg</td>
</tr>
</tbody>
</table>
Physiologically based model prediction and SAD

- PBPK was developed based on pre-clinical data and used to predict the human pharmacokinetics prior to the first in human studies in 2005.

- Predicted: CL: 1 mL/min/kg; Vss = 3 L/kg; F% (<80 mg) = 90%.

- The predicted pharmacokinetics were found to be in good agreement with the clinical data from the single ascending dose study at 3, 6, 12, 24, 50, 80, 120, 180 and 240 mg.

![Graph showing plasma concentration over time for a 50 mg dose.](image1)

![Graph showing AUCinf/Dose for different doses.](image2)
Further model verification - MAD and DDI

- High simulated fraction absorbed is in line with mass balance study.
  - 86% recovery of 80 mg dose only 5 to 15% parent in feces

- Multiple dose PK well predicted confirming time independent PK

- DDI studies with strong CYP3A inhibitor well simulated confirming very minor role of hepatic and intestinal first pass metabolism
Further model verification - food effect

- Simulation of the effect of a high fat/high calorie breakfast on PK after a single 80 mg dose

<table>
<thead>
<tr>
<th></th>
<th>fasted</th>
<th>fed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric emptying</td>
<td>0.25 hr</td>
<td>1 hr</td>
</tr>
<tr>
<td>Solubility (µg/mL)</td>
<td>25</td>
<td>100</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>fed/fasted</th>
<th>Cmax ratio</th>
<th>AUC ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Simulated</td>
<td>1.4</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Observed</td>
<td>1.4</td>
<td>1.1</td>
<td></td>
</tr>
</tbody>
</table>

### Graphs

- **Simulation**
  - Plasma Conc. (ng/mL) vs Time (hrs)
- **Observation**
  - Plasma Conc. (ng/mL) vs Time (hrs)
Parameter sensitivity analysis

GastroPlus Baseline parameters

Permeability scaled from Caco2 $3.5 \times 10^{-4}$ cm/s

Solubility in fasted state simulating fluid $25 \text{ ug/mL}$

Particle size $6 \text{ um}$ radius
Further model verification – particle size

Relative BA study performed to bridge from capsules to tablets

Also compared 30 mg tablets containing powder prepared with either jet milling or hammer milling

<table>
<thead>
<tr>
<th>Particle radius (µm)</th>
<th>JET milled</th>
<th>HAMMER milled</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1.8</td>
<td>12.5</td>
</tr>
</tbody>
</table>

N= 22 NHVs

Relative BA of HAMMER to JET (90% CI)

78% for AUCinf/dose (72% – 80%)
62% for Cmax/dose (57% – 67%)
PBPK model prediction of an oral suspension vs tablet

At this time the FDA did not consider modelling was sufficient to waive the relative BA study
Predicted and observed suspension vs tablet

Bioequivalent

90% CIs Cmax and AUC0-inf within 80% to 125%.
Discussion

• We considered that the simulation of the relative bioavailability of a solution vs tablet should be reliable because the PBPK model captured the pharmacokinetics well.

• In particular absorption related factors were well captured as shown by particle size and food effect studies.

• 1st pass metabolism was well described and simulations of ascending doses indicated that the prediction of solubility limited absorption at higher dose was valid.

• Therefore in this dose range exposures are unlikely to be increased substantially through a different oral formulations.
Use of oral absorption modelling to characterize drug release and absorption of a BCS II compound from IR formulations

Cordula Stillhart

# Compound properties and clinical formulations

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecular weight</td>
<td>445 g/mol</td>
</tr>
<tr>
<td>pKa</td>
<td>2.07 (b)</td>
</tr>
<tr>
<td>logD</td>
<td>1.86 (pH 7.4)</td>
</tr>
<tr>
<td>Solubility</td>
<td>Aqueous buffer pH 1-9: &lt; 1 μg/mL</td>
</tr>
<tr>
<td></td>
<td>FaSSIF: 10 μg/mL</td>
</tr>
<tr>
<td></td>
<td>FeSSIF: 32 μg/mL</td>
</tr>
<tr>
<td>Permeability</td>
<td>High ($P_{\text{eff}} 3.7 \times 10^{-4}$ cm/s)</td>
</tr>
<tr>
<td>Physical state</td>
<td>Crystalline</td>
</tr>
</tbody>
</table>

**Clinical formulations**

- **Phase 1**: IR **tablet** (dose strength 0.5 / 5 / 40 / 250 mg)
- **Phase 2**: IR **film-coated tablet** and IR **granules** in sachet (dose strength 120 mg)
Clinical pharmacokinetics

**Overview**

- **Tablet (Phase 1):** dose proportional exposure for oral doses between 1.5 and 130 mg, less than dose proportional exposure for higher doses ($C_{max}$ and AUC)
- **Granules in sachet:** similar exposure as tablet formulation
- **Film-coated tablet:** lower exposure compared to granules/Phase 1 tablet ($AUC_{inf}$ -30%, $C_{max}$ -35%)
Objectives

- To characterize the **mechanism of drug release and absorption** from immediate release formulations

- To understand the **root cause for different drug exposure** following administration of film-coated tablets and granules

- To develop an **in vitro-in vivo correlation** (IVIVC) model for future formulation development
Development of oral absorption model

*Input parameters*

**Compound:**
- Experimental physicochemical properties
- Formulation: IR tablet / IR suspension
- Dissolution model: Johnson

**Gut Physiology:**
- Human – Physiological – Fed (default)
- ASF model: Opt logD Model SA/V 6.1 (default)

**Pharmacokinetics:**
- Two-compartment PK
- Disposition PK: model fitting using iv microdosing data (PKPlus®)

**Graph:**
- Plasma concentration (ng/ml) vs Time (h)
- iv microdosing
Accurate prediction of oral exposure following administration of tablet formulations in the dose range from 1.5 to 1250 mg

GastroPlus model captured dose-dependency in $C_{\text{max}}$ and AUC
• Accurate prediction of oral exposure for granules in sachet formulation
• However, exposure from film-coated tablet (same dose) was significantly overpredicted
IVIVC model development

**In vitro data**

- **In vitro dissolution method:**
  - USP 2 paddle apparatus (50 rpm)
  - Medium: 900 mL FeSSIF pH 5.0, 37°C
  - Formulation: equivalent to 40 mg API

**In vivo data**

- **Deconvolution method:**
  - GastroPlus Mechanistic Absorption method
  - For comparison: traditional deconvolution methods (numerical and Loo-Riegelmann)

**Model development:** in vitro and in vivo data using granules and film-coated tablet formulation (120 mg dose), fed state

**Model verification:** in vitro and in vivo data using tablet formulation (dose strength 0.5, 5, 40, and 250 mg), dose range: 1.5-1250 mg, fed state
The GastroPlus Mechanistic Absorption deconvolution method resulted in a very good correlation between in vitro and in vivo dissolution profiles.

Data sets used for model development: in vitro and in vivo data obtained from 120 mg granules in sachet and 120 mg film-coated tablet formulations.
IVIVC model verification

- Good prediction of oral exposure from tablet formulation over the entire dose range from 1.5 to 1250 mg
Discussion

• The IVIVC model was predictive for oral drug exposure from IR formulations exhibiting different release rates (FCT, granules in sachet) over a large dose range, which made it suitable for guiding future formulation development.

• Mechanistic absorption method was superior to traditional deconvolution methods (e.g., Loo-Riegelmann, numerical) mainly due to consideration of:
  – dissolution- and solubility-limited absorption (dose-dependent)
  – administration in fed state (e.g., prolonged gastric emptying)

• In vitro dissolution method did not provide real sink conditions, however, it captured the difference in release rate between formulations and resulted in an accurate IVIVC.
Prediction of relative bioavailability between IR and OROS formulation of oxybutynin

Andrés Olivares

Oxybutynin’s (OXY) OROS formulation

Higher bioavailability than its IR counterpart

- BCS class 1, highly cleared, CYP3A substrate, low oral bioavailability

- OROS formulation vs. IR:
  - Parent exposure ~30-70% higher than IR
  - Exposure of the main metabolite decreased by ~30%
  - Improved safety profile (anti-muscarinic side effects), yet similar efficacy as the IR formulations

Gupta and Sathyan, 1999; Gupta et al. 1999; Sathyan et al. 2001
Mechanistic prediction of OXY’s PK

**Bottom up PBPK predictions of IR formulation**

### Oxybutynin parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MW (g/mol)</td>
<td>357.5</td>
</tr>
<tr>
<td>$\log P_{o:w}$</td>
<td>3.7</td>
</tr>
<tr>
<td>$D_{\text{eff}}$ (cm$^2$/h)</td>
<td>0.025</td>
</tr>
<tr>
<td>Particle radius (µm)</td>
<td>10</td>
</tr>
<tr>
<td>Intrinsic solubility @37°C (mg/mL)</td>
<td>0.012</td>
</tr>
<tr>
<td>$pK_a$ (basic)</td>
<td>8.04</td>
</tr>
<tr>
<td>$f_{up}$</td>
<td>0.003</td>
</tr>
<tr>
<td>Blood/plasma ratio (BP)</td>
<td>0.69</td>
</tr>
<tr>
<td>$P_{\text{eff}}$ ($10^{-4}$ cm/s)</td>
<td>4.3</td>
</tr>
</tbody>
</table>

Observed data: Douchamps et al., 1988; Janssen clinical trial
Predicting OXY’s OROS formulation

Integration of the in vitro release into the PBPK model


Conley et al, 2006; Sathyan et al., 2004; Pitsiu et al. 2001
Predicting OXY’s OROS formulation

Excellent IVIVC predicted for OROS formulation

- Observed data
- Model prediction

Simulated IVIVC

$$R^2 = 0.95$$

Observed data kindly supplied by Janssen
Prediction of OXY’s relative bioavailability

**Intestinal interplay between absorption and metabolism**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>AUC$_{0-t}$ (ng/mL/h) (obs.)</th>
<th>AUC$_{0-t}$ (ng/mL/h) (pred.)</th>
<th>F$_{rel}$ (%) (obs.)</th>
<th>F$_{rel}$ (%) (pred.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IR (3x 5 mg)</td>
<td>21.7 ± 13.0</td>
<td>17.3</td>
<td>139 ± 44</td>
<td>172</td>
</tr>
<tr>
<td>OROS (10 mg)</td>
<td>18.6 ± 10.5</td>
<td>19.9</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Discussion

• A PBPK approach predicted differences in oral bioavailability between OXY’s IR and OROS were in good agreement with the observed data.

• In vitro release from the OROS tablet correlates very well with its in vivo dissolution.

• Major driver of higher bioavailability observed for oxybutynin OROS is the intestinal first-pass metabolism rather than the absorption differences between the two formulations. This particularly affects CYP3A4 substrates due to the uneven distribution of the CYP3A4 enzymes along the GI tract.
Overall discussion

• We showed three examples of the used mechanistic absorption/dissolution modelling provided further insights with respect to the key factors contributing to oral drug absorption and bioavailability.

• The use of the right *in vitro* experimental and modelling approaches such as mechanistic-deconvolution can guide clinical design and address team’s questions related to formulation.

• Validation of modelling approaches with external datasets are essential to generate confidence in the utility mechanistic modelling approach for addressing clinical questions.

• In our development projects this approach helped to define product specifications (i.e., particle size limits) under a QbD paradigm.
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Janssen
Avijit Ghosh
Doing now what patients need next
Parameter sensitivity analysis

Drug particle size

- Drug particle radius has significant impact on $C_{\text{max}}$
- Mean drug particle radius of API used in clinical formulations is in a sensitive range with regard to its impact on $C_{\text{max}}$, especially for the 120 mg dose
In vitro dissolution profiles
Granules vs film-coated tablets

- Dissolution rate from granules in sachet >>> film-coated tablet
- Dissolution rate from granules in sachet >>> granules for compression of film-coated tablets
- Manufacturing process and formulation composition affect dissolution rate

Dissolution method:
- USP II
- Medium: FeSSIF
- 40 mg API per 900 mL FeSSIF
Understanding differences in drug release

Comparison of clinical formulations

- Almost same manufacturing process and qualitative composition
- Comparatively high drug load in 120 mg FCT and 250 mg tablet formulation:

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Drug load (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mg tablet</td>
<td>0.07</td>
</tr>
<tr>
<td>5 mg tablet</td>
<td>0.70</td>
</tr>
<tr>
<td>40 mg tablet</td>
<td>5.30</td>
</tr>
<tr>
<td>250 mg tablet</td>
<td>33.33</td>
</tr>
<tr>
<td>120 mg granules in sachet</td>
<td>12.82</td>
</tr>
<tr>
<td>120 mg film-coated tablet</td>
<td>25.81</td>
</tr>
</tbody>
</table>

→ Potential exceedance of percolation threshold in the tablet matrix
Understanding differences in drug release

*Percolation threshold*

- If the percolation threshold is exceeded, the API may not be released as single micronized particle, but as larger aggregate of multiple particles.
- API surface area $\downarrow$ and dissolution rate $\downarrow$

**Percolation threshold:**
Critical drug concentration necessary to form a coherent network, which dominates the properties of the whole system.

Figure source: [http://www.tda.com/eMatls/composites.htm](http://www.tda.com/eMatls/composites.htm)
Raman imaging

Granules, tablet, film-coated tablet

- All formulations exhibit regions with high drug particle density $\rightarrow$ cohesive properties of API
- Tablet compression increases cohesion of API particles
- 120 mg granules and 40 mg tablet formulation show API-rich regions which still include excipient particles
- 120 mg film-coated tablet shows large agglomerated clusters forming a coherent network in the tablet matrix
Doing now what patients need next