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

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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.

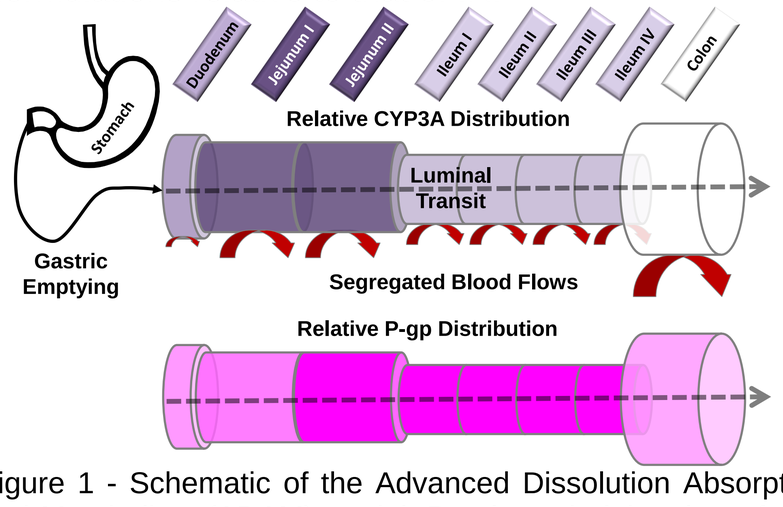

Figure 1 - Schematic of the Advanced Dissolution Absorption and Metabolism (ADAM) model. Purple and pink color refer to regional CYP3A and P-gp abundance, respectively.

Method

- Various hypothetical compounds were simulated based on oxybutynin (molecular weight: 357.45 and $LogP_{o:w,pH\ 6}$: 2.6) by varying drug and formulation specific parameters including: pKa, solubility, permeability, K_m for CYP3A4 ($K_{m\text{-}CYP3A4}$), the 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**).
- AUC, fraction of drug absorbed into the gut wall (f_a), and fraction of drug that escapes gut wall extraction (F_G) were simulated for IR and three different ER formulations (ER) where the first order rate of release from the formulation (K_{rel}: 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, f_a and F_G under various conditions (**Figure 2, and 3**).

Table 1 Physicochemical and Pharmacokinetic parameters on hypothetical compounds

Parameter	Unit	Value		
		Low	Medium	High
Solubility (Sol)	mg/mL	0.04	0.06	0.12
Permeability in Caco-2 cell (Papp)	× 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

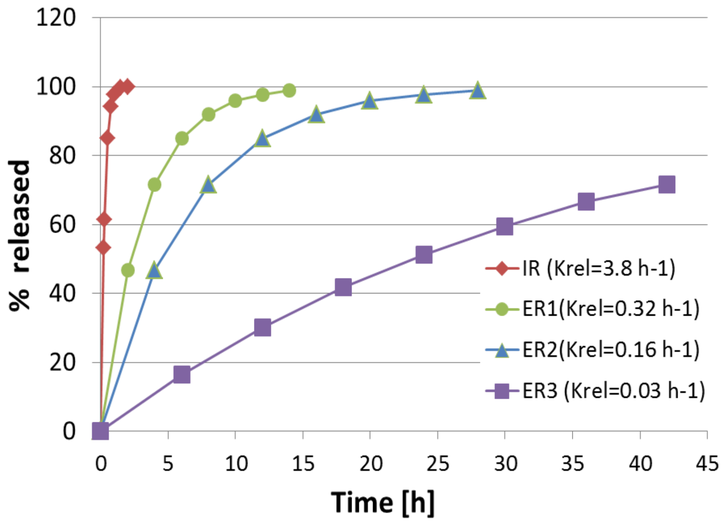

Figure 2 - Release profiles of IR and three types of ER formulations (ER1, ER2, and ER3).

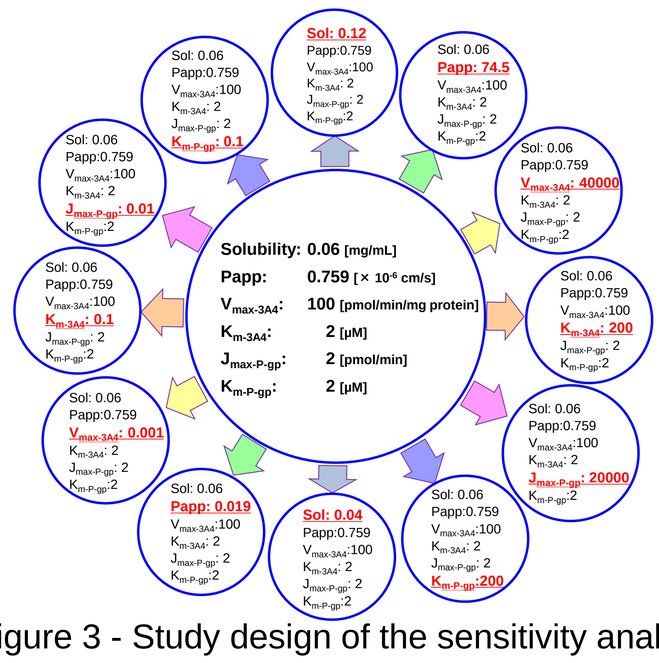

Figure 3 - Study design of the sensitivity analysis.

Results

- Increasing $V_{max\text{-}CYP3A4}$ from 0.001 to 40,000 pmol/min/mg Ms 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 to $K_{m\text{-}P\text{-}gp}$ from 0.1 to 200 µM did not significantly increase F_G ratios 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**).

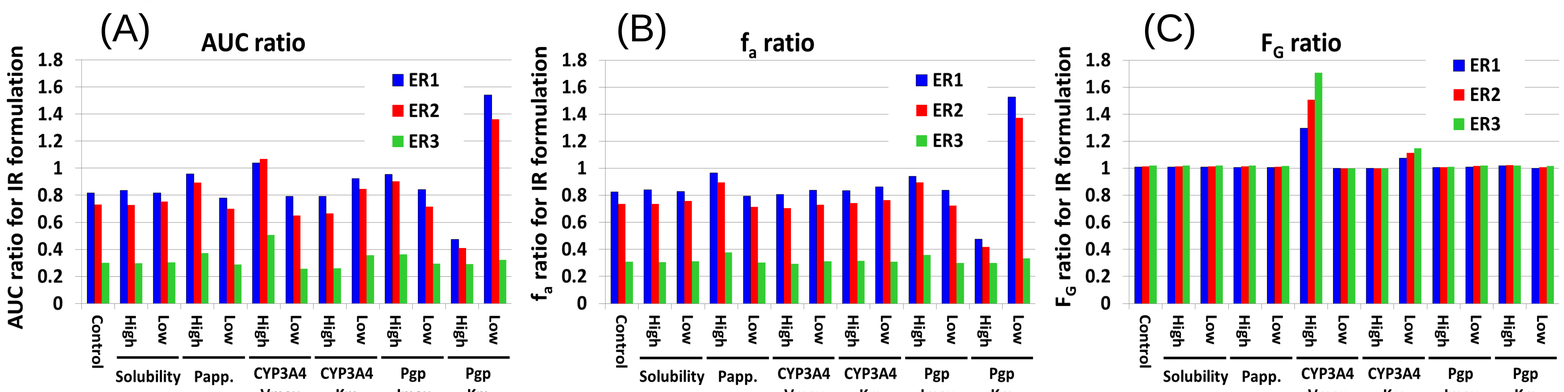

Figure 4 - Ratio of pharmacokinetic parameters of three types of extended release formulations over immediate release formulation in basic compounds. (A) AUC ratio, (B) f_a ratio, and (C) F_G ratio.

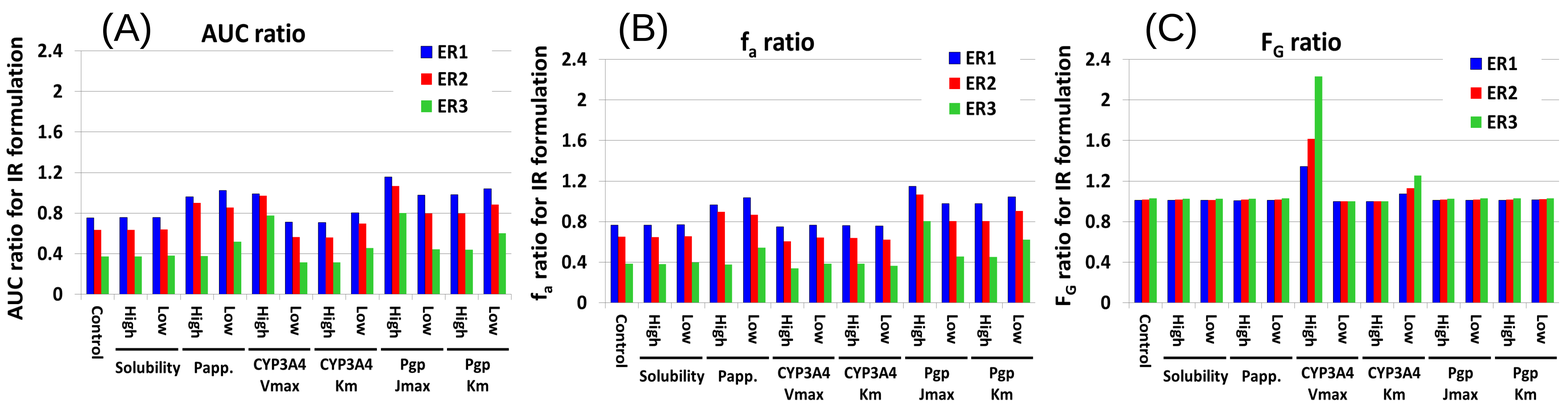

Figure 5 - Ratio of pharmacokinetic parameters of three types of extended release formulations over immediate release formulation in neutral compounds. (A) AUC ratio, (B) f_a ratio, and (C) F_G ratio.

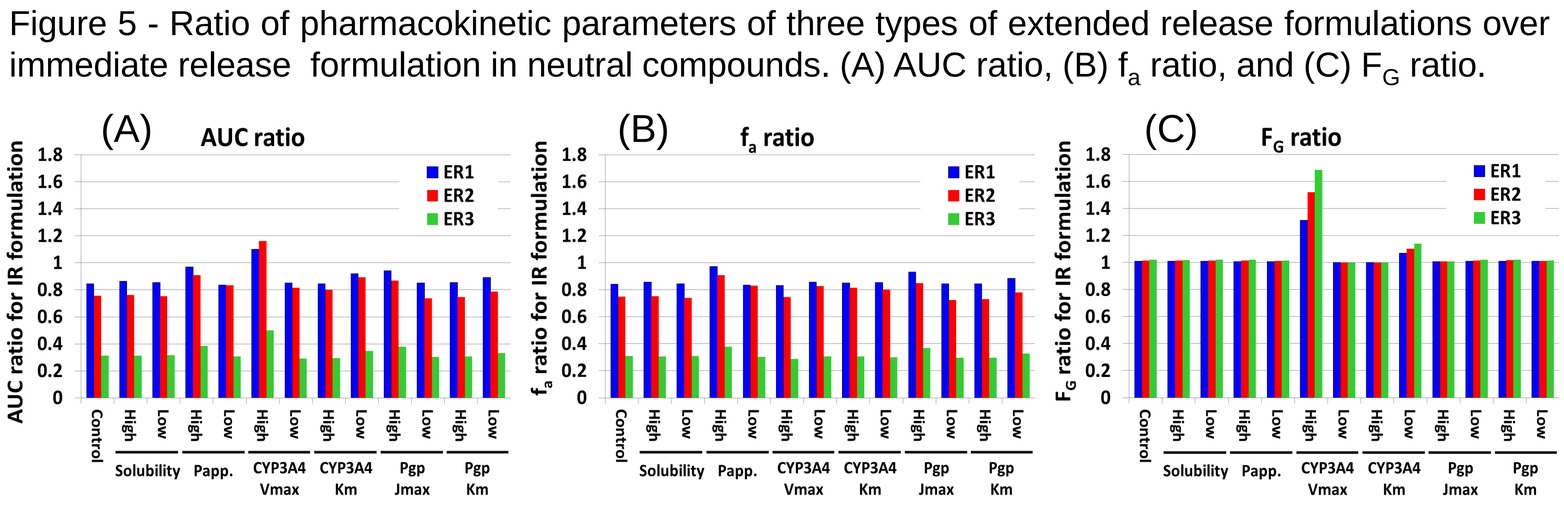

Figure 6 - Ratio of pharmacokinetic parameters of three types of extended release formulations over immediate release formulation in acid compounds (A) AUC ratio, (B) f_a ratio, and (C) F_G ratio.

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 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.