T3197

Higher relative bioavailability following extended release oral formulations: Exploring the potential mechanisms and associated parameter space using a physiologically-based pharmacokinetic approach

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Introduction and Purpose

- Gastrointestinal (GI) absorption and metabolism are important for determining the disposition of orally administered 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 displayed an altered extent of oral drug bioavailability as compared to immediate-release (IR) formulations, this may vary based on the interplay between the physicochemical characteristics of the drug and GI disposition such as: metabolic enzyme and efflux transporter affinity [1].
- The Advanced Dissolution, Absorption and Metabolism (ADAM) model (**Figure 1**), incorporated into the physiologically-based pharmacokinetic (PBPK) simulator Simcyp® v.12 [2] was used to assess pharmacokinetic parameters associated with an altered bioavailability for ER formulations relative to that of IR.

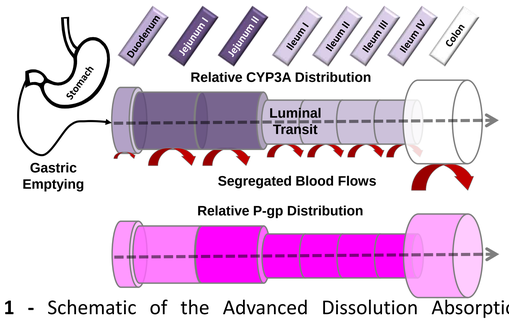

Figure 1 - Schematic of the Advanced Dissolution Absorption and Metabolism (ADAM) model. Purple and pink color refer to regional CYP3A and P-glycoprotein abundance, respectively.

Method

- Information on relative bioavailability of ER and IR was collated from published literature. Weighted mean ($W\bar{X}$), ER/IR, AUC ratios and variances (s^2) were calculated based on number of subjects (w) and mean AUC ratio (x) in the i^{th} study (Eq. 1 and 2).

$$W\bar{X} = \frac{\sum_{i=1}^{n} w_i x_i}{\sum_{i}^{n} w_i} \qquad s^2 = \frac{\sum_{i=1}^{n} w_i}{(\sum_{i=1}^{n} w_i)^2 - (\sum_{i=1}^{n} {w_i}^2)} \sum_{i=1}^{N} w_i (x_i - W\bar{X})^2 \quad \textbf{Eq. 1 \& 2}$$

- Hypothetical compounds were simulated based on oxybutynin (molecular weight: 357.45 g/mol and $LogP_{o:w}$: 2.6) by varying drug and formulation specific parameters including: pKa, solubility, permeability, K_m for CYP3A4 ($K_{m\text{-}CYP3A4}$), maximum metabolic rate ($V_{max\text{-}CYP3A4}$), K_m and J_{max} for P-gp ($J_{max\text{-}P\text{-}gp}$ and $K_{m\text{-}P\text{-}gp}$, respectively) (**Table 1**).
- Simulated AUC, fraction of drug absorbed into the gut wall (f_a), and fraction that escapes gut wall extraction (F_G) were examined for differences between IR and three ER formulations (ER) where first order rate of release from formulation (K_{rel}: h^{-1}) were 3.79 (IR), 0.32 (ER1), 0.16 (ER2), and 0.03 (ER3) (**Figure 2**).

Table 1. Pharmacokinetic parameters of simulated hypothetical compounds.

Parameter	Unit	Value		
		Low	Medium	High
Solubility (Sol)	mg/mL	0.04	0.06	0.12
Permeability in Caco-2 cell (Papp)	$\times 10^{-6}$ cm/s	0.019	0.759	74.5
V_{max} for CYP3A4 ($V_{max\text{-}3A4}$)	pmol/min/mg Ms protein	0.001	100	40000
K_m for CYP3A4 ($K_{m\text{-}3A4}$)	µM	0.1	2	200
J_{max} for P-gp ($J_{max\text{-}P\text{-}gp}$)	pmol/min	0.01	2	20000
K_m for P-gp ($K_{m\text{-}P\text{-}gp}$)	µM	0.1	2	200
pKa	-	4.5	Neutral	8

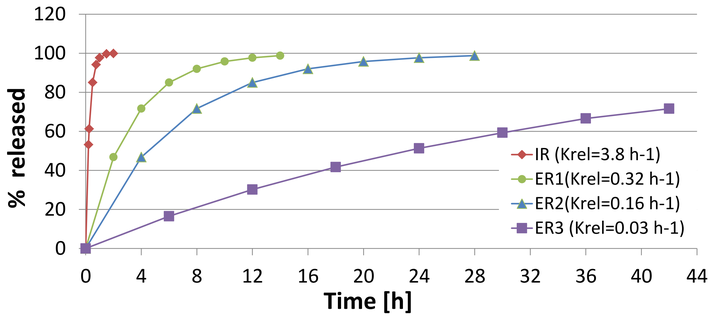

Figure 2 – Simulated release profiles of immediate-release (IR) and extended-release (ER) formulations (ER1, ER2, and ER3) at varying rate of release (k_{rel}).

Results

- A large variation of ER/IR AUC ratios was observed among the 21 identified drugs (**Figure 3**).

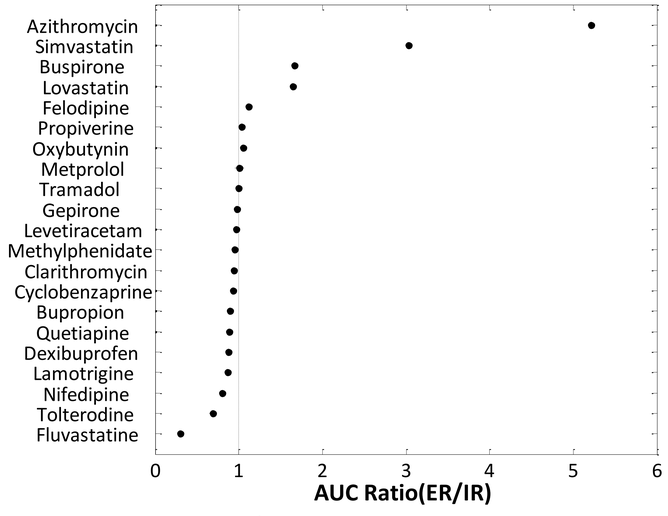

Figure 3 – Comparison of ER/IR AUC ratios of 21 orally administered drugs from published data.

- An increase in $V_{max\text{-}CYP3A4}$ from 0.001 to 40,000 pmol/min/mg microsomal protein resulted in an increase in F_G of up to 2.2-fold for the ER formulations as compared to IR for all ionic classes (**Figure 4-6**).
- Alternation of $K_{m\text{-}3A4}$ from 0.1 to 200 µM caused a minor increase in F_G when comparing between ER and IR formulations (**Figure 4-6**).
- The ER/IR ratios of f_a and AUC displayed up to a 1.6-fold increase for basic compounds at a low $K_{m\text{-}P\text{-}gp}$ (**Figure 4**).

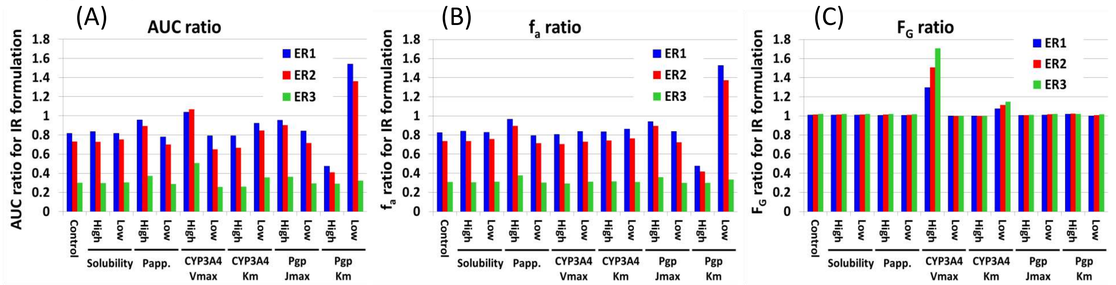

Figure 4 - Ratio of pharmacokinetic parameters of three types of extended-release (ER) formulations over immediate-release (IR) formulation in basic compounds. (A) AUC ratio, (B) f_a ratio, and (C) F_G ratio.

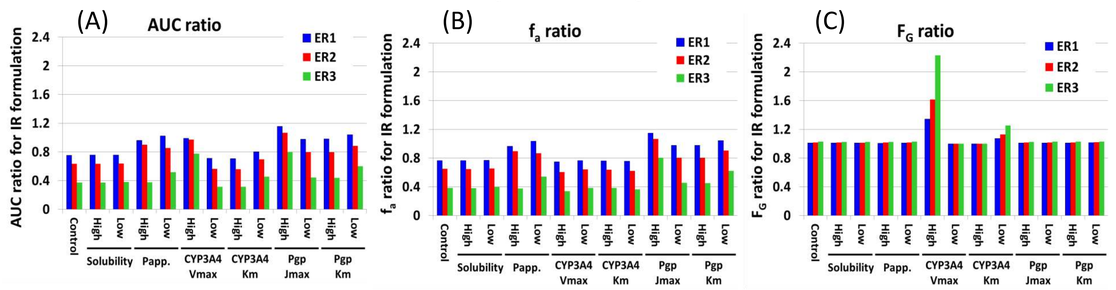

Figure 5 - Ratio of pharmacokinetic parameters of three types of extended-release (ER) formulations over immediate-release (IR) formulation in neutral compounds. (A) AUC ratio, (B) f_a ratio, and (C) F_G ratio.

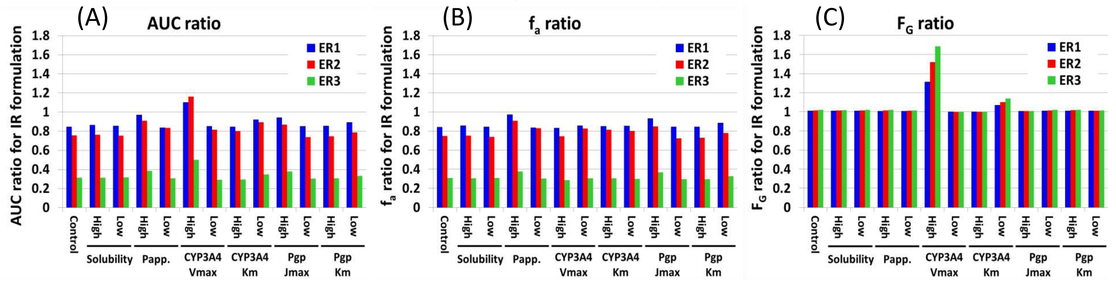

Figure 6 - Ratio of pharmacokinetic parameters of three types of extended-release (ER) formulations over immediate-release (IR) formulation in acidic compounds (A) AUC ratio, (B) f_a ratio, and (C) F_G ratio.

Conclusions

Analysis of the simulation study identified a higher affinity for CYP3A4 and P-gp to be associated with a larger relative bioavailability for ER as compared to IR formulations. These findings may have implications for study design and pharmacotherapy as well as the relative exposure of metabolite versus the parent compound.

References

1. Gupta SK, Sathyan G. J Clin Pharmacol 1999; 39, 289-296.
2. Jamei M, Turner D, Yang J, Neuhoff S, Polak S, Rostami-Hodjegan A, Tucker G. AAPS J. 2009; 11, 225-237.