Application of Physiologically-Based Oral Absorption & Pharmacokinetic Modeling to Investigate Formulation Factors Influencing the Pharmacokinetics of Novel Oral Anticoagulants

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Introduction

- Physiologically-Based Oral Absorption & Pharmacokinetics (PBA-PK) utilizes both biopharmaceutical properties of API (e.g., solubility, permeability, particle size, etc.) and gut physiology (e.g., transit time, pH, bile salt effect, etc.) to predict oral absorption of drugs. PBA-PK models can thus be used to evaluate the effect of biopharmaceutical properties of drug on oral absorption.
- In recent years, the FDA has approved several Novel Oral Anticoagulants (NOACs). The exposure-response relationship for NOACs for bleeding risk is steep, and consequently, small increases in exposure may lead to a high risk of bleeding.
- The objective of this study was to determine the impact of changes in formulation of three prototypical NOACs (apixaban, rivaroxaban, & edoxaban) on their absorption and PK using PBA-PK modeling and simulation strategy.

Methods

- Three prototypical NOACs: apixaban (BCS Class 3), rivaroxaban (BCS Class 2), and edoxaban (BCS Class 4) were selected to determine the effect of changes in formulation on the oral absorption and PK of these drugs.

PBA-PK model Development

PBA-PK models for each of the selected NOACs were developed in GastroPlus™ 9.5 software.

- Data used for the development and verification of the PBA-PK models were obtained from the literature containing information on dose, demographics, plasma profiles (fasted) and physicochemical properties of the NOACs.
- Compartmental PK models were used to describe drug distribution and elimination. Respective PK parameters (such as V_d, CL, K_{12}, k_{21}, etc.) as well as associated variability were determined by model fitting to PK data following IV or oral administrations of immediate release (IR) formulation products digitized from various literatures.
- PBA models were developed using information on: particle size, particle density, pka, solubility, permeability in conjunction with information on gut physiology as implemented in the advanced compartmental absorption and transit (ACAT™) module in GastroPlus™.
- Developed PBA-PK models were externally verified by overlaying model-predicted plasma concentrations with observed PK data from the literature at various dose levels.

Parameter Sensitivity Analysis (PSA)

- PSA was conducted for each of the selected NOACs following single administration of the highest dose under fasted conditions: apixaban: 5 mg; rivaroxaban: 20 mg; edoxaban: 60 mg.
- PSA were carried out to explore to what extent the absorption and PK of NOACs is affected due to variation in four selected formulation specific properties which are expected to affect dissolution of API. The formulation properties evaluated are: particle radius, particle radius standard deviation (SD), particle density, and particle shape factor.
- A formulation parameter was considered to have significant effect on the absorption and PK of NOACs if changes in either $AUC0_{-\infty}$ or C_{max} were not within the limits of 0.8 – 1.25 fold.

Results

APIXABAN

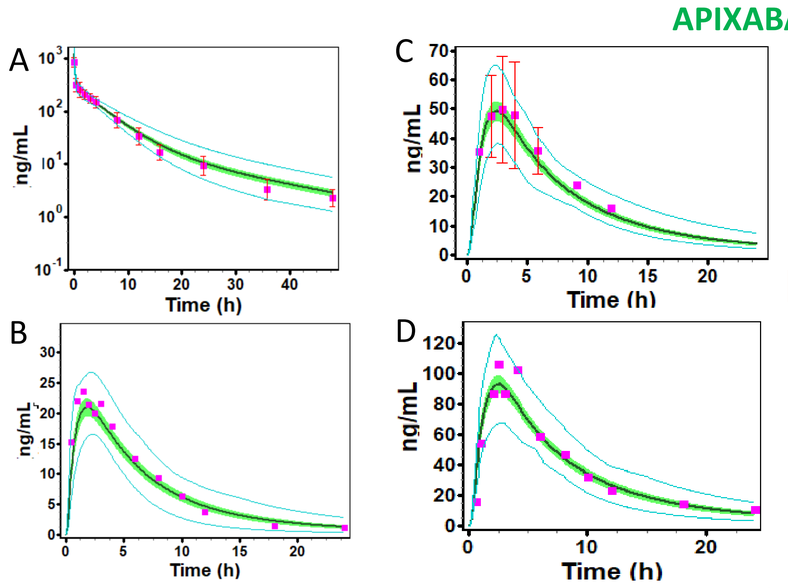

Figure 1: PBA-PK model simulated plasma profiles of apixaban: A) 5 mg IV; B) 1 mg oral solution, C) 2.5 mg IR tablet, D) 5 mg IR tablet. Pink dots: observed values; Blue line: 90% probability; Green Band: 90% confidence interval

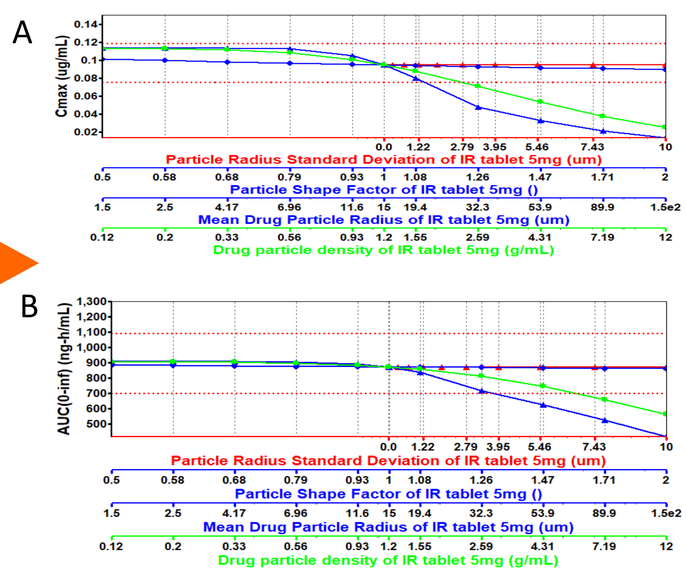

Figure 2: PSA for apixaban IR tablet for: A) C_{max}, B) $AUC_{0-\infty}$. Red doted lines represent 0.8-1.25 range.

RIVAROXABAN

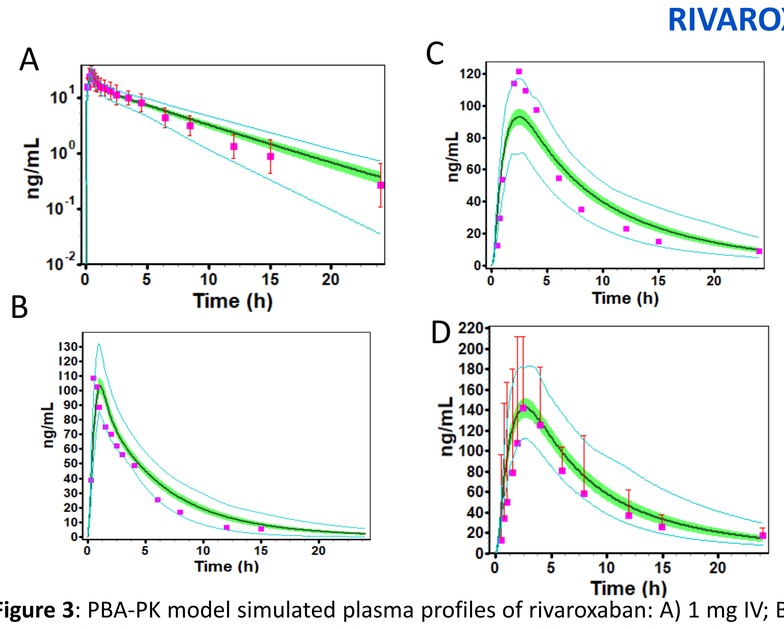

Figure 3: PBA-PK model simulated plasma profiles of rivaroxaban: A) 1 mg IV; B) 5 mg oral solution, C) 10 mg IR tablet, D) 20 mg IR tablet. Pink dots: observed values; Blue line: 90% probability; Green Band: 90% confidence interval

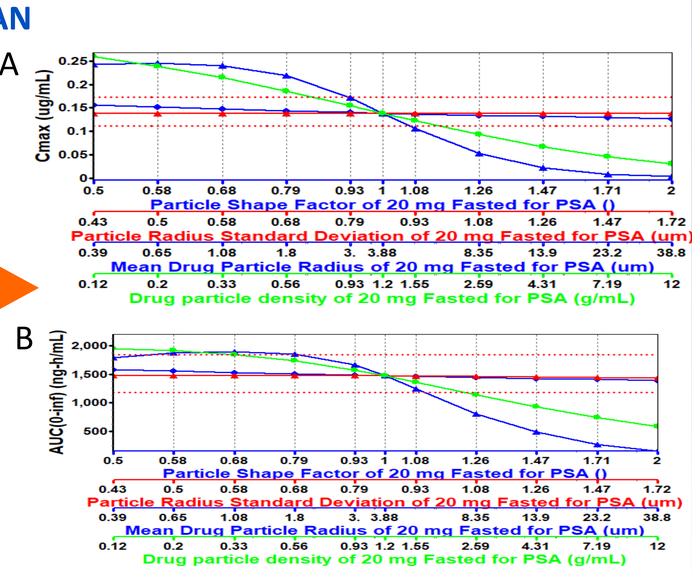

Figure 4: PSA for rivaroxaban IR tablet for: A) C_{max}, B) $AUC_{0-\infty}$. Red doted lines represent 0.8-1.25 range.

EDOXABAN

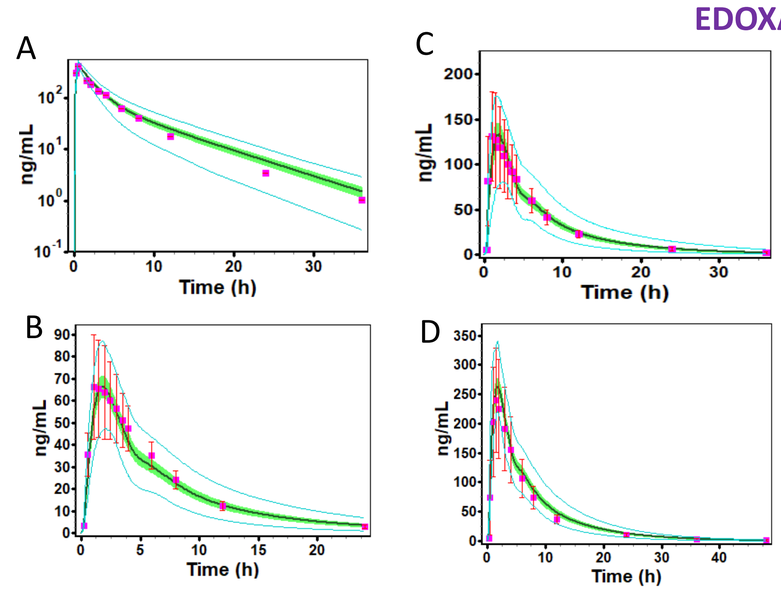

Figure 5: PBA-PK model simulated plasma profiles of edoxaban: A) 30 mg IV; B) 15 mg IR tablet, C) 30 mg IR tablet, D) 60 mg IR tablet. Pink dots: observed values; Blue line: 90% probability; Green Band: 90% confidence interval

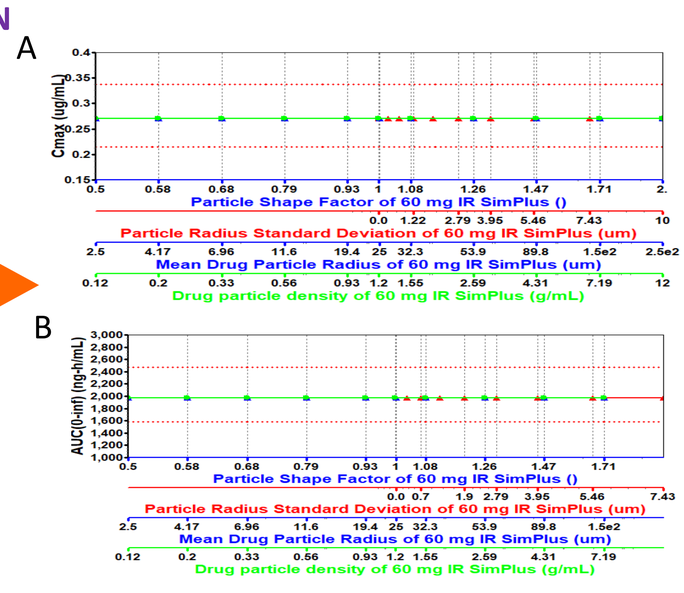

Figure 6: PSA for edoxaban IR tablet for: A) C_{max}, B) $AUC_{0-\infty}$. Red doted lines represent 0.8-1.25 range.

	Apixaban	Rivaroxaban	Edoxaban
Particle Radius	< 137.2 %	75.7 – 124.3 %	*No significant effect*
Particle Radius SD	*No significant effect*	*No significant effect*	*No significant effect*
Particle Density	< 188.17%	56.7 – 158.5 %	*No significant effect*
Particle Shape Factor	*No significant effect*	*No significant effect*	*No significant effect*

Table: Percent range for acceptable changes in formulation factors required to contain both C_{max} and $AUC_{0-\infty}$ within 80 – 125% of the reference formulation (baseline). SD: Standard Deviation

Conclusions

- Among tested formulation factors, particle size and density are the most relevant formulation properties for apixaban and rivaroxaban.
- None of the studied parameters are influential for edoxaban absorption and PK.
- Our results suggest that changes in formulation will affect absorption and PK of Rivaroxaban >> Apixaban >> Edoxaban.

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