Evaluating the impact of extended release formulations on absorption and gut-wall metabolism using a physiologically-based pharmacokinetic simulation approach

Yoshiteru Kamiyama¹,², Andrés Olivares-Morales¹, Adam S. Darwich¹, Amin Rostami-Hodjegan¹,³

¹- Centre of Applied Pharmacokinetic Research, University of Manchester, UK
²- Analysis & Pharmacokinetics Labs, Astellas Pharma Inc., Japan
³- Simcyp Ltd, Sheffield, UK

Introduction and Objectives

- Drug absorption to the gut wall and first-pass gut metabolism play important roles in the development of oral drugs.
- Extended-release (ER) formulations are used to prolong the duration of drug delivery to the systemic circulation and to reduce the frequency of dose administration.
- However, ER formulations may alter the extent of oral drug bioavailability as compared to an immediate-release (IR) formulation and this may vary based on the interplay between the physicochemical characteristics of the drug and gastrointestinal (GI) disposition involving metabolic enzymes and efflux transporters[1].
- The Advanced Dissolution, Absorption, Metabolism (ADAM) model (Figure 1), incorporated into PBPK simulator Simcyp® (v.12)[2] was used to assess kinetic parameters associated with higher bioavailability for ER formulations relative to that of IR.

Method

- Various hypothetical compounds were simulated based on ondansetron (molecular weight: 357.45 and LogP≤8±2.6) by varying drug and formulation specific parameters including: pKa, solubility, permeability, Km for CYP3A4 (Km,CYP3A4), the maximum metabolic rate (Vmax,CYP3A4), Km and Jmax for P-gp (Jmax,P-gp and Km,P-gp, respectively) (Table 1).
- AUC, fraction of drug absorbed into the gut wall (fA), and fraction of drug that escapes gut wall extraction (F0) were simulated for IR and three different ER formulations (ER) where the first order rate of release from the formulation (Kw, h⁻¹) were 3.79 (IR), 0.32 (ER1), 0.16 (ER2), and 0.03 (ER3), respectively (Figure 2).
- The differences between IR and ER formulations were investigated for AUC, fA and F0 under various conditions (Figure 2, and 3).

Table 1 Physicochemical and Pharmacokinetic parameters on hypothetical compounds

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Unit</th>
<th>Value</th>
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<tr>
<td>Solubility (Sol)</td>
<td>mg/mL</td>
<td>0.04 0.06 0.12</td>
</tr>
<tr>
<td>Permeability in Caco-2 cell (Papp)</td>
<td>x 10⁻⁶ cm/s</td>
<td>0.019 0.759 74.5</td>
</tr>
<tr>
<td>Vmax for CYP3A4 (Vmax,CYP3A4)</td>
<td>pmol/min/mg Ms protein</td>
<td>0.001 1 400000</td>
</tr>
<tr>
<td>Km for CYP3A4 (Km,CYP3A4)</td>
<td>µM</td>
<td>0.1 2 200</td>
</tr>
<tr>
<td>Jmax for P-gp (Jmax,P-gp)</td>
<td>µM/min</td>
<td>0.01 2 20000</td>
</tr>
<tr>
<td>Km for P-gp (Km,P-gp)</td>
<td>µM</td>
<td>0.1 2 200</td>
</tr>
<tr>
<td>pKa</td>
<td>-</td>
<td>4.5 Neutral 8</td>
</tr>
</tbody>
</table>

Figure 2 - Release profiles of IR and three types of ER formulations (ER1, ER2, and ER3).

Results

- Increasing Vmax,CYP3A4 from 0.001 to 40,000 pmol/min/mg Ms protein resulted in an increase in F0 of up to 2.2-fold for the ER formulations as compared to IR for all ionic classes (Figure 4-6).
- Alteration to Km,P-gp from 0.1 to 200 µM did not significantly increase F0 ratios between ER and IR formulations (Figure 4-6).
- The ER/IR ratios of fA and AUC displayed up to a 1.6-fold increase for basic compounds at a low Km,P-gp (Figure 4).

Figure 3 - Study design of the sensitivity analysis.

Figure 4 - Ratio of pharmacokinetic parameters of three types of extended release formulations over immediate release formulation in basic compounds. (A) AUC ratio, (B) fA ratio, and (C) F0 ratio.

Figure 5 - Ratio of pharmacokinetic parameters of three types of extended release formulations over immediate release formulation in neutral compounds. (A) AUC ratio, (B) fA ratio, and (C) F0 ratio.

Figure 6 - Ratio of pharmacokinetic parameters of three types of extended release formulations over immediate release formulation in acid compounds (A) AUC ratio, (B) fA ratio, and (C) F0 ratio.

Conclusions

The analysis identified that affinity values for CYP3A4 and P-gp could be associated with higher relative bioavailability of ER as compared to IR formulations. These findings may have implications for study design and pharmacotherapy as well as the relative exposure to metabolite vs parent compound.

References