An *in silico* physiologically-based pharmacokinetic (PBPK) study of the impact of the drug release rate on oral absorption, gut wall metabolism and relative bioavailability

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• Intended to control the absorption rate

• Advantages compared to conventional dosage forms (IR):
  ✓ Reduction in peak to trough fluctuations
  ✓ Prolonged exposure (drugs with short half life)
  ✓ Targeted drug delivery

• When developing a CR formulation the goal is to achieve similar exposure as the marketed formulation
Motivating example: Oxybutynin IR vs. CR

- Bioavailability of CR formulation ~50% higher than IR\(^1\)
- Exposure of the main metabolite decreased by ~30%\(^1\)
  - Improved safety profile (antimuscarinic side effects), but similar efficacy as the IR formulations\(^2,3\)

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\(^1\)Gupta and Sathyan, 1999; \(^2\)Gupta et al. 1999; \(^3\)Sathyan et al. 2001
Oral absorption of solid dosage forms

\[ F = f_a \cdot F_G \cdot F_H \]

- \( F_H = 1 - E_H \)
- \( F_G = 1 - \sum E_{G_i} \)
- \( 1 - f_a \) (faeces)
Possible interplay between absorption and gut wall metabolism

Stomach $ightarrow$ Duodenum $ightarrow$ Jejunum $ightarrow$ Ileum $ightarrow$ Colon

Systemic circulation (F)

Portal vein $(f_a \cdot F_G)$

Liver $F_H$

IR

Possible interplay between absorption and gut wall metabolism

Relative CYP3A4 Abundance

Project aims

• To investigate the impact of the interplay between drug release, physicochemical and biochemical properties on oral drug absorption and CYP3A4-mediated gut wall metabolism using a PBPK modelling and simulation (M&S) approach.

• To identify the drug and formulation specific factors associated with the higher relative bioavailability observed for some CR formulations of CYP3A substrates
Is this common for other CYP3A substrates?

- IR and CR in the same sets of healthy adults volunteers
- Fasted
A PBPK M&S factorial study

The Simcyp's Advanced Dissolution, Absorption and Metabolism (ADAM) model

(Darwich et al, 2012)

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A PBPK M&S factorial study

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value (Percentile)</th>
<th>1 (1&lt;sup&gt;st&lt;/sup&gt;)</th>
<th>2 (25&lt;sup&gt;th&lt;/sup&gt;)</th>
<th>3 (50&lt;sup&gt;th&lt;/sup&gt;)</th>
<th>4 (75&lt;sup&gt;th&lt;/sup&gt;)</th>
<th>5 (99&lt;sup&gt;th&lt;/sup&gt;)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{rel}$ ($h^{-1}$)</td>
<td></td>
<td>4.6</td>
<td>2.3</td>
<td>0.38</td>
<td>0.19</td>
<td>0.096</td>
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<tr>
<td>Solubility ($mg/mL$)&lt;sup&gt;9&lt;/sup&gt;</td>
<td></td>
<td>0.001</td>
<td>0.1</td>
<td>1</td>
<td>10</td>
<td>100</td>
</tr>
<tr>
<td>$P_{app}$ (Caco-2) ($10^{-6} , cm/s$)&lt;sup&gt;10,11&lt;/sup&gt;</td>
<td></td>
<td>0.01</td>
<td>0.5</td>
<td>5</td>
<td>10</td>
<td>80</td>
</tr>
<tr>
<td>$V_{max}$ CYP3A4 (pmol/min/mg)&lt;sup&gt;12&lt;/sup&gt;</td>
<td></td>
<td>1</td>
<td>100</td>
<td>500</td>
<td>2,500</td>
<td>10,000</td>
</tr>
<tr>
<td>$K_{M}$ CYP3A4 ($\mu M$)&lt;sup&gt;12&lt;/sup&gt;</td>
<td></td>
<td>1</td>
<td>10</td>
<td>50</td>
<td>100</td>
<td>10,000</td>
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<tr>
<td>$J_{max}$ P-gp (Efflux) (pmol/min)&lt;sup&gt;13&lt;/sup&gt;</td>
<td></td>
<td>1</td>
<td>30</td>
<td>300</td>
<td>500</td>
<td>1,500</td>
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<tr>
<td>$K_{M}$ P-gp ($\mu M$)&lt;sup&gt;13&lt;/sup&gt;</td>
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<td>1</td>
<td>50</td>
<td>150</td>
<td>300</td>
<td>2,000</td>
</tr>
</tbody>
</table>

How to analyse such large dataset?

Number of simulations = Levels^{Factors} = 5^7

Biopharmaceutics classification system (BCS)

<table>
<thead>
<tr>
<th>Solubility</th>
<th>Permeability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Class 2</td>
<td>Class 1</td>
</tr>
<tr>
<td>Class 4</td>
<td>Class 3</td>
</tr>
</tbody>
</table>

\[
Dn = \frac{Dose/250\ ml}{Solubility} \\
fa = 1 - e^{-\frac{2P_{eff}T_{SI}}{R}}
\]

Scenarios of interest (one-at-at-time)

1. Release and CYP3A4
2. Release, CYP3A4 and P-gp
Impact on absorption, first pass metabolism and systemic exposure

SIMULATION OUTCOME
1. Release & $CL_{CYP3A4}$
1. Release & $\text{CL}_{\text{CYP3A4}}$
2. Release, $\text{CL}_{\text{CYP3A4}}$ and $\text{CL}_{\text{P-gp}}$ (fixed)
2. Release, $\text{CL}_{\text{CYP3A4}}$ and $\text{CL}_{\text{P-gp}}$ (fixed)
Higher relative bioavailability: Parameter space

Relative bioavailability (CR/IR) of CYP3A4 substrates
BCS Class 1

$F_{rel} (%)$ (CR/IR)

$CL_{int, CYP3A4} (\mu L/min/mg)$

$k_{rel}(h^{-1})$
Simulations vs. observed data

Relative bioavailability (CR/IR) of CYP3A4 substrates
BCS Class 1

$F_{rel} (%)$ (CR/IR)

$CL_{int}$, CYP3A4 ($\mu$L/min/mg)

$k_{rel}$ (h$^{-1}$)
Conclusions

- The use of an absorption PBPK model allowed the simultaneous consideration of both formulation and drug-specific properties and their impact on oral bioavailability.

- In almost all the cases, a reduced absorption, *i.e.* reduced $f_a$, was observed when employing a CR formulation. However, in some cases this was compensated by a reduction on intestinal metabolism (higher $F_G$), thus leading to a net increase in systemic exposure.

- CR formulations of highly permeable and highly CYP3A4 -cleared compounds are more likely to display higher relative bioavailability than the IR formulations. This can be used as an advantage when developing and CR formulation.
Acknowledgments

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Thank you all for listening!