

Building and evaluation of a PBPK model for Fluvoxamine in adults

Version	1.1-OSP10.0
based on <i>Model Snapshot</i> and <i>Evaluation Plan</i>	https://github.com/Open-Systems-Pharmacology/Fluvoxamine-Model/releases/tag/alt_v1.0
OSP Version	10.0
Qualification Framework Version	2.3

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1 Introduction

The presented PBPK model of fluvoxamine has been developed to be used in a PBPK Drug-Drug-Interactions (DDI) network with fluvoxamine as an inhibitor of CYP2C19 and CYP1A2.

Fluvoxamine is a selective serotonin reuptake inhibitor. After oral administration, fluvoxamine-maleate is absorbed moderately fast with peak plasma concentrations reached at approx. 2-4 hours post-dose. Approximately 77% of the drug is bound to plasma proteins. The concentration-time profile elicits a bi-phasic shape ([Perucca 1994](#)). Fluvoxamine is extensively metabolized via CYP2D6 and CYP1A2. Plasma concentrations increase non-proportionally with increasing doses, suggesting (partially) saturable metabolism. Fluvoxamine is a strong inhibitor of CYP2C19 and CYP1A2 ([FDA DDI Labeling](#)), and a weak inhibitor of CYP3A (AUCR <2) ([Lam 2003](#)). Only a very minor part of the dose is recovered unchanged in the urine.

2 Methods

2.1 Modeling Strategy

The general workflow for building an adult PBPK model has been described by Kuepfer et al. ([Kuepfer 2016](#)). Relevant information on the anthropometry (height, weight) was gathered from the respective clinical study, if reported. Information on physiological parameters (e.g. blood flows, organ volumes, hematocrit) in adults was gathered from the literature and has been incorporated in PK-Sim® as described previously ([Willmann 2007](#)). The applied activity and variability of plasma proteins and active processes that are integrated into PK-Sim® are described in the publicly available 'PK-Sim® Ontogeny Database Version 7.3' ([PK-Sim Ontogeny Database Version 7.3](#)).

In general, the following step-wise modeling workflow was followed:

1. Predict i.v.-profiles based on in vitro data alone and optimize distribution model and metabolism parameters
2. Predict single dose data following oral solution
3. Optimize intestinal permeability and revisit metabolism model
4. Predict single dose data following enteric-coated tablet
5. Multiple dose predictions with preliminary model
6. Refine model and optimize permeability and metabolism parameters.

Selection of the distribution model was performed with i.v. data ([Iga 2015](#)) with a place-holder linear clearance. A typical Japanese subject (age = 30 y, weight = 61.87 kg, height = 168.99 cm, BMI = 21.67 kg/m²) was created in PK-Sim from predefined database “Japanese (2015)” by adding CYP1A2 and CYP2D6 expression from PK-Sim RT PCR database.

Intestinal permeability and the kinetics of the CYP1A2 and CYP2D6 clearance processes were estimated using the Parameter Identification module provided in PK-Sim® with the concentration-time data listed in [Section 2.2](#). The predefined “Standard European Male for DDI” individual (age = 30 y, weight = 73 kg, height = 176 cm, BMI = 23.57 kg/m²) with CYP1A2 and CYP2D6 expression obtained from PK-Sim RT PCR database was used for simulations of European individuals. Additionally, fractions metabolized via CYP1A2 and CYP2D6 were fitted to 29.5% and 66.5%, respectively ([Alqahtani 2016](#), [Britz 2018](#)). For simulations of poor metabolizers ([Carillo 1996](#), [Spigset 1997](#)), the CYP2D6 pathway was turned off.

Details about input data (physicochemical, *in vitro* and clinical) can be found in [Section 2.2](#).

Details about the structural model and its parameters can be found in [Section 2.3](#).

2.2 Data

2.2.1 In vitro and physico-chemical data

A literature search was performed to collect available information on physico-chemical properties of fluvoxamine ([Table 1](#)).

Parameter	Unit	Value	Source	Description
MW ⁺	g/mol	318.33	DrugBank DB00176	Molecular weight of free base. Dose of commercial product usually refers to amount of fluvoxamine maleate – conversion factor is 0.733
pK _{a,base} ⁺		9.16	Alqahtani 2016	Basic dissociation constant
Solubility (pH) ⁺	mg/mL	0.06 (7.4)	PubChem 9560989	Aqueous Solubility
logP ⁺		3.38	Alqahtani 2016	Partitioning coefficient
f _u ⁺	%	23	Alqahtani 2016	Fraction unbound in plasma
K _i CYP1A2 ⁺	nmol/L	2.97	Iga 2016	CYP1A2 inhibition constant
K _i CYP2C19 ⁺	nmol/L	3.6	Iga 2016	CYP2C19 inhibition constant (omeprazole as substrate)
K _i CYP2C19 ⁺	nmol/L	2.6	Iga 2016	CYP2C19 inhibition constant (s-mephenytoin as substrate)

Table 1: Physico-chemical and *in-vitro* metabolization properties of fluvoxamine extracted from literature. ⁺: Value used in final model

2.2.2 Clinical data

A literature search was performed to collect available clinical data on fluvoxamine in adults. Data used for model development and validation is listed in [Table 2](#).

Source	Route	Dose [mg]/ Schedule *	Pop.	Age [yrs] (mean)	Weight [kg] (mean)	Sex	N	Form.	Comment
Carrillo 1996	p.o.	50	HV	-	-	m/f	5	e.c. Tab	Non-smoking EM / Smoking EM
Carrillo 1996 ⁺	p.o.	50	HV	-	-	m/f	5	e.c. Tab	Non-smoking PM
Spigset 1997 ⁺	p.o.	50	HV	-	-		5	e.c. Tab	PM
Spigset 1997	p.o.	50	HV	-	-		5	e.c. Tab	EM
Iga 2015 ⁺	i.v.	50	Japanese	-	-	-	-	-	-
Iga 2015	p.o.	50	Japanese	-	-	-	-	-	-
Orlando 2009	p.o.	50	HV	35	79	male	10	-	-
Spigset 1998 ⁺	p.o.	50 / 100 b.i.d.	HV	28.9	85.6	male	10	e.c. Tab	-
Spigset 1998	p.o.	12.5/ 25 b.i.d.	HV	28.9	85.6	male	10	e.c. Tab	-
DeVries 1993 ⁺	p.o.	25 / 50/ 100	HV	-	-	male	12	solution	-
VanHarten 1994	p.o.	50	HV	-	-	male	17	capsule	-
VanHarten 1991	p.o.	50	HV	24	73	m/f	12	e.c. Tab	With/ without food
Kunii 2005	p.o.	50	HV	29.7	69.3	m	10	e.c. Tab	-
Fukasawa 2006	p.o.	50	HV	29.6	68.3	m	12	e.c. Tab	-
Fleishaker 1994 ⁺	p.o.	12.5 - 25 - 50 - 100 q.d.	HV	32	80	m	20	e.c. Tab	-
Labellarte 2004 ⁺	p.o.	25 / 50 / 100/ 150 b.i.d.	Adole- scents	14	60	m/f	23	e.c. Tab	-
Spigset 1997	p.o.	50	HV	34.7	66.5	m/f	12	e.c. Tab	non-smokers / smoker
FDA_ClinPharmReview LuvoxCR ⁺	p.o.	100	HV	-	-	-	20	e.c. Tab / CR	-
FDA_ClinPharmReview LuvoxCR ⁺	p.o.	100 q.d.	HV	-	-	-	20	e.c. Tab / CR	-
FDA_ClinPharmReview LuvoxCR	p.o.	200 / 300 q.d.	HV	-	-	-	20	e.c. Tab / CR	-

Table 2: Literature sources of clinical concentration data of fluvoxamine used for model development and validation. *e.c.*: enteric coated; -: respective information was not provided in the literature source; *:single dose unless otherwise specified; ⁺: Data used for final parameter identification

2.3 Model Parameters and Assumptions

2.3.1 Absorption

The model parameter `specific_intestinal_permeability` was optimized to best match clinical data (see [Section 2.3.4](#)). The default solubility was assumed to be the measured value in the FaSSiF medium (see [Section 2.2.1](#)).

The dissolution of enteric-coated tablets was implemented via an empirical Weibull dissolution equation with `Dissolution_time (50% dissolved)` = 10 min and `Lag_time` = 30 min.

2.3.2 Distribution

Physico-chemical parameter values were set to the reported values (see [Section 2.2.1](#)). It was assumed that the major binding partner in plasma is albumin.

After testing the available organ-plasma partition coefficient and cell permeability calculation methods available in PK-Sim, observed clinical data were best described by choosing the partition coefficient calculation by `Rodgers and Rowland` and cellular permeability calculation by `PK-Sim Standard`.

2.3.3 Metabolism and Elimination

Two metabolic pathways were implemented in the model:

- CYP2D6 (saturable Michaelis-Menten)
- CYP1A2 (linear)

As the single elimination route via CYP2D6 was not sufficient to correctly describe the multiple dose administrations, elimination through CYP1A2 has been added as suggested by others ([Alqahtani 2016](#)).

Expression profiles for CYP1A2 and CYP2D6 were obtained from PK-Sim RT PCR database.

Additionally, renal glomerular filtration was implemented with `GFR fraction` = 1, that resulted in less than 2% of parent fluvoxamine being excreted in urine (4% observed in [DeVries 1993](#)).

2.3.4 Inhibition

Competitive inhibition of CYP1A2 and CYP2C19 was added with K_i values as listed in [Section 2.2.1](#). For inhibition of CYP2C19, multiple substrate-specific K_i values are reported, and the modeler has to decide which to select depending on the substrate.

2.3.5 Automated Parameter Identification

Following parameter values were estimated for the base model:

- `Specific intestinal permeability (transcellular)`
- `Km` (CYP2D6)
- `kcat` (CYP2D6)
- `In vitro CL/recombinant enzyme` (CYP1A2)

3 Results and Discussion

The next sections show:

1. Final model input parameters for the building blocks: [Section 3.1](#).
2. Overall goodness of fit: [Section 3.2](#).
3. Simulated vs. observed concentration-time profiles for the clinical studies used for model building and for model verification: [Section 3.3](#).

3.1 Final input parameters

The parameter values of the final PBPK model are illustrated below.

Formulation: Fluvoxamine tablet

Type: Weibull

Parameters

Name	Value	Value Origin
Dissolution time (50% dissolved)	10 min	Manual Fit
Lag time	30 min	Manual Fit
Dissolution shape	0.92	
Use as suspension	Yes	

Compound: Fluvoxamine

Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	0.062 mg/ml	Database-PubChem 9560989	Water Solubility - Pubchem	True
Reference pH	7.4	Database-PubChem 9560989	Water Solubility - Pubchem	True
Lipophilicity	3.38 Log Units	Publication-Alqahtani 2016	LogP Alqahtani2016	True
Fraction unbound (plasma, reference value)	0.23	Publication-Alqahtani 2016	fu Alqahtani2016	True
Specific intestinal permeability (transcellular)	1.2322894625E-05 cm/min	Parameter Identification-Parameter Identification	Fit	True
F	3	Database-DrugBank DB00176		
Is small molecule	Yes			
Molecular weight	318.3346 g/mol	Database-DrugBank DB00176		
Plasma protein binding partner	Albumin			

Calculation methods

Name	Value
Partition coefficients	Rodgers and Rowland
Cellular permeabilities	PK-Sim Standard

Processes

Metabolizing Enzyme: CYP1A2-Linear_Fit_1A2_rec

Molecule: CYP1A2

Parameters

Name	Value	Value Origin
In vitro CL/recombinant enzyme	0.5382573259 µl/min/pmol rec. enzyme	

Metabolizing Enzyme: CYP2D6-MM_2D6_rec

Molecule: CYP2D6

Parameters

Name	Value	Value Origin
In vitro Vmax/recombinant enzyme	55 nmol/min/pmol rec. enzyme	
Km	0.00097708157358 µmol/l	Parameter Identification-Parameter Identification
kcat	0.0362433252 1/min	Parameter Identification-Parameter Identification

Systemic Process: Glomerular Filtration-GFR

Species: Human

Parameters

Name	Value	Value Origin
GFR fraction	1	Other-Assumption

Inhibition: CYP1A2-Iga2016_Tab2_CAF

Molecule: CYP1A2

Parameters

Name	Value	Value Origin
Ki	2.97 nmol/l	Publication-Iga 2016

Inhibition: CYP2C19-Iga 2016 in vivo unbound KI - Omeprazole

Molecule: CYP2C19

Parameters

Name	Value	Value Origin
Ki	3.6 nmol/l	Publication-Iga 2016

Inhibition: CYP2C19-Iga 2016 in vivo unbound KI - S-mephenytoine

Molecule: CYP2C19

Parameters

Name	Value	Value Origin
Ki	2.6 nmol/l	Publication-Iga 2016

Inhibition: CYP1A2-Fit-Tizanidine

Molecule: CYP1A2

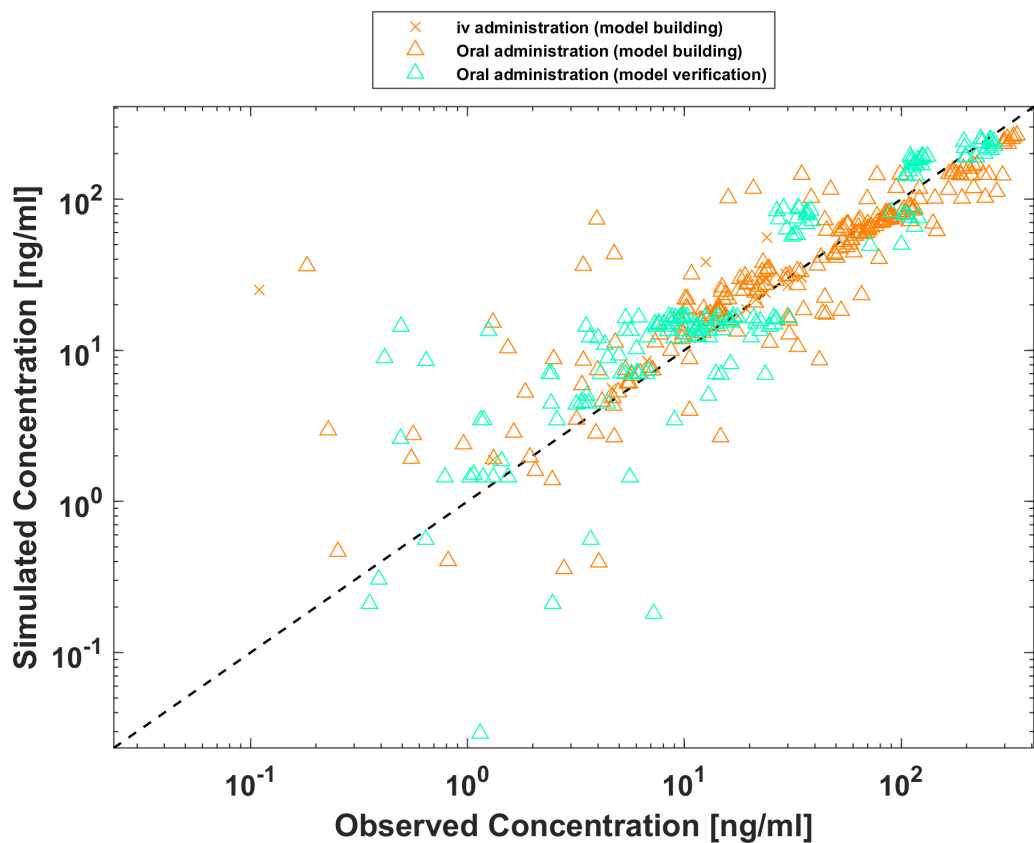
Parameters

Name	Value	Value Origin
Ki	0.8697 nmol/l	Parameter Identification-Fit to tizanidine concentrations

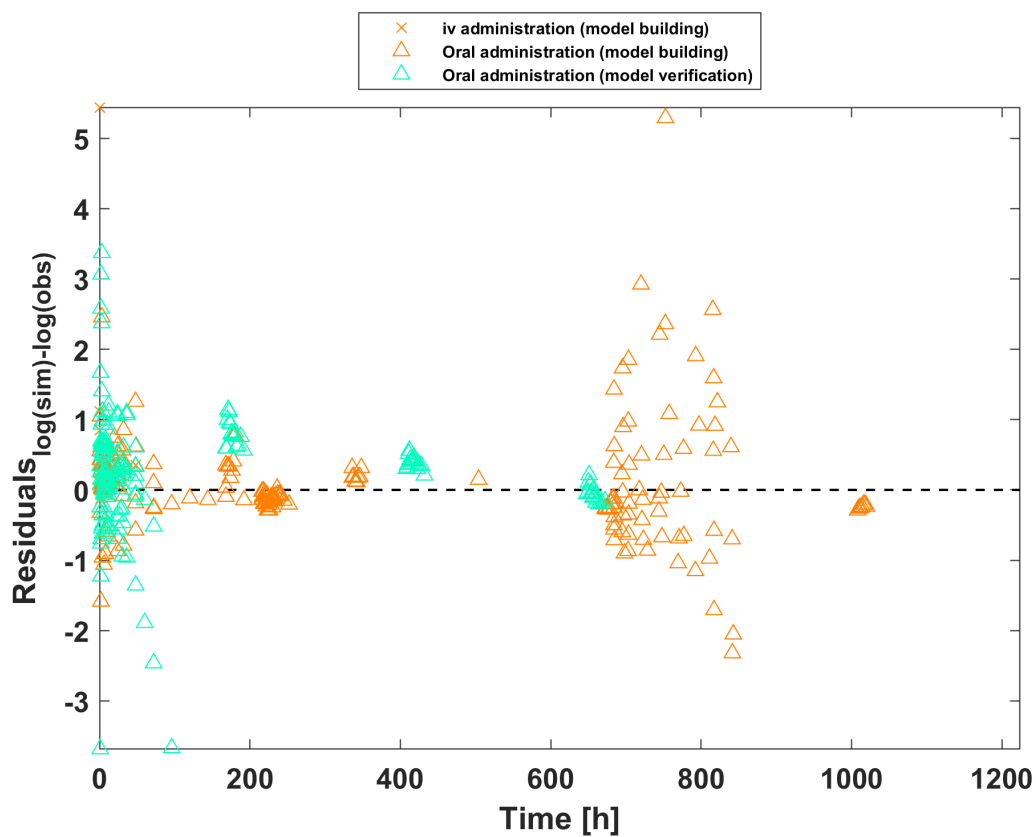
3.2 Diagnostics Plots

The following section displays the goodness-of-fit visual diagnostic plots for the PBPK model performance of all data listed in [Section 2.2.2](#).

The first plot shows observed versus simulated plasma concentration, the second weighted residuals versus time.



Fluvoxamine concentration in plasma - mean data



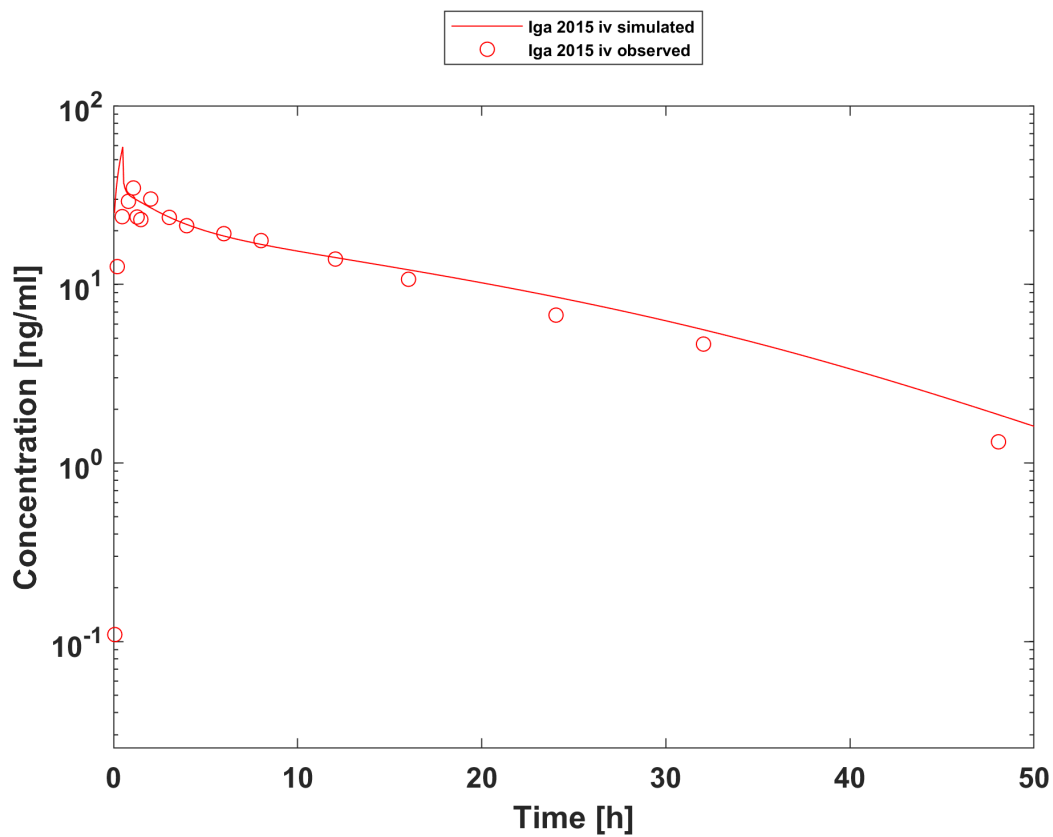
Fluvoxamine concentration in plasma - mean data

GMFE = 1.679152

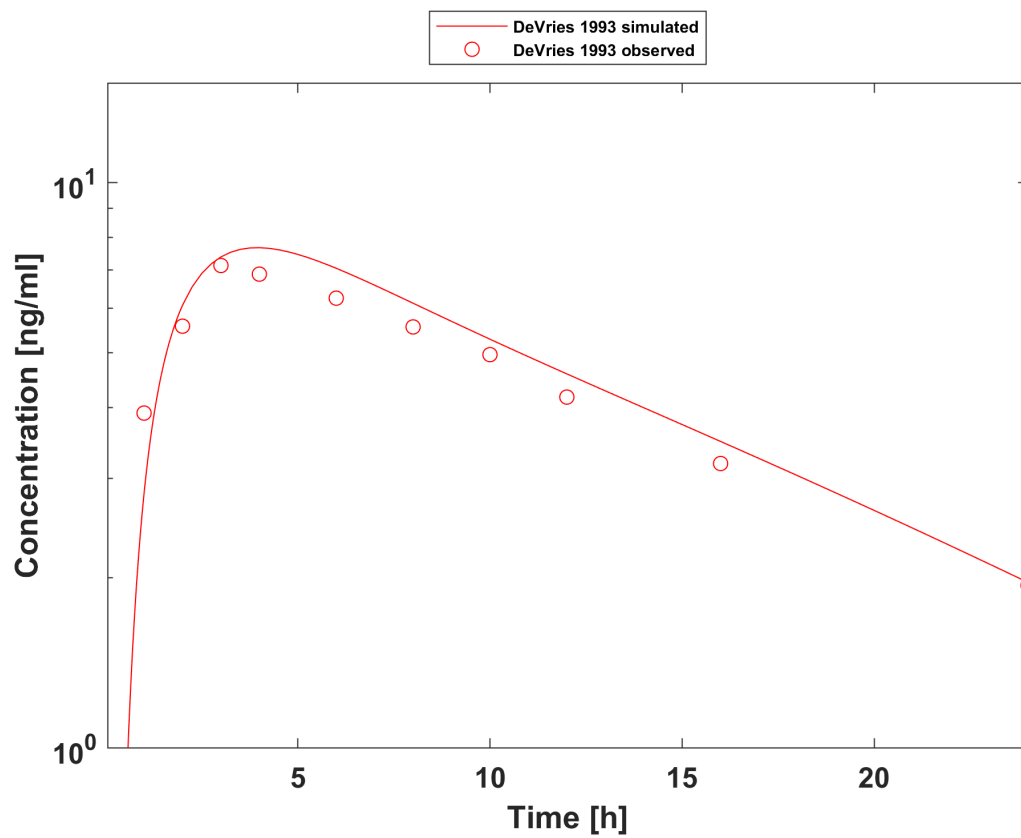
3.3 Concentration-Time Profiles

Simulated versus observed concentration-time profiles of all data listed in [Section 2.2.2](#) are presented below.

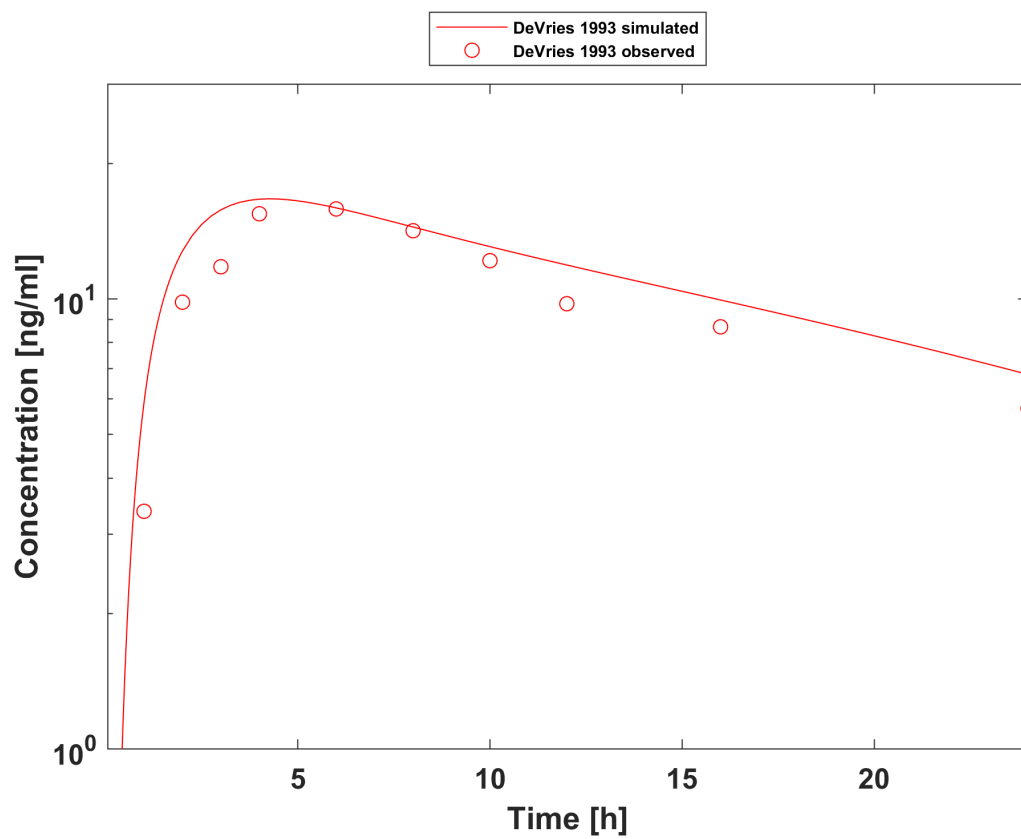
3.3.1 Model Building



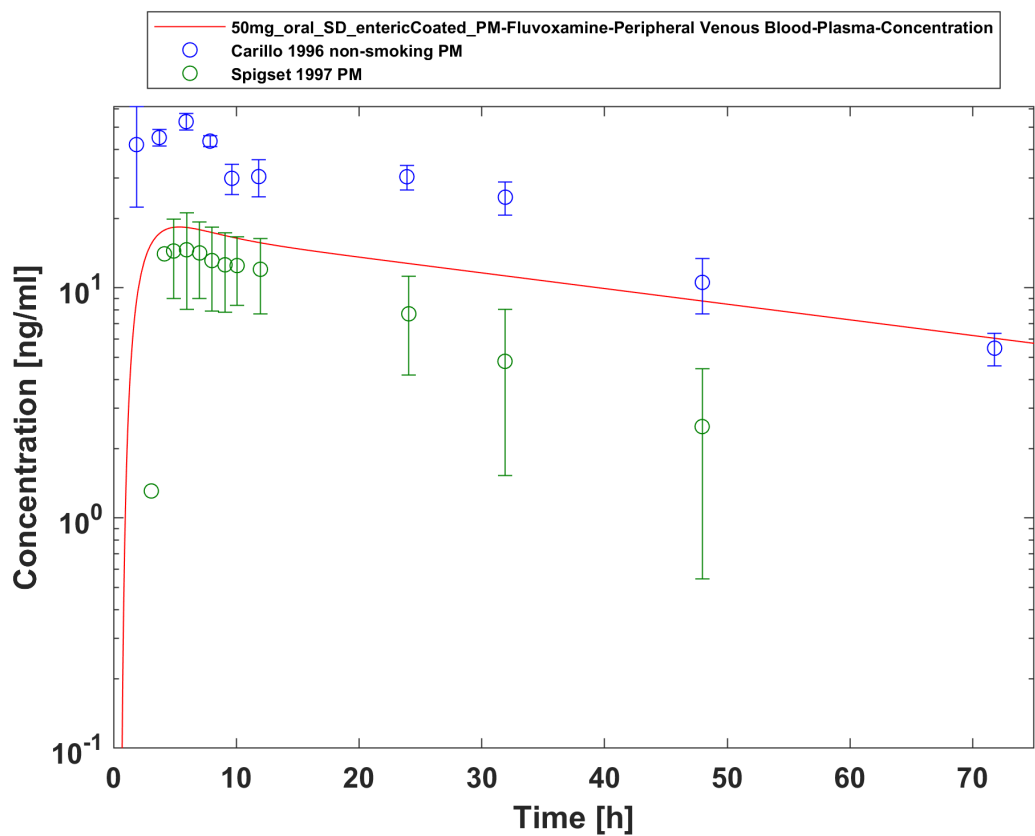
Iga 2015 50 mg iv infusion



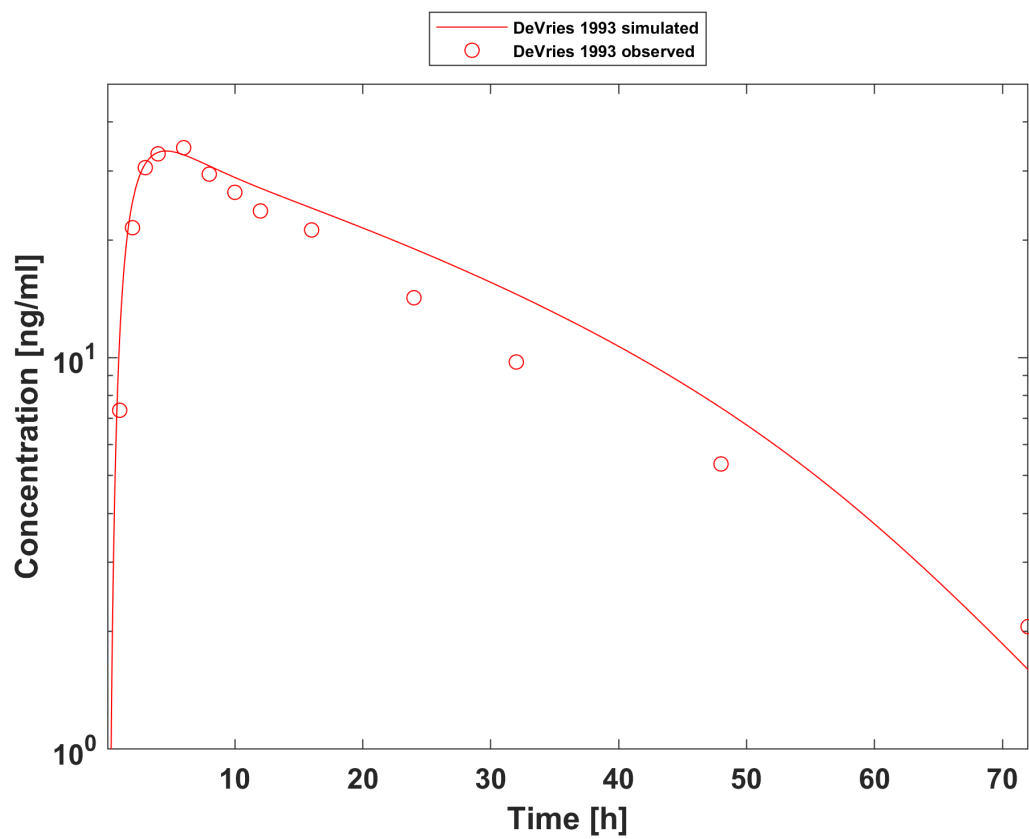
25mg sd po solution



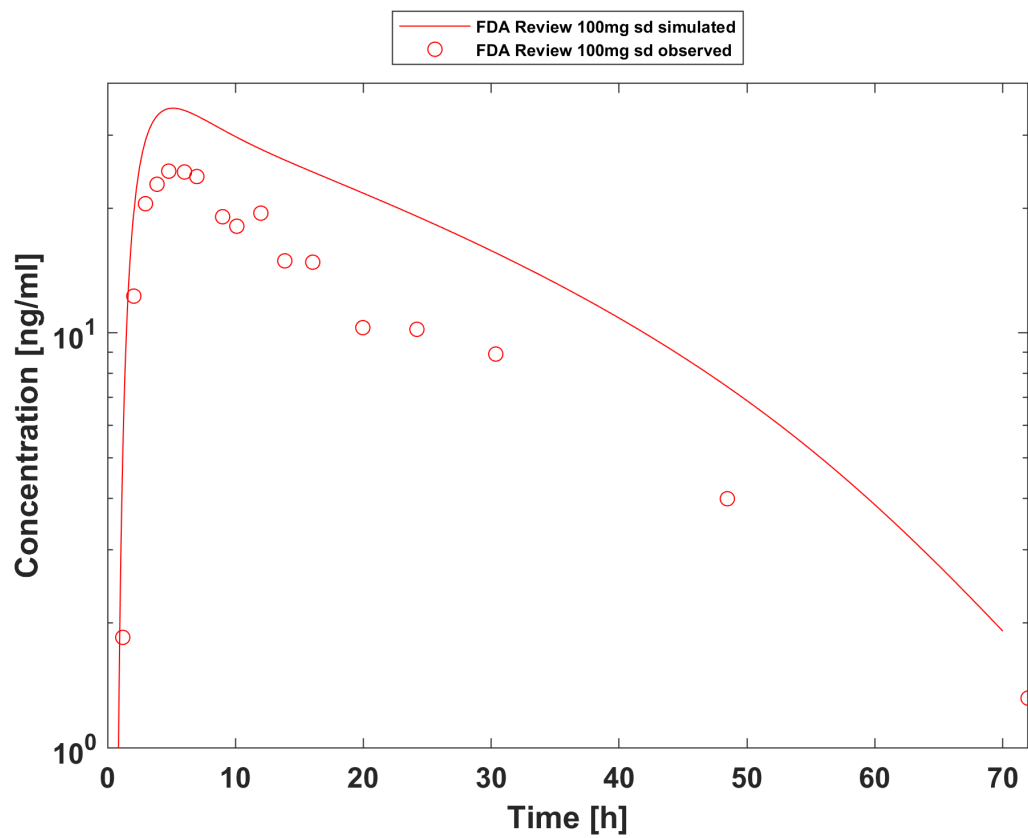
50mg sd po solution



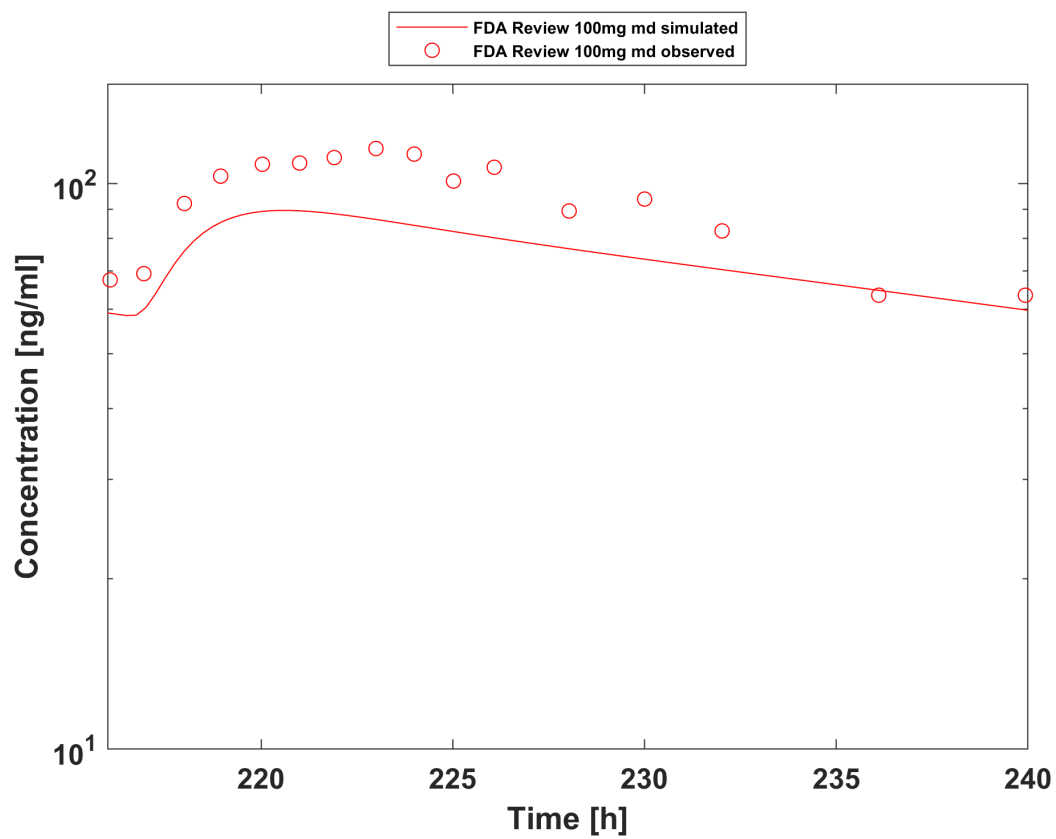
50mg sd po ec tablet PM



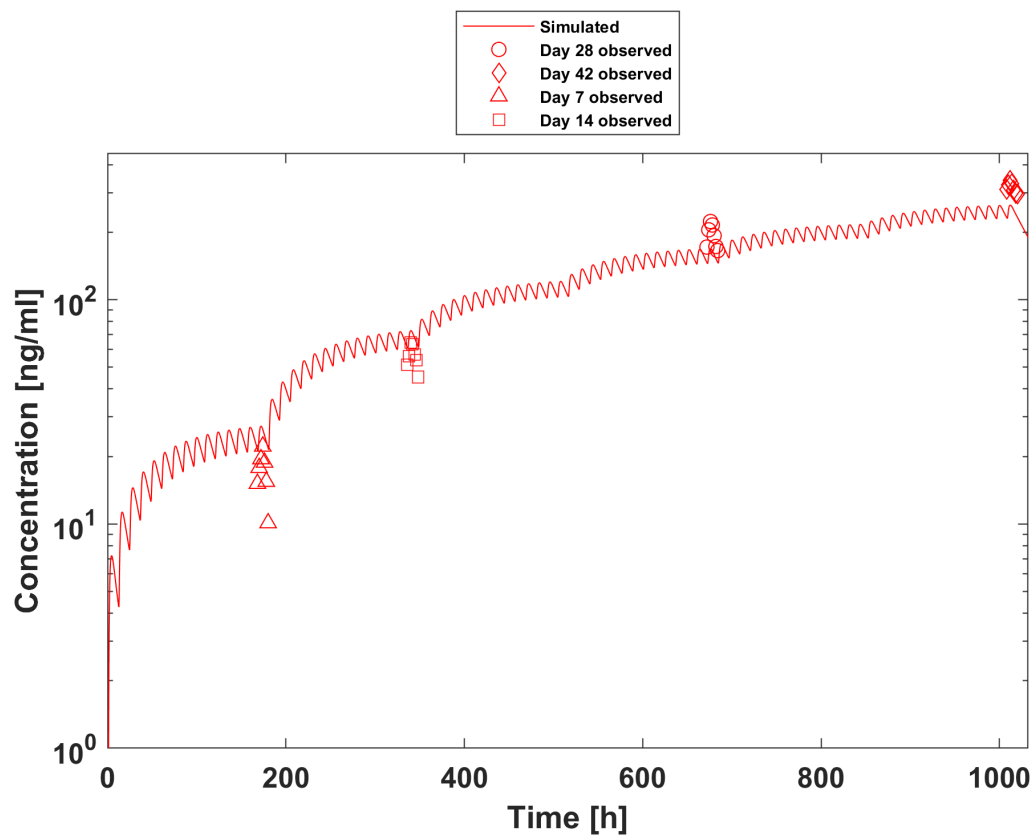
100mg sd po solution



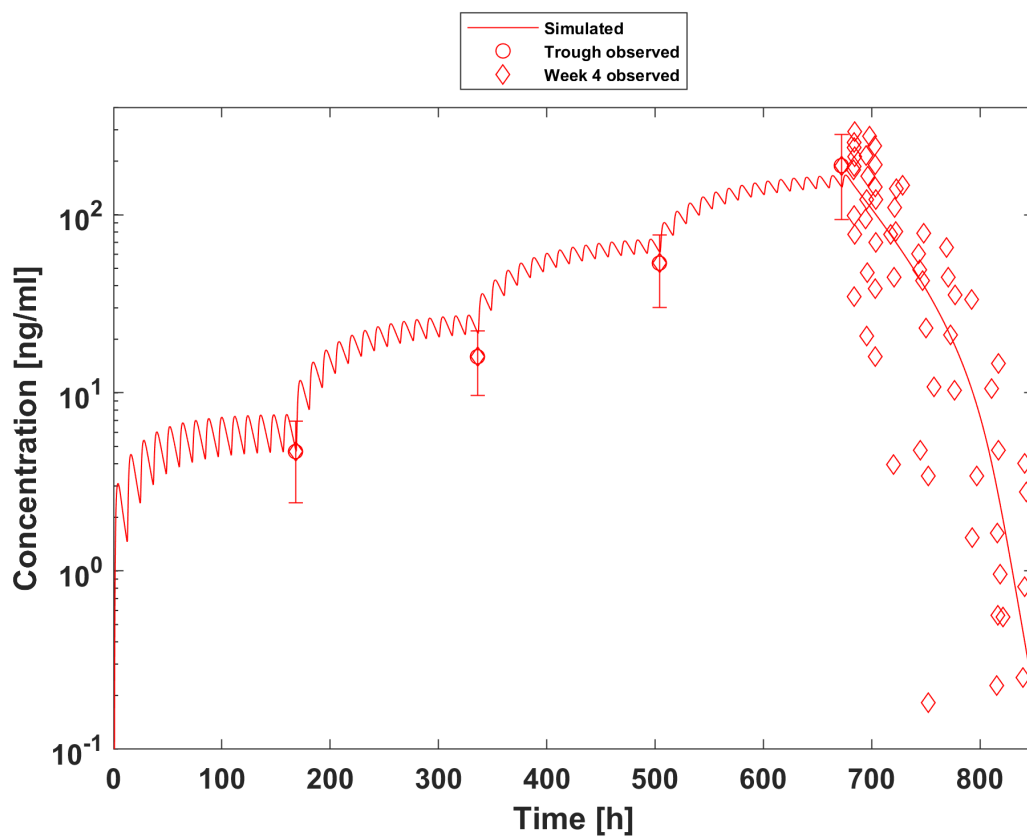
100mg sd po tablet



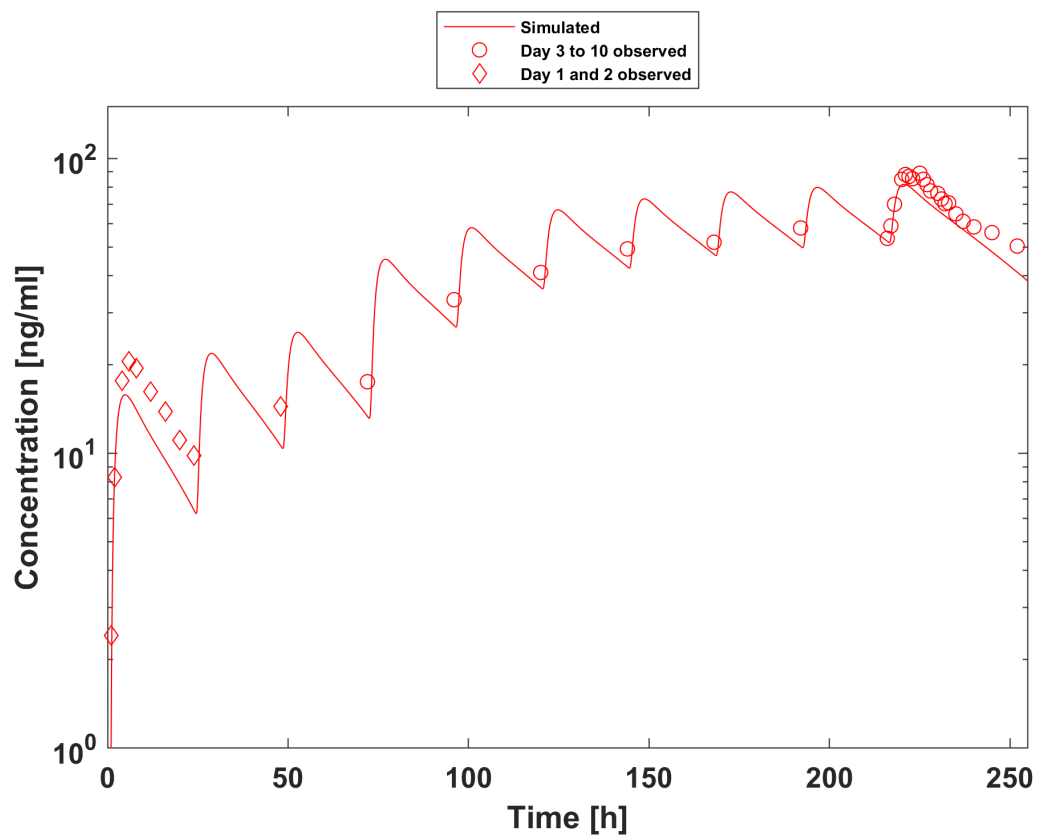
100mg md 10 days po tablet



Labellarte 2004

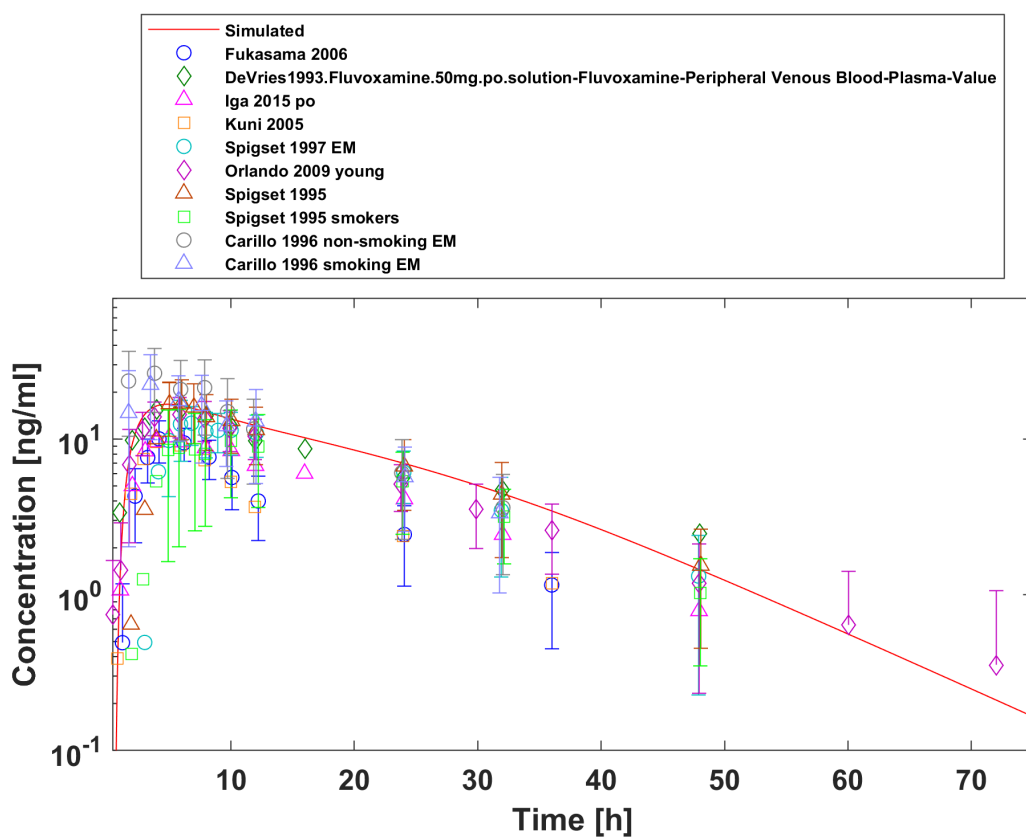


Spigset 1998 MD b.i.d.

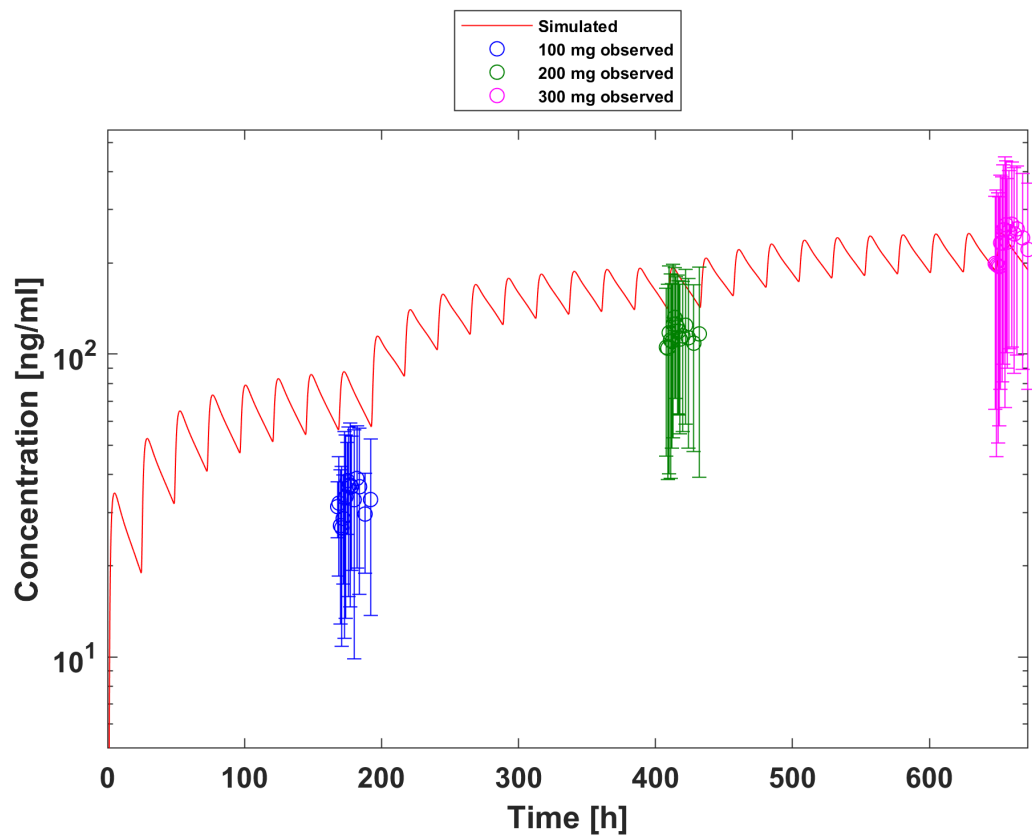


Fleishaker 1994 50mg 100m mg q.d.

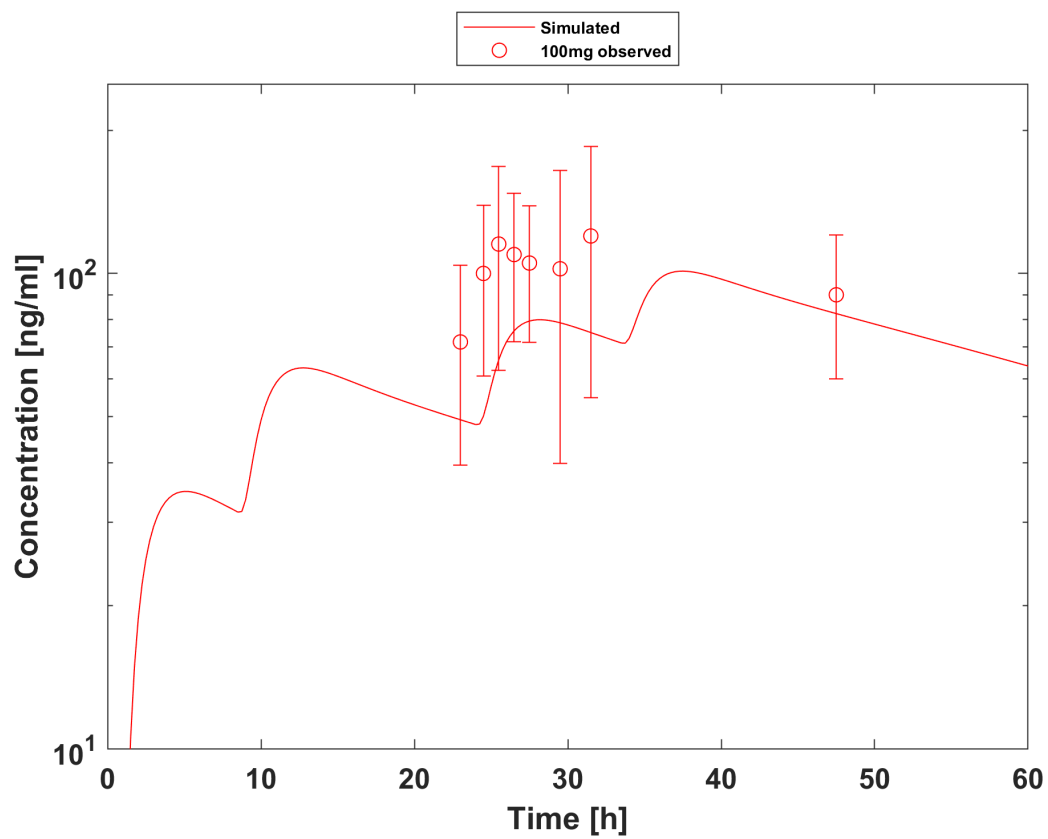
3.3.2 Model Verification



50mg sd po ec tablet



FDA Review 100-200-300 mg



Culm-Merdek 100mg

4 Conclusion

The developed PBPK model of fluvoxamine describes the PK data after administrations of single as well as multiple doses well. The predictions of the 50 mg dose align closer to the studies where higher concentrations were observed. The most likely explanation is the smoking status of the subjects in the studies showing lower concentrations. Cigarette smoke is known to induce the CYP1A2 enzyme system. Hence, lower fluvoxamine concentrations would be expected in smokers due to the higher metabolism. Although there is no built-in smoking status in PK-Sim, this could be modeled by adapting CYP1A2 expression.

In two studies, data from poor metabolizers were available ([Carillo 1996](#), [Spigset 1997](#)). Concentrations reported by [Carillo 1996](#) were much higher than what [Spigset 1997](#) reported for the subset of PM data. However, notice that plasma levels of extensive metabolizers were also higher in the Carillo-study compared to the other reports. Subjects in the Spigset 1997 dataset were all non-smokers. The reason for this discrepancy is unclear.

The estimated values for K_m and K_{cat} defining the metabolization of fluvoxamine by CYP2D6 were highly correlated (correlation of 0.93), indicating that more data would still be needed to estimate the saturable process with more precision.

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6 Glossary

ADME	Absorption, Distribution, Metabolism, Excretion
AUC	Area under the plasma concentration versus time curve
AUCinf	AUC until infinity
AUClast	AUC until last measurable sample
AUCR	Area under the plasma concentration versus time curve Ratio
b.i.d.	Twice daily (bis in diem)
CL	Clearance
Clint	Intrinsic liver clearance
Cmax	Maximum concentration
CmaxR	Maximum concentration Ratio
CYP	Cytochrome P450 oxidase
CYP1A2	Cytochrome P450 1A2 oxidase
CYP2C19	Cytochrome P450 2C19 oxidase
CYP3A4	Cytochrome P450 3A4 oxidase
DDI	Drug-drug interaction
e.c.	Enteric coated
EE	Ethinylestradiol
EM	Extensive metabolizers
fm	Fraction metabolized
FMO	Flavin-containing monooxygenase
fu	Fraction unbound
FDA	Food and Drug administration
GFR	Glomerular filtration rate
HLM	Human liver microsomes
hm	homozygous
ht	heterozygous
IM	Intermediate metabolizers
i.v.	Intravenous
IVIVE	In Vitro to In Vivo Extrapolation
Ka	Absorption rate constant
kcat	Catalyst rate constant
Ki	Inhibitor constant
Kinact	Rate of enzyme inactivation
Km	Michaelis Menten constant
m.d.	Multiple dose
OSP	Open Systems Pharmacology

ADME	Absorption, Distribution, Metabolism, Excretion
PBPK	Physiologically-based pharmacokinetics
PK	Pharmacokinetics
PI	Parameter identification
PM	Poor metabolizers
RT-PCR	Reverse transcription polymerase chain reaction
p.o.	Per os
q.d.	Once daily (quaque diem)
SD	Single Dose
SE	Standard error
s.d.SPC	Single dose Summary of Product Characteristics
SD	Standard deviation
TDI	Time dependent inhibition
t.i.d	Three times a day (ter in die)
UGT	Uridine 5'-diphospho-glucuronosyltransferase
UM	Ultra-rapid metabolizers