



The use of PBBM for biopharmaceutics risk assessment, with apixaban as a model drug

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Introduction

- Physiologically Based Biopharmaceutics Modeling (PBBM) has emerged as a powerful tool in pharmaceutical development, offering a mechanistic approach to predicting in vivo drug performance based on in vitro data.
- By integrating drugs' physicochemical properties, formulation characteristics, and physiological parameters, PBBM allows for the simulation of absorption and bioavailability (BA) under various conditions.
- Recent advancements in computational tools and biopharmaceutics modeling highlight the regulatory potential of PBBM in bioequivalence (BE) predictions, biowaivers, and the establishment of dissolution safe spaces, as emphasized in recent EMA and FDA guidance, along with the ICH M13 series and ICH M15.

Available Literature Data on Apixaban

- **non-ionizable** with a water **solubility of 40 µg/mL** and a **Caco-2** permeability of **0.9×10^{-6} cm/s**.
- Highest single dose is 10 mg - **borderline BCS Class III** drug (dose number of 1).
- Literature **dissolution profiles** (Type I apparatus, 75 rpm, 900 mL, in pH 6.8 with 0.05% SDS or 0.1 N HCl media) of several oral tablet differing in their production process (dry vs. wet granulation), particle size (D90 from 10 µm to 120 µm), and dosage strength (2.5 mg to 20 mg).
- In vivo data after the **single dose IV administration** of apixaban 5 mg to 20 healthy subjects.
- In vivo data after the **oral administration** of apixaban's doses of 0.5 mg, 1.0 mg, and 2.5 mg as **solution** to groups of 6 healthy subjects and apixaban's doses of 2.5 mg, 5 mg, 10 mg, 25 mg, and 50 mg as **immediate release tablets** for 6 to 12 healthy subjects after fasting using single dose administration.
- It was assumed that the formulations used in the general clinical studies were made through **dry granulation**, with an apixaban crystal particle size of 83 µm.
- **BE study** results from two **non-bioequivalent** formulations with in vitro dissolution.

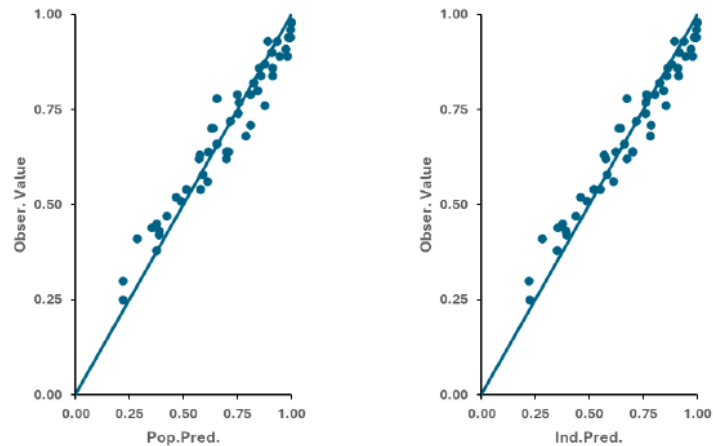
Dissolution Model of Apixaban

- A **PopPK** approach was developed using ADAPT 5
- **Noyes–Whitney** semi-mechanistic equation to the dissolution data as the base model and the **dose** (5 mg vs. 20 mg), the **production process** (wet granulation vs. dry granulation), the **dissolution media** (pH 6.8 with 0.05% SDS vs. 0.1 N HCl), and the **particle size** (10 µm to 120 µm) as covariates according to the following equations:

$$\begin{cases} \frac{dSolid}{dt} = -Z \frac{3 \times CD}{ro \times h \times Size} \times Solid \times \left(Cs - \frac{Soluble}{V} \right) \\ \frac{dSoluble}{dt} = +Z \frac{3 \times CD}{ro \times h \times Size} \times Solid \times \left(Cs - \frac{Soluble}{V} \right) \end{cases}$$

- where $Z = Z_{wet} + A \times Z_{dry} + B \times Z_{HCl}$ with Z_{wet} is the Z value for the wet granulation formulations, Z_{dry} is the added Z value for the dry granulation process, and Z_{HCl} is the added Z value for the HCl dissolution media. **A** and **B** are the activators (0 vs. 1) of dry granulation and the 0.1 N HCl dissolution media, **CD** is the diffusion coefficient with a value of 0.018 cm²/h, **ro** is the density of the drug with a value of 1200 mg/cm³, **h** is the diffusion layer thickness with a value of 0.003 cm, and **Size** is the variable particle size (cm) of the drug crystals [17,18]. **Solid** and **soluble** are the amounts of apixaban in each of the respective physical forms.

Dissolution Model of Apixaban



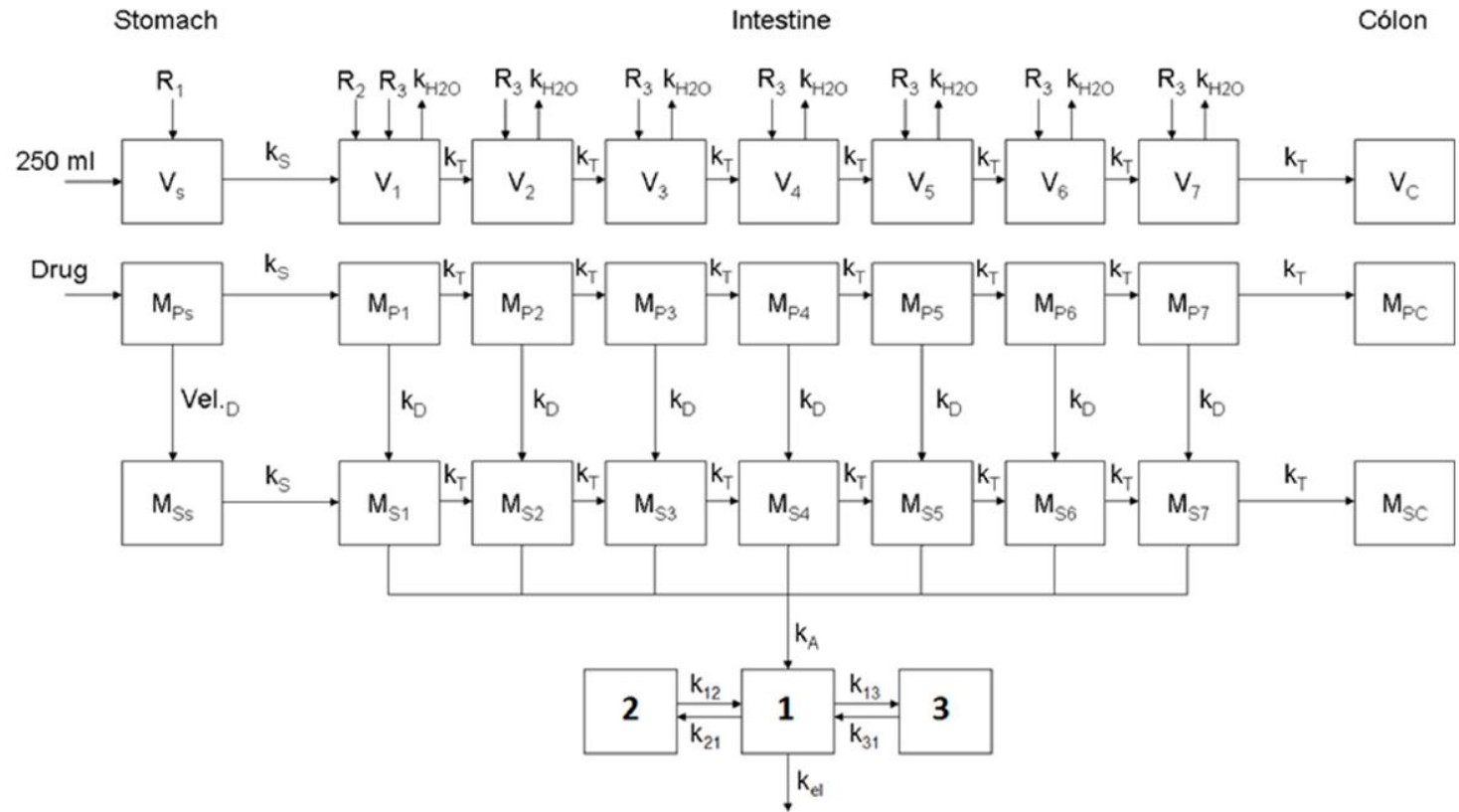
- --- Population Standard Deviation ---

Parameter	SD as CV%	%RSE
• Z	6.93	86.7

- --- Covariate Model Parameters ---

Parameter	Estimate	%RSE
• Zwet	44.8	6.92
• Zdry	8.63	78.1
• ZHCl	-22.5	50.8

Implemented using the
Berkeley–Madonna
software package
(version 8.3.18)



Previous use of the PBBM

Physiological parameters used in the pharmacokinetic model.

Transit rate constants

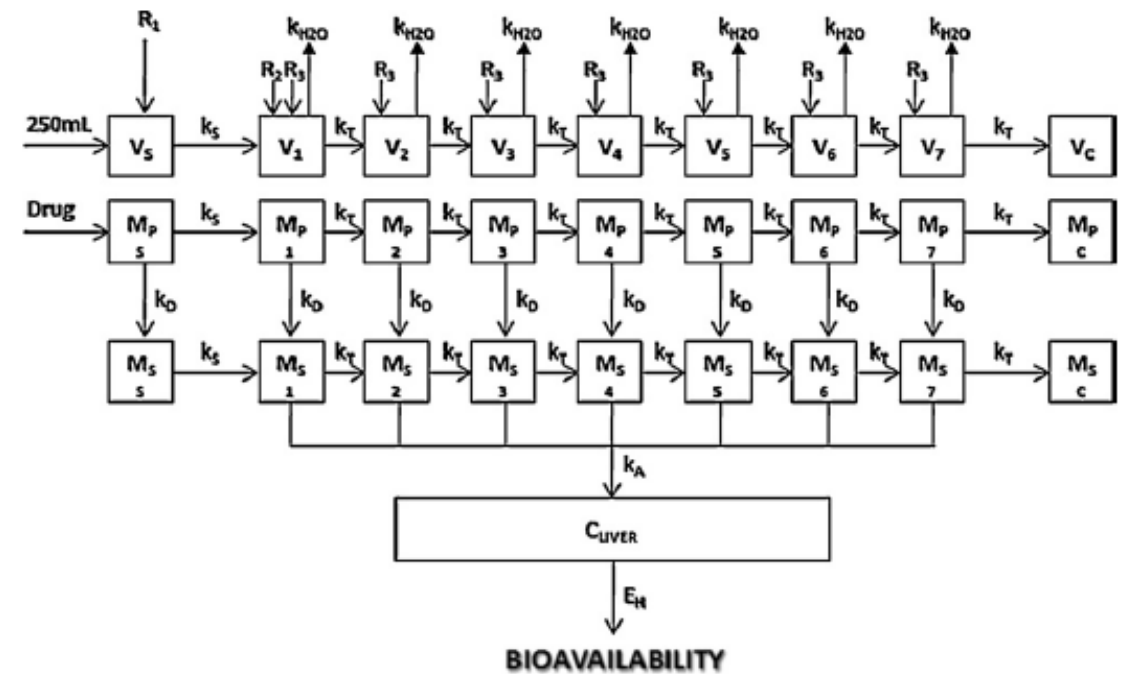
$k_s = 4.00$ h^{-1}
 $k_T = 2.11$ h^{-1}

Intestine radius

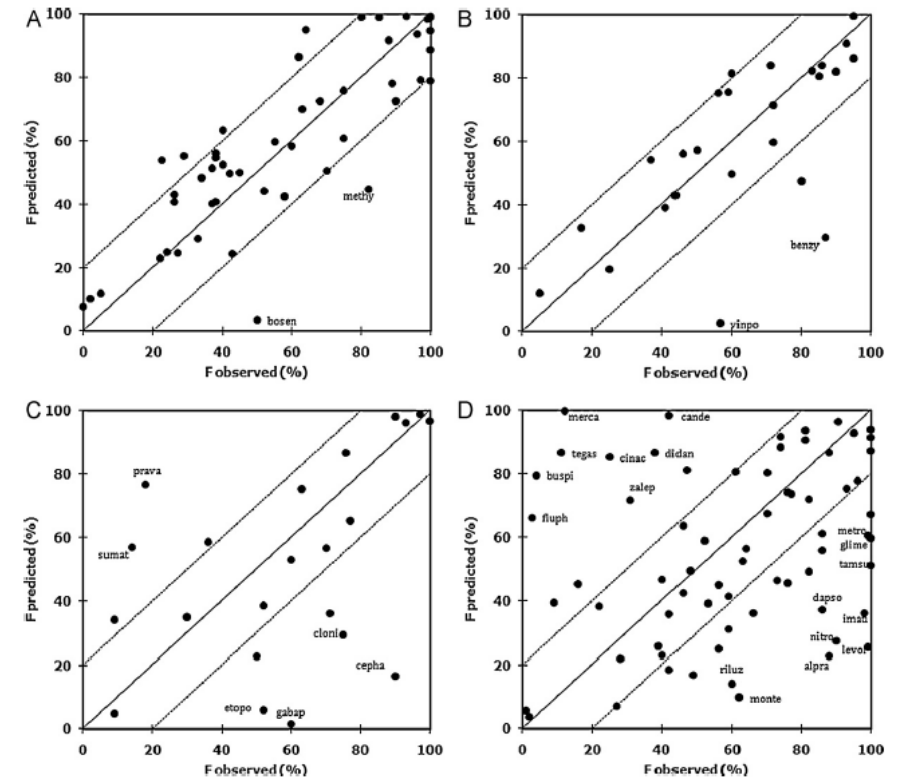
$r_1 = 1.70$ Cm
 $r_2 = 1.58$ Cm
 $r_3 = 1.47$ Cm
 $r_4 = 1.37$ Cm
 $r_5 = 1.26$ Cm
 $r_6 = 1.16$ Cm
 $r_7 = 1.05$ Cm

Water model parameters

$R_1 = 104.2$ $ml\ h^{-1}$
 $R_2 = 91.70$ $ml\ h^{-1}$
 $R_3 = 10.70$ $ml\ h^{-1}$
 $V_s = 26.04$ ml
 $V_1 = 73.47$ ml
 $V_2 = 58.95$ ml
 $V_3 = 48.05$ ml
 $V_4 = 39.87$ ml
 $V_5 = 33.73$ ml
 $V_6 = 29.13$ ml
 $V_7 = 25.67$ ml
 $k_{H_2O} = 0.7015$ h^{-1}



Prediction of Oral Bioavailability



A

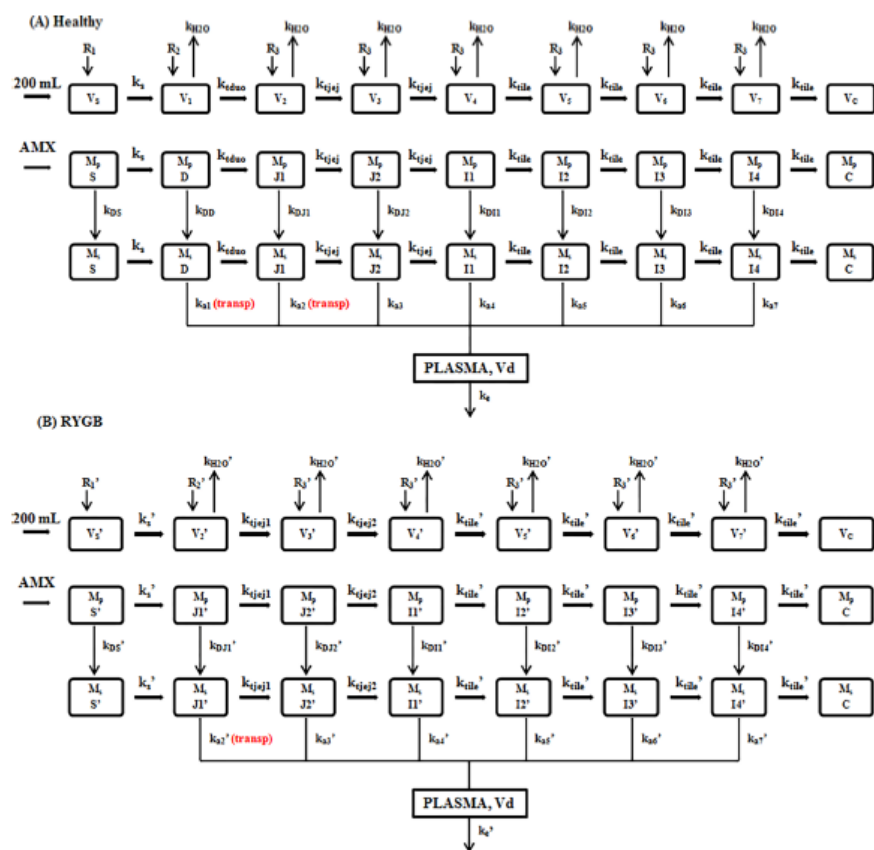
B

C

D

	<i>In vitro</i> P_{app} <i>In vitro</i> Cl_{int}	<i>In silico</i> P_{app} <i>In vitro</i> Cl_{int}	<i>In vitro</i> P_{app} <i>In silico</i> Cl_{int}	<i>In silico</i> P_{app} <i>In silico</i> Cl_{int}
r_s	0.824	0.718	0.532	0.284
RMSE (%F)	16.0	19.8	31.9	34.6
ME (%F)	1.9	-2.7	-6.7	-4.5
%Correct values within $\pm 20\%$	83.7	84.0	54.5	52.9
%Correct values within $\pm 35\%$	95.9	92.0	72.7	73.5

PBBM for Roux-en-Y Gastric Bypass



parameter	healthy model	simulation i	simulation ii	reference
dosage form	capsule	suspension	tablet	
dose (mg)	500	800	875	
absorption				
$P_{eff(human)}$ (10^{-4} cm/s)	0.46 ± 0.12	0.46 ± 0.12	0.46 ± 0.12	18
$Transp$	6.78	6.78	6.78	estimated by fitting to the mean observed healthy pharmacokinetic profile ^{37,39}
pH solubility mean values in mg/mL (respective pH)	7.69 (1.5), 3.55 (4.6), 5.4 (6.8)	5.4 (6.8)	5.4 (6.8)	21
k_{disint} (h^{-1})	30	-	30	assumed based on AMX dissolution profiles ²¹
t_{lag} (h)	-	-	0.25	assumed
$R_{t_{intestine}}$ (minutes)	199	159.20	159.20	27,32
distribution				
V_d (L/kg)	0.38	0.38	0.38	35,36
elimination				
k_e (h^{-1})	$0.63^{(a)}$	$0.55^{(b)}$	$0.55^{(b)}$	calculated from the mean of ^(a) healthy ³⁷ and ^(b) RYGB ³⁹ pharmacokinetic profiles

^a $P_{eff(human)}$, human jejunal effective permeability of AMX; $Transp$, transporter; k_{disint} , disintegration rate of AMX; t_{lag} , time delay between drug administration and first concentration observed; $R_{t_{intestine}}$, intestinal transit time; V_d , volume of distribution; k_e , elimination rate.

Amoxicillin Tablet and Suspension

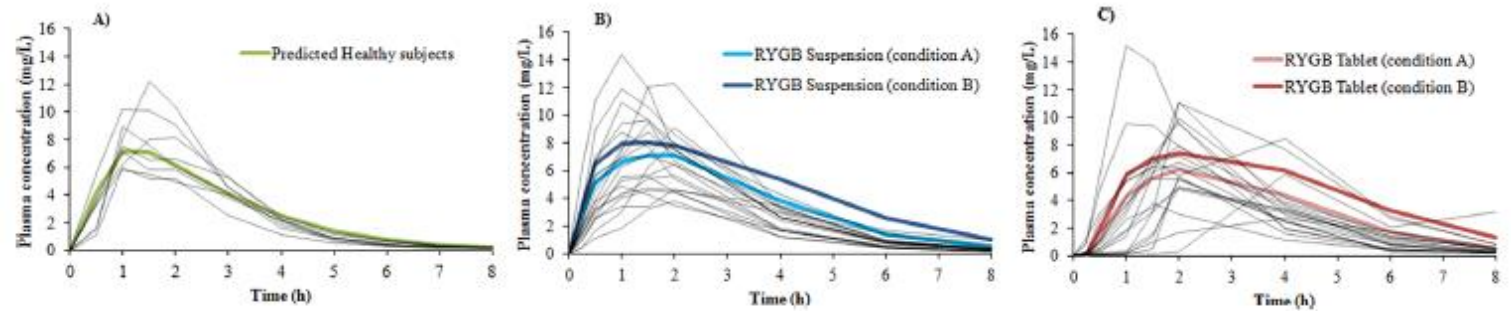


Figure 2. (A) Predicted mean plasma profile after administration of 500 mg of AMX capsule to healthy subjects. (B) Simulated RYGB mean plasma profile under condition A and condition B after administration of 800 mg of AMX suspension to RYGB patients. (C) Simulated RYGB mean plasma profile under condition A and condition B after administration of 875 mg of AMX tablet to RYGB patients; gray lines, individual observed data.

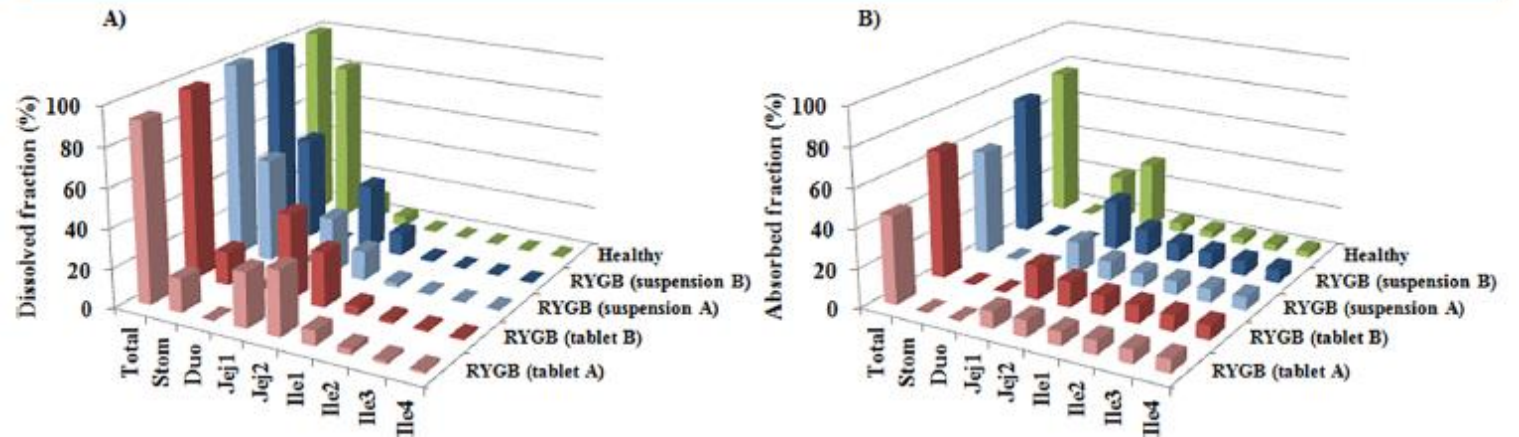
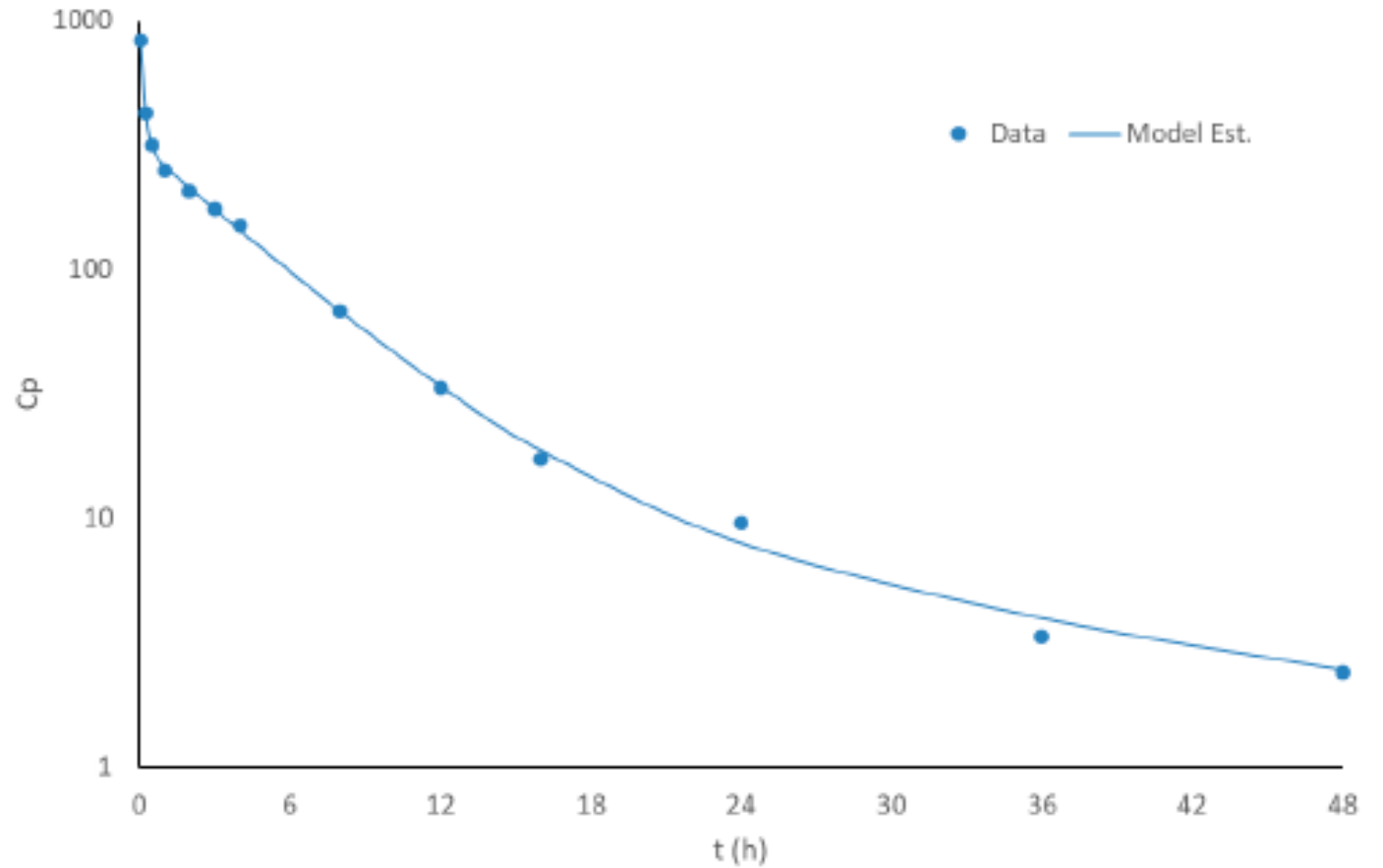


Figure 3. Model prediction of dissolved (A) and absorbed (B) fractions of AMX by each GI compartment (stomach, duodenum, jejunum (1–2), and ileum (1–4)) after administration of 500 mg of AMX capsule to healthy subjects (healthy), 800 mg of AMX suspension to RYGB patients (RYGB suspension, conditions A and B), and 875 mg of AMX tablet to RYGB patients (RYGB tablet, conditions A and B).

Optimization of the PBBM

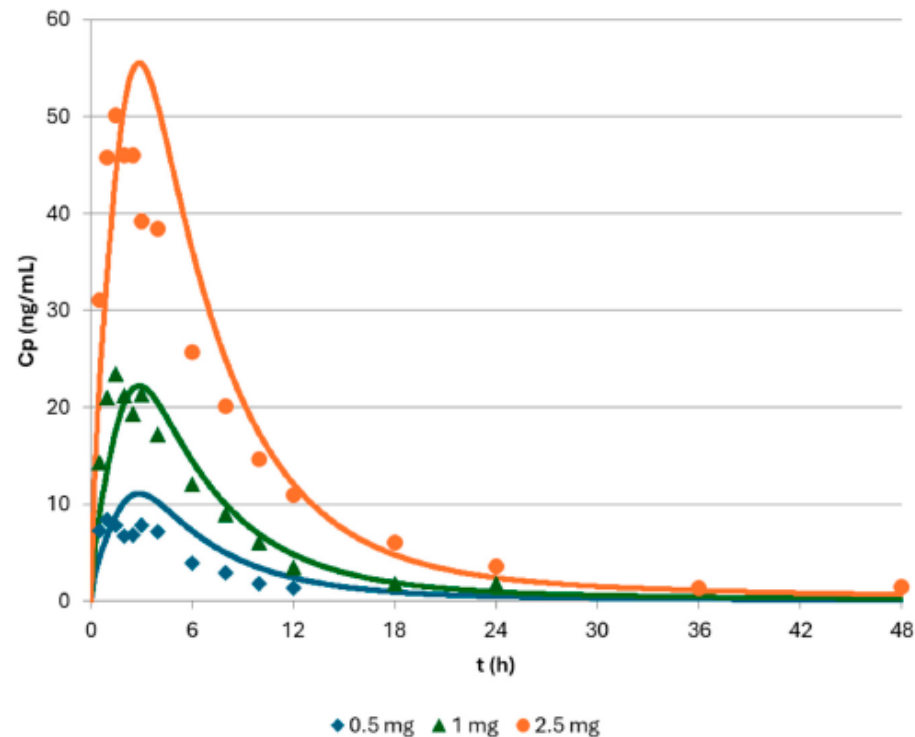


N = 20 subjects

Optimization of the PBBM

Parameter	Solution	Tablets	BE Study	Origin
Dose (mg)	0.5, 1, 2.5	2.5, 5, 10, 25, 50	5	
Absorption				
Peff (cm/h)		1.57×10^{-1}		in vitro
Dissolution				
Solubility ($\mu\text{g/mL}$)		40		in vitro
Z	-	31	22.3	in vitro fitting
Particle size (μm)	-	83	50/89	in vitro
Disposition				
k_{10} (h^{-1})		0.5409		in vivo fitting
k_{12} (h^{-1})		0.086		in vivo fitting
k_{21} (h^{-1})		0.0441		in vivo fitting
k_{13} (h^{-1})		4.319		in vivo fitting
k_{31} (h^{-1})		2.24		in vivo fitting
V_1 (L)		4.756		in vivo fitting

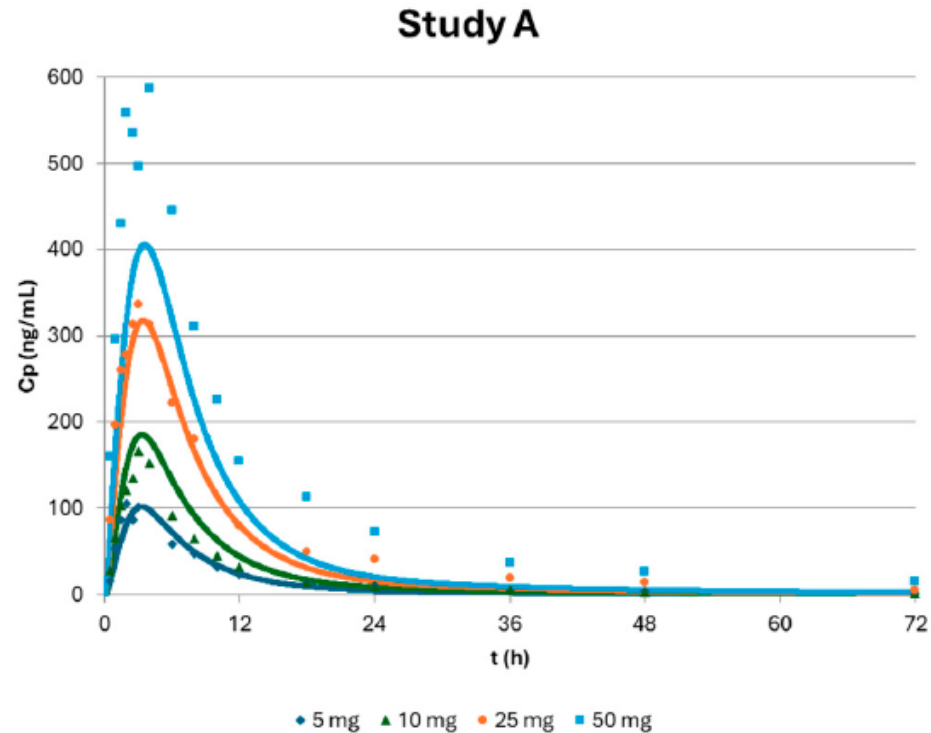
Validation of the PBBM - Solution



	Obs	0.5 mg Pred	%PE	Obs	1 mg Pred	%PE	Obs	2.5 mg Pred	%PE
C_{max} (ng/mL)	8.42	11.09	-32	23.46	22.19	5	50.15	55.46	-11
T_{max} (h)	1.00	3.00	-200	1.50	3.00	-100	1.50	3.00	-100
AUC (ng·h/mL)	54.10	78.06	-44	176.32	197.88	-12	454.96	494.69	-9

N = 6 subjects

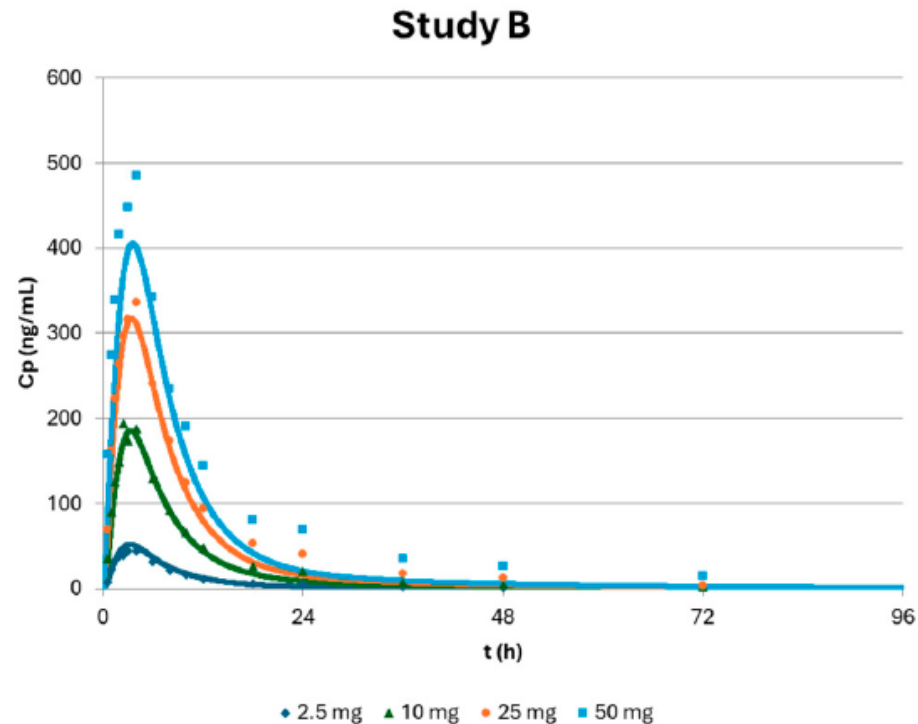
Validation of the PBBM - Tablets



Study A	Obs	5 mg Pred	%PE	Obs	10 mg Pred	%PE	Obs	25 mg Pred	%PE	Obs	50 mg Pred	%PE
C _{max} (ng/mL)	105.68	101.20	4	166.54	183.75	-10	336.84	312.63	7	587.95	401.38	32
T _{max} (h)	2.00	3.00	-50	3.00	3.00	0	3.00	3.00	0	4.00	4.00	0
AUC (ng·h/mL)	982.48	906.13	8	1347.37	1667.98	-24	3658.83	2961.29	19	6759.43	3906.82	42

N = 6 subjects

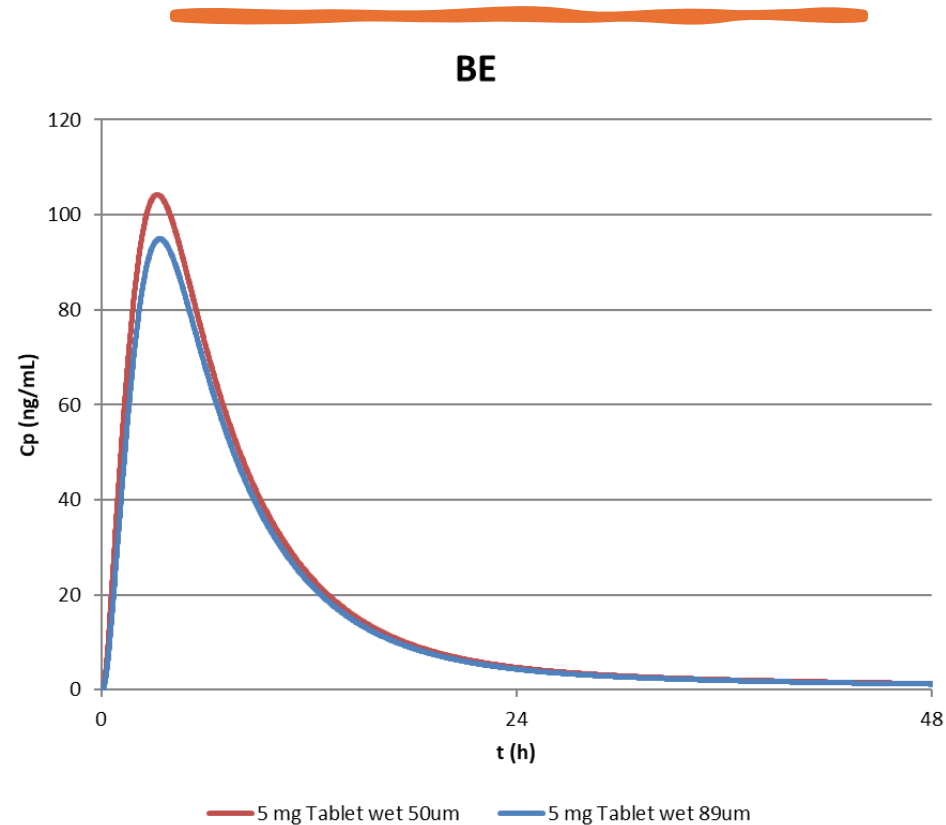
Validation of the PBBM - Tablets



Study B	Obs	2.5 mg Pred	%PE	Obs	10 mg Pred	%PE	Obs	25 mg Pred	%PE	Obs	50 mg Pred	%PE
C_{max} (ng/mL)	44.21	51.74	-17	194.09	183.75	5	335.98	312.63	7	484.65	401.38	17
T_{max} (h)	4.00	3.00	25	2.50	3.00	-20	4.00	3.00	25	4.00	4.00	0
AUC (ng·h/mL)	451.03	461.70	-2	1917.80	1667.98	13	3653.04	2961.29	19	5681.64	3906.82	31

N = 12 subjects

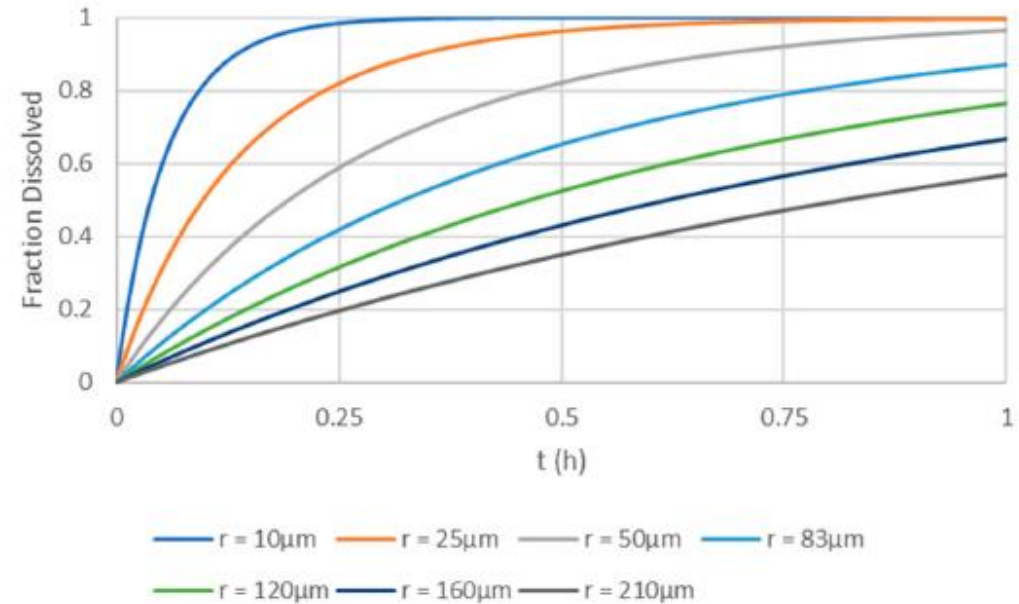
Validation of the PBBM - Tablets



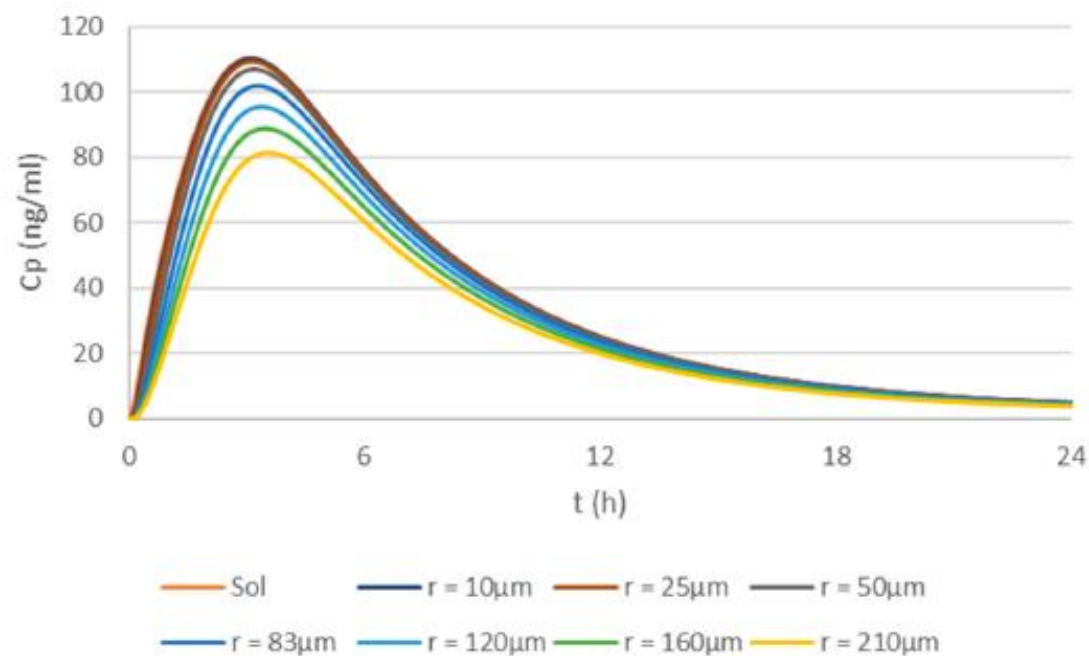
	5 mg/50 μ m			5 mg/89 μ m			BE		
	Obs	Pred	%PE	Obs	Pred	%PE	Obs	Pred	%PE
Cmax (ng/mL)	101.80	104.23	-2	87.80	94.93	-8	0.86	0.91	-6
AUC (ng·h/mL)	1088.00	938.55	14	1030.00	856.75	17	0.95	0.91	4

Simulations

Dissolution profiles (apparatus II, 75 rpm, 0.1 N HCl) for the 5 mg dry granulation tablets with particle sizes increasing from 10 μm to 210 μm



Simulations



T/R ₁ Ratio	Solution	10 μm	25 μm	50 μm	83 μm	120 μm	160 μm	210 μm
C _{max}	1.00	1.00	0.99	0.97	0.92	0.86	0.80	0.74
T _{max}	1.00	1.01	1.02	1.04	1.06	1.10	1.12	1.15
AUC	1.00	1.00	0.99	0.96	0.91	0.86	0.80	0.74

T/R ₂ Ratio	Solution	10 μm	25 μm	50 μm	83 μm	120 μm	160 μm	210 μm
C _{max}	1.08	1.08	1.07	1.05	1.00	0.94	0.87	0.80
T _{max}	0.94	0.95	0.95	0.97	1.00	1.03	1.05	1.08
AUC	1.09	1.09	1.08	1.05	1.00	0.94	0.88	0.81

Article

Physiologically Based Biopharmaceutics Model of Apixaban for Biopharmaceutics Risk Assessment

Paulo Paixão , Zvonimir Petric  and José A. G. Morais

Conclusions

- PBBM optimization was performed through a middle-out approach by combining bottom-up in vitro predictions with limited top-down fitting of key model disposition parameters for clinical data
- Regarding validation, this was performed following the typical regulatory requirements by assessing the ability of the model to predict the range of the observed outcome of representative in vivo pharmacokinetic studies, e.g., different dose levels of different types of formulations under single dose administrations, as well as in a BE study with two formulations not able to show BE
- %PE were dependent of the clinical study, highlighting the challenges of validation if the focus is on a single study rather than evaluating the model's performance across multiple datasets.
- BE assessment was performed only based on the mean plasma profile simulated without considering variability in either the physiological or drug-related parameters. Thus, considering a 10% difference in AUC or Cmax between two different drug product simulations as a cut-off point for BE may be a more suitable simulation-based approach.
- Simulation results are in line with previous reports and supports the current regulatory framework for BCS biowaivers by confirming a conservative in vitro based dissolution waiver. However, it also opens the door for the possibility of accepting the same dissolution conditions for BCS Class III drugs as requested for BCS Class I drugs in the future.
- Under a drug development context, this information could be used either for setting the dissolution conditions for batch release, if the drug product is already approved, or to help develop a generic formulation with increased confidence that will result in a BE for the required in vivo studies.

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Thank You

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