Building and evaluation of a PBPK model for Omeprazole in adults

Version	**1.1-OSP10.0**
based on *Model Snapshot* and *Evaluation Plan*	https://github.com/Open-Systems-Pharmacology/Omeprazole-Model/releases/tag/v1.1
OSP Version	10.0
Qualification Framework Version	2.3

This evaluation report and the corresponding PK-Sim project file are filed at:

https://github.com/Open-Systems-Pharmacology/OSP-PBPK-Model-Library/

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1 Introduction

The presented PBPK model of omeprazole has been developed to be used in a PBPK Drug-Drug-Interactions (DDI) network with omeprazole as a substrate of CYP2C19 and CYP3A4 and an inhibitor of CYP2C19.

Omeprazole is a proton pump inhibitor (PPI) for the treatment of gastric acid related diseases. Omeprazole is administered as a racemic mixture of its two enantiomers, S-omeprazole and R-omeprazole.

The following ADME characteristics for (R-/S-) omeprazole were taken from omeprazole 20 mg capsule FDA SPC:

Absorption: Absorption of (R-/S-) omeprazole is rapid, with peak plasma levels occurring approximately 1-2 hours after dose. Absorption of omeprazole takes place in the small intestine and is usually completed within 3-6 hours. The systemic availability (bioavailability) from a single oral dose of omeprazole is approximately 40%. After repeated once-daily administration, the bioavailability increases to about 60%.

Distribution: The apparent volume of distribution in healthy subjects is approximately 0.3 l/kg body weight. Omeprazole is 97% plasma protein bound.

Metabolism: (R-/S-) Omeprazole is completely metabolized by the cytochrome P450 system (CYP). The major part of its metabolism is dependent on the polymorphically expressed CYP2C19, responsible for the formation of hydroxyomeprazole, the major metabolite in plasma. The remaining part is dependent on another specific isoform, CYP3A4, responsible for the formation of omeprazole sulphone. As a consequence of high affinity of omeprazole to CYP2C19, there is a potential for competitive inhibition and metabolic drug-drug interactions. No metabolite has been found to be pharmacologically active.

Elimination: Almost 80% of an oral dose of omeprazole is excreted as metabolites in the urine, the remainder in the faeces, primarily originating from bile secretion.

Linearity/non-linearity: The AUC of omeprazole increases with repeated administration following a non-linear dose-AUC relationship. This time- and dose- dependency is due to a decrease of first pass metabolism and systemic clearance probably caused by an inhibition of the CYP2C19 enzyme by omeprazole and/or its metabolites (e.g. the sulphone).

Stereoselectivity: Because both enantiomers are substrates and inhibitors of CYP2C19, the PK profile of each enantiomer is expected to differ when the racemic mixture is administered as compared to as a single agent because of mutual inhibition between the enantiomers (Äbelö 2000). The Ki for R-omeprazole is 2-5 higher compared to S-omeprazole (Liu 2005, Wu 2014).

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).

The model includes distinct molecules for S- and R-omeprazole, the racemic omeprazole is represented by an observer that sums up the concentrations of S- and R-omeprazole. It was assumed that both isomers correspond to the half of the racemic omeprazole dose.

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

1a Define distribution and metabolism for S-omeprazole

1b.Mechanism based inactivation of CYP2C19 by omeprazole

2.Define S-omeprazole absorption based on p.o.

3.Capsule formulation

- 3a. Building racemic omeprazole
- 3b. Adjust CYP2C19 expression in gut

4.Define metabolism for R-omeprazole

5.Refine CYP3A4 metabolism on CYP2C19 PM data

6.Refine CYP2C19 metabolism on CYP2C19 EM data

The predefined “Standard European Male for DDI” individual was used (age = 30 y, weight = 73 kg, height = 176 cm, BMI = 23.57 kg/m2) until stated otherwise. CYP2C19 expression from the PK-Sim in-built RT-PCR database was added and adjusted as described in Section 2.3.3.

Selection of the distribution model for S-omeprazole and estimation of the lipophilicity parameter were performed with i.v. data (Wilder-Smith 2005, Hassan-Alin 2000).

The kinetics of CYP2C19 and CYP3A4 metabolization processes of S-omeprazole and R-omeprazole were estimated using the Parameter Identification module provided in PK-Sim® with i.v. and p.o. data including administration of S-, R- or racemic omeprazole, see Table 3, Table 4, and Table 5 for more details. The kinetic parameters were assumed not to be identical for the isomers. For simulations of CYP2C19 poor metabolizers, the CYP2C19 pathway was switched off.

For studies in Japanese subjects, 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 CYP3A4 and CYP2C19 expression from PK-Sim RT PCR database, and adapting CYP2C19 expression in gut as described in Section 2.3.3.

Intestinal permeability of S-omeprazole was estimated by fitting the model to concentration-time data measured after p.o. administration of 20 or 40 mg given as solution (Hassan-Alin 2005).

Parameters `Dissolution time (50% dissolved)` and `Dissolution shape` describing the dissolution of capsule formulation were fitted to the data after single dose S-omeprazole 40 mg capsule (Wilder-Smith 2005).

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.

Population simulations of single and multiple i.v. or p.o. administration over a wide range of dose levels were conducted to visually compare the predicted concentration-time profile to the observed concentrations reported in the literature, in terms of mean and variability. The simulated populations matched the race (European or Asian) and the age-weight ranges reported in the respective clinical studies. A total of 1000 individuals were generated for studies in males only, while 2000 were generated for mixed gender populations. The concentration time profile was simulated for each virtual subject and summarized as geometric mean and 95% CI. The simulations were performed for extensive and poor CYP2C19 metabolizers.

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 S- and R-omeprazole and summarized in Table 1 and Table 2, respectively.

Parameter	Unit	Value	Source	Description
MW^{+}	g/mol	345.42	DrugBank DB00338	Molecular weight.
$pK_{a,acid}{}^{+}$		9.29	DrugBank DB00338	Acidic dissociation constant
$pK_{a,base}{}^{+}$		4.77	DrugBank DB00338	Basic dissociation constant
Solubility (pH)$^{+}$	mg/mL	0.36 (7)	DrugBank DB00338	Aqueous Solubility
logD		2.23	Ogilvie 2011	Distribution coefficient
fu^{+}	%	3	Nexium prescribing information	Fraction unbound in plasma
Kinact CYP2C19^{+}	l/h	5	Wu 2014	Kinact of time dependent inhibition on CYP2C19
K_i CYP2C19^{+}	µM	0.3	Wu 2014	KI of time dependent inhibition on CYP2C19
K_i CYP2C19 (competitive inhibition)$^{+}$	µM	3.1	Liu 2005	The total ki value reported by Liu was 3.4 µmol/L and corrected with an fu_mic of 0.92
Renal Elimination^{+}	l/h	0.037	Wu 2014	Assumed same as omeprazole

Table 1: Physico-chemical and *in-vitro* metabolization properties of S-omeprazole extracted from literature. $^{+}$*: Value used in final model*

Parameter	Unit	Value	Source	Description
MW^{+}	g/mol	345.42	DrugBank DB00338	Molecular weight.
$pK_{a,acid}{}^{+}$		9.29	DrugBank DB00338	Acidic dissociation constant
$pK_{a,base}{}^{+}$		4.77	DrugBank DB00338	Basic dissociation constant
Solubility $(pH)^{+}$	mg/mL	0.36 (7)	DrugBank DB00338	Aqueous Solubility
logD		2.23	Ogilvie 2011	Distribution coefficient
fu^{+}	%	4	Ogilvie 2011	Fraction unbound in plasma; assumed same as omeprazole
Kinact $CYP2C19^{+}$	l/h	4	Wu 2014	Kinact of time dependent inhibition on CYP2C19
K_i $CYP2C19^{+}$	µM	1.6	Wu 2014	KI of time dependent inhibition on CYP2C19
K_i CYP2C19 (competitive inhibition)$^{+}$	µM	5.3	Liu 2005	The total ki value reported by Liu was 5.7 µmol/L and corrected with an fu_mic of 0.92
Renal $Elimination^{+}$	l/h	0.037	Wu 2014	Assumed same as omeprazole

Table 2: Physico-chemical and *in-vitro* metabolization properties of R-omeprazole extracted from literature. $^{+}$*: Value used in final model*

2.2.2 Clinical data

A literature search was performed to collect available clinical data on omeprazole in adults. Data used for model development and validation for omeprazole, S-omeprazole, and R-omeprazole are listed in Table 3, Table 4, and Table 5, respectively.

Source	Route	Dose [mg]/ Schedule *	Pop.	Sex	N	Form.	Comment
Andersson 1990+	i.v.	40 - 80	HV	M	10	solution	
Andersson 1990	p.o.	40 - 80	HV	M	10	Oral solution	
Andersson 1991	p.o.	10 - 20 – 40 q.d.	HV	M	12	e.c. granules	
Andersson 1991+	i.v.	10 - 20 - 40	HV	M	12	solution	
Andersson 1998	p.o.	20 q.d.	HV	M	12	capsule	EM
Andersson 1998	p.o.	20 q.d.	HV	M	2	capsule	PM
Oosterhuis 1992+	i.v.	40 - 80	HV	M	8	solution	
Uno 2007+	i.v.	20	HV japanese	M - F	6	solution	hmEM
Uno 2007+	i.v.	20	HV japanese	M - F	6	solution	PM
Uno 2007	p.o.	40	HV japanese	M - F	6	tablet	hmEM
Uno 2007	p.o.	40	HV japanese	M - F	6	tablet	PM
Regårdh 1990+	i.v.	10	HV	M	8	solution	
Regårdh 1990	p.o.	20	HV	M	8	Oral solution	
Andersson 2000	p.o.	15 q.d.	HV	-	4	Oral solution	EM
Andersson 2000	p.o.	60 q.d.	HV	-	5	Oral solution	PM
Hassan-Alin 2005	p.o.	20 – 40 q.d.	HV	-	-	Oral solution	
Cho 2002	p.o.	20	HV asian	-	-	capsule	EM +/- moclobemide
Cho 2002	p.o.	20	HV asian	-	-	capsule	PM +/- moclobemide
Yasui-Furukori 2004	p.o.	40	HV japanese	M - F	6	omepral	
Yasui-Furukori 2004	p.o.	40	HV japanese	M - F	6	omepral	PM +/- fluvoxamine
Wu 2016	p.o.	40 q.d.	HV caucasian	M - F	15	gastro-resistant hard capsule	

Table 3: Literature sources of clinical concentration data of omeprazole used for model development and validation. *e.c.: enteric coated; -: respective information was not provided in the literature source; *:single dose unless otherwise specified; EM: extensive metabolizers; PM: pooor metabolizers; +: Data used for final parameter identification*

Source	Route	Dose [mg]/ Schedule *	Pop.	Sex	N	Form.	Comment
Wilder-Smith 2005+	i.v.	40 q.d.	HV	M - F	39	solution	
Wilder-Smith 2005+	p.o.	40 q.d.	HV	M - F	37	capsule	
Hassan-Alin 2000+	i.v.	20 - 40	HV	-	-	solution	
Andersson 2000	p.o.	15 q.d.	HV	-	4	oral solution	EM
Andersson 2000+	p.o.	60 q.d.	HV	-	5	oral solution	PM
Hassan-Alin 2005+	p.o.	20 - 40 q.d.	HV	-	-	oral solution	
FDA Nexium Review	p.o.	40	HV	M	-	-	EM
FDA Nexium Review+	p.o.	40	HV	M	-	-	PM
Rohss 2007+	i.v.	120mg(30min)+8mg/h - 120mg(2h)+8mg/h - 80mg(30min)+4mg/h - 80mg(30min)+8mg/h - 40mg(30min)+8mg/h	HV	-	25	solution	

Table 4: Literature sources of clinical concentration data of S-omeprazole used for model development and validation. *e.c.: enteric coated; -: respective information was not provided in the literature source; *:single dose unless otherwise specified; EM: extensive metabolizers; PM: pooor metabolizers; +: Data used for final parameter identification*

Source	Route	Dose [mg]/ Schedule *	Pop.	Sex	N	Form.	Comment
Andersson 2000+	p.o.	15 q.d.	HV	-	4	oral solution	EM
Andersson 2000+	p.o.	60 q.d.	HV	-	5	oral solution	PM
Hassan-Alin 2005+	p.o.	20 - 40 q.d.	HV	-	-	oral solution	

Table 5: Literature sources of clinical concentration data of R-omeprazole used for model development and validation. *e.c.: enteric coated; -: respective information was not provided in the literature source; *:single dose unless otherwise specified; EM: extensive metabolizers; PM: pooor metabolizers; +: Data used for final parameter identification*

2.3 Model Parameters and Assumptions

2.3.1 Absorption

The model parameter `Specific intestinal permeability` for S-omeprazole was optimized to best match clinical data (see Section 2.3.4). The same parameter value was assumed for R-omeprazole.

The dissolution of the capsule formulation was implemented via an empirical Weibull dissolution equation with parameters `Dissolution time (50% dissolved)` and `Dissolution shape` fitted to observed data. A `Lag time` = 30 min was used to account for the gastric emptying time.

2.3.2 Distribution

Physico-chemical parameter values of S- and R-omeprazole were set to the reported values (see Section 2.2.1) except for lipophilicity of S-omeprazole, which was estimated with i.v. data. 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`.

The same distribution model and parameter values were assumed for R-omeprazole, as no i.v. data are available for R-omeprazole.

2.3.3 Metabolism and Elimination

Two linear metabolic pathways for S- and R-omeprazole were implement in the model:

- CYP2C19
- CYP3A4

To describe multiple dose oral solution data, time-dependent autoinhibition (TDI) on CYP2C19 was added as irreversible inhibition / Mechanism-based inactivation as described by Wu 2014.

Competitive inhibition of CYP2C19 by both isomers was implemented in addition to TDI (Liu 2005).

Simulation results suggested that the expression of CYP2C19 isoenzymes in the GI tract as provided by the RT-PCR PK-Sim database is significantly preventing R-omeprazole from entering the circulation. This was less apparent for S-omeprazole. To note, while the absolute mean CYP3A4 abundance in liver (1.03e7 pmol per liver) and the intestinal/liver CYP3A4 ratio in PK-Sim default individual are similar to values used in other models, the relative intestinal CYP2C19 and CYP2D6 abundances differ (Table 6). The relative expression of CYP2C19 in gut was therefore reduced according to Olivares-Morales 2016 for the final model.

Ratio	Olivares-Morales 2016[1]	Galetin and Houston 2006[2]	Gastroplus	RT-PCR PKsim	Comment
CYP3A4/2C19 relative abundance liver	9.8	11.1	8.1	5.68	CYP2C19 abundance in liver 1.8-fold higher than other literature sources
CYP3A4/2C19 relative abundance intestine	43.8	43.0	-	1.28	CYP2C19 abundance in intestine 22-fold higher than other literature sources
CYP3A4/2D6 relative abundance liver	17.1	19.4	14.2	10.80	CYP2D6 abundance in liver 1.6-fold higher than other literature sources
CYP3A4/2D6 relative abundance intestine	83.8	86.0	-	8.64	CYP2D6 abundance in intestine 6-fold higher than other literature sources
CYP3A4 abundance Small intestine/liver	0.66%	-	-	0.44%	in range with literature
CYP2C19 abundance Small intestine/liver	0.15%	-	-	1.95%	23-fold higher than in literature
CYP2D6 Small intestine/liver	0.14%	-	-	0.55%	4-fold higher than in literature

Table 6: Comparison of CYP3A4, CYP2C19 and CYP2D6 relative abundance in liver and small intestine from different literature sources. [1] Based on Sjörgen 2014: CYP relative expressions (pmol/mg_mic_p) from Paine 2006 calibrated against total intestinal CYP3A4 abundance. [2] Mean hepatic and intestinal relative abundance based on Rowland and Yeo 2003 and Paine 2006

Additionally, renal plasma clearance was implemented (Wu 2014).

2.3.4 Observer for racemic omeprazole

Omeprazole concentrations in peripheral venous blood plasma at any specific time points were obtained by adding the simulated concentrations of two enantiomers together at the corresponding time points to generate the omeprazole PK profiles, according to the following formula:

fQ_art(C_pls_art_Eso+C_pls_art_R_O) +fQ_bon*(C_pls_bon_Eso+C_pls_bon_R_O)+fQ_fat* (C_pls_fat_Eso + C_pls_fat_R_O)+fQ_mus*(C_pls_mus_Eso + C_pls_mus_R_O) +fQ_skn* (C_pls_skn_Eso + C_pls_skn_R_O)*

where *fQ_* are fraction of blood flow and *C_pls_* concentrations in plasma compartment respectively in the arterial (*art*), bone (*bon*), fat (*fat*), muscle (*mus*) or skin (*skn*) tissues. *Eso* and *R_O* stand for S- and R-omeprazole respectively.

2.3.5 Automated Parameter Identification

Following parameter values were estimated for the base model:

Parameter	Compound
Lipophilicity	S-Omeprazole
Specific intestinal permeability (transcellular)	S-Omeprazole
Dissolution time (Weibull)	S-Omeprazole
Dissolution shape (Weibull)	S-Omeprazole
Specific CL_2C19	S-Omeprazole
Specific CL_2C19	R-Omeprazole
Specific CL_3A4	S-Omeprazole
Specific CL_3A4	R-Omeprazole

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.

Compound: Esomeprazole

Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	0.359 mg/ml	Database-DrugBank DB00338	Measurement	True
Reference pH	7	Database-DrugBank DB00338	Measurement	True
Lipophilicity	1.6835584938 Log Units	Parameter Identification-Parameter Identification	LogP fit	True
Fraction unbound (plasma, reference value)	0.03	Database-DrugBank DB00338	Fu DrugBank	True
Specific intestinal permeability (transcellular)	9.79E-05 cm/min	Parameter Identification-Parameter Identification	Fit	True
Is small molecule	Yes			
Molecular weight	345.416 g/mol	Database-DrugBank DB00338		
Plasma protein binding partner	Albumin			

Calculation methods

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

Processes

Metabolizing Enzyme: CYP2C19-2C19 Linear Fit

Species: Human
Molecule: CYP2C19

Parameters

Name	Value	Value Origin
Intrinsic clearance	0 l/min	
Specific clearance	13.98 1/min	Parameter Identification-Parameter Identification

Metabolizing Enzyme: CYP3A4-3A4 Linear Fit

Species: Human
Molecule: CYP3A4

Parameters

Name	Value	Value Origin
Intrinsic clearance	0 l/min	
Specific clearance	0.3707655759 1/min	Parameter Identification-Parameter Identification

Systemic Process: Renal Clearances-Wu2014 - Table1 - CLr

Species: Human

Parameters

Name	Value	Value Origin
Fraction unbound (experiment)	0.05	
Plasma clearance	0.000507 l/h/kg	Unknown-0.037l/h/73kg

Inhibition: CYP2C19-Liu 2005 - Ki in vivo unbound

Molecule: CYP2C19

Parameters

Name	Value	Value Origin
Ki	3.1 µmol/l	Publication-Liu 2005

Inhibition: CYP2C19-Wu2014 - Table1 - TDI

Molecule: CYP2C19

Parameters

Name	Value	Value Origin
kinact	5 1/h	Publication-Wu 2014
K_kinact_half	0.3 µmol/l	

Formulation: Omeprazole capsule

Type: Weibull

Parameters

Name	Value	Value Origin
Dissolution time (50% dissolved)	41.65 min	Parameter Identification-Parameter Identification
Lag time	30 min	Other-Assumption-Gastric emptying
Dissolution shape	1.02	Parameter Identification-Parameter Identification
Use as suspension	Yes	

Compound: R-omeprazole

Parameters

Name	Value	Value Origin	Alternative	Default
Solubility at reference pH	0.359 mg/ml	Database-DrugBank DB00338	Measurement	True
Reference pH	7	Database-DrugBank DB00338	Measurement	True
Lipophilicity	1.6835584938 Log Units	Other-Assumption-Same as S-omeprazole	LogP fit	True
Fraction unbound (plasma, reference value)	0.04	Publication-Ogilvie 2011	Fu DrugBank	True
Specific intestinal permeability (transcellular)	9.79E-05 cm/min	Other-Assumption-Assumend same as S-omeprazole	Fit	True
Is small molecule	Yes			
Molecular weight	345.416 g/mol	Database-DrugBank DB00338		
Plasma protein binding partner	Albumin			

Calculation methods

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

Processes

Metabolizing Enzyme: CYP2C19-2C19 Linear Fit

Species: Human
Molecule: CYP2C19

Parameters

Name	Value	Value Origin
Intrinsic clearance	0 l/min	
Specific clearance	50 1/min	Parameter Identification-Parameter Identification-Uppder bound lilmited

Metabolizing Enzyme: CYP3A4-3A4 Linear Fit

Species: Human
Molecule: CYP3A4

Parameters

Name	Value	Value Origin
Intrinsic clearance	0 l/min	
Specific clearance	0.161397262 1/min	Parameter Identification-Parameter Identification

Systemic Process: Renal Clearances-Wu2014 - Table1 - CLr

Species: Human

Parameters

Name	Value	Value Origin
Fraction unbound (experiment)	0.03	
Plasma clearance	0 ml/min/kg	
Specific clearance	0.0282095334 1/min	Publication-Wu 2014

Inhibition: CYP2C19-Liu 2005 - Ki in vivo unbound

Molecule: CYP2C19

Parameters

Name	Value	Value Origin
Ki	5.3 µmol/l	Publication-Liu 2005

Inhibition: CYP2C19-Wu2014 - Table1 - TDI

Molecule: CYP2C19

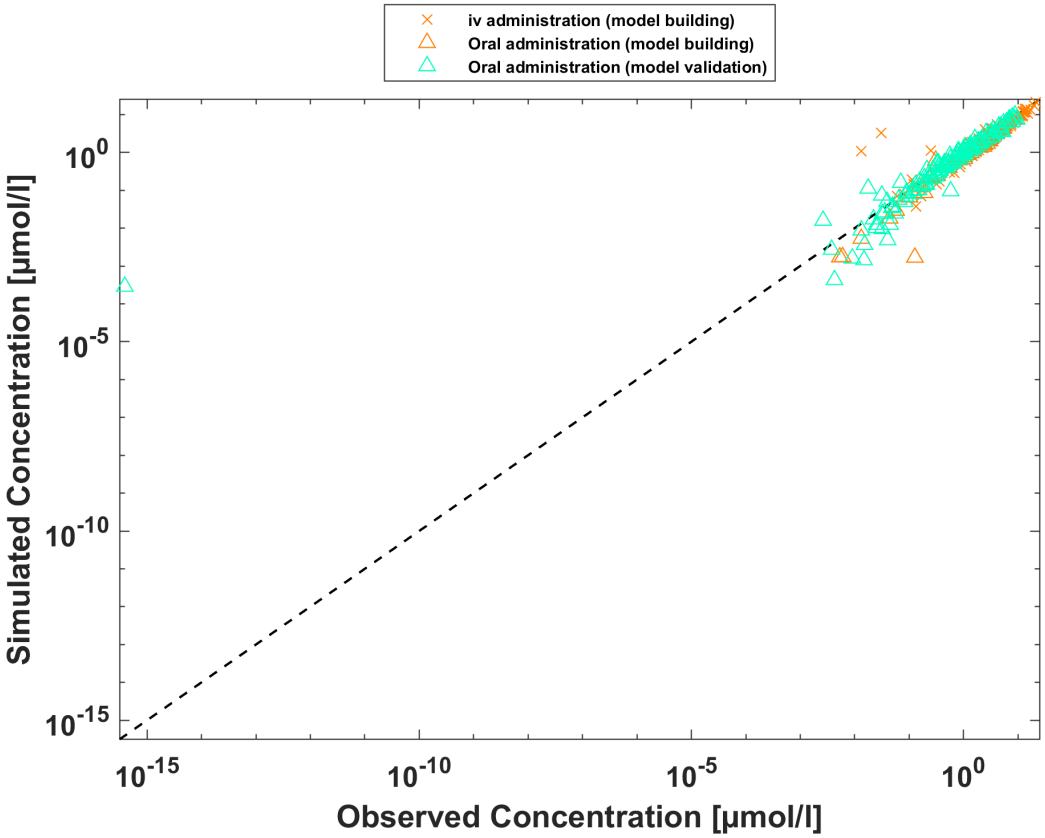
Parameters

Name	Value	Value Origin
kinact	4 1/h	Publication-Wu 2014
K_kinact_half	1.6 µmol/l	

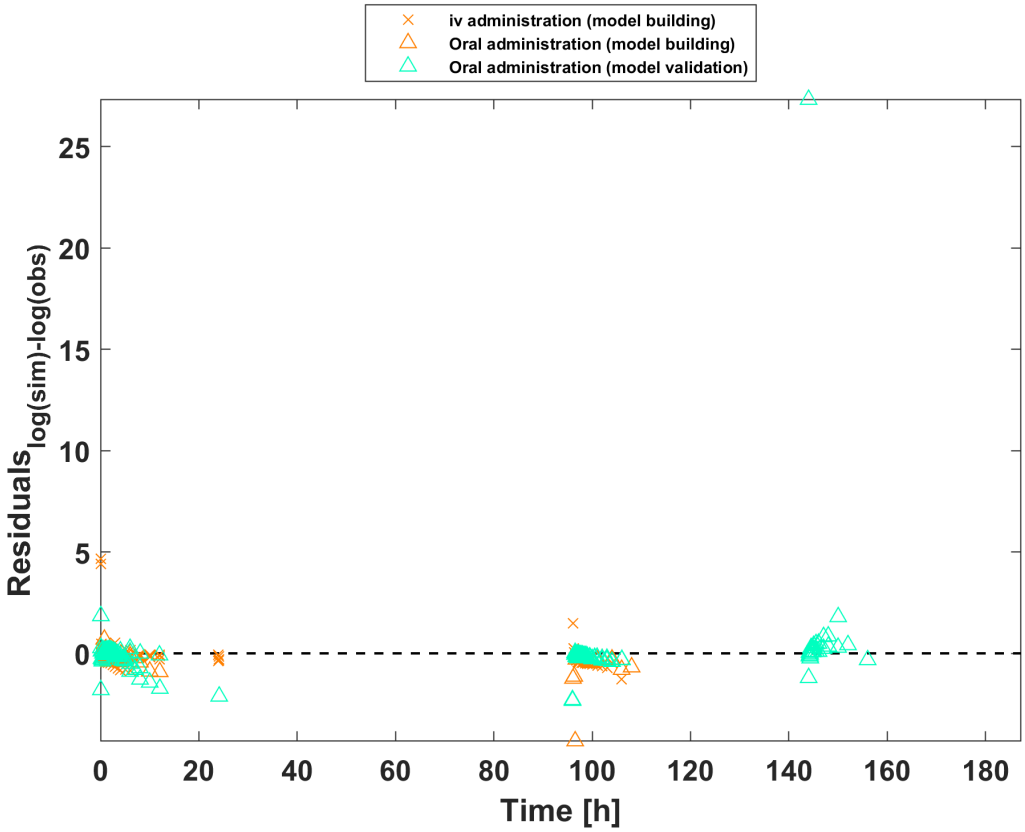
3.2 Diagnostics Plots

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.

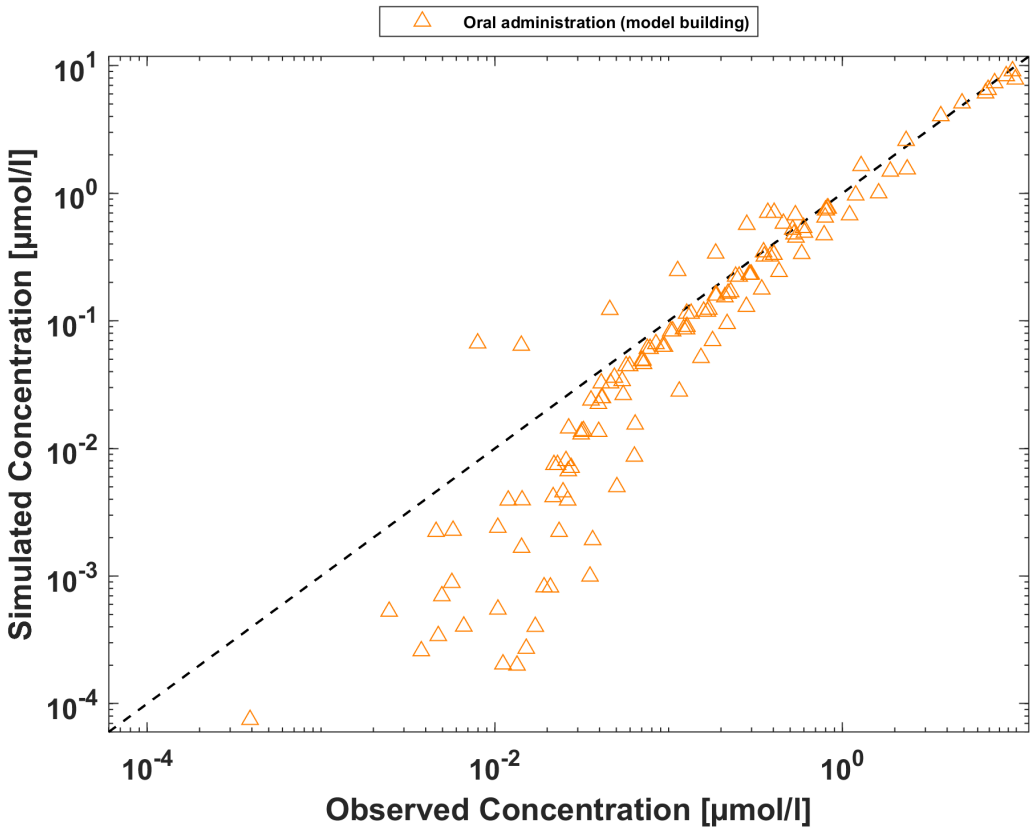


S-omeprazole concentration in plasma - mean data

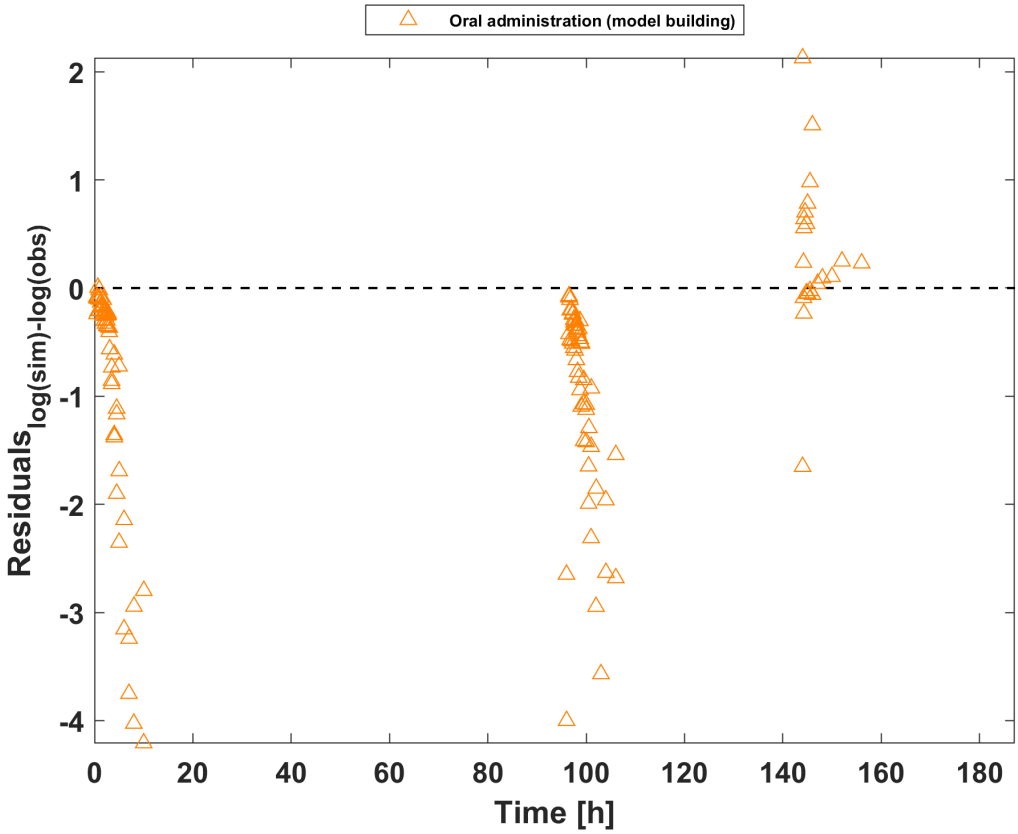


S-omeprazole concentration in plasma - mean data

GMFE = 1.503354

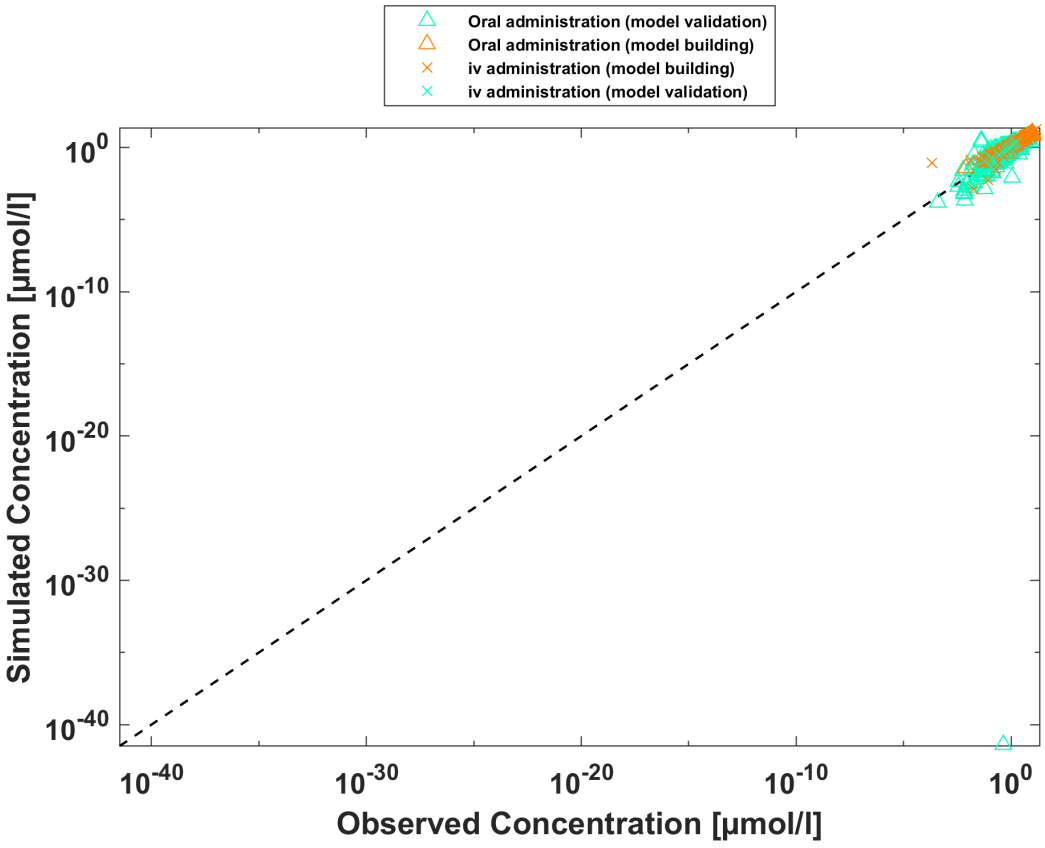


R-omeprazole concentration in plasma - mean data

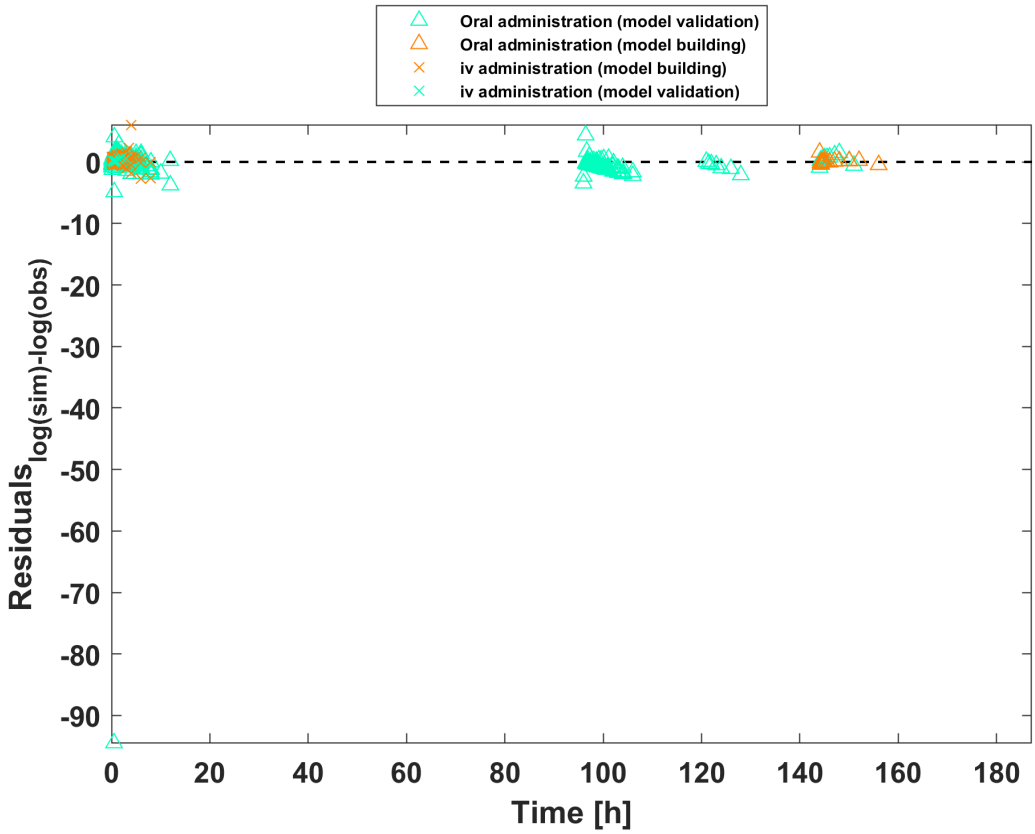


R-omeprazole concentration in plasma - mean data

GMFE = 2.395866



Omeprazole concentration in plasma - mean data



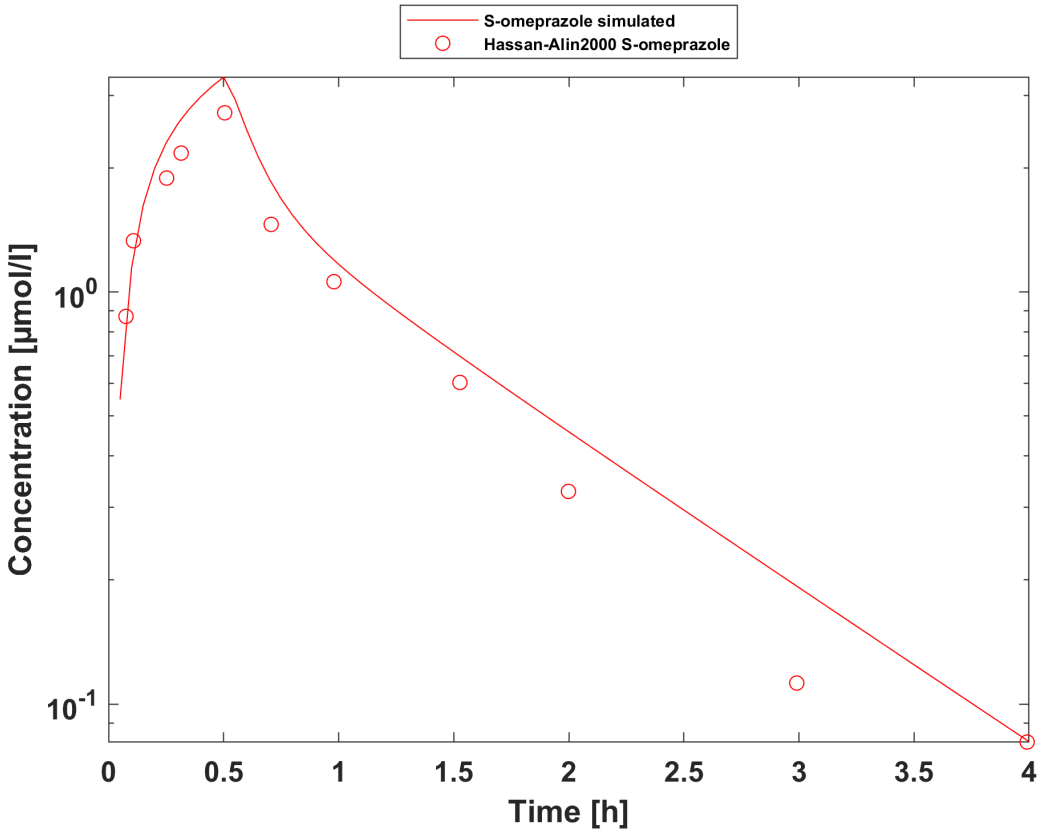
Omeprazole concentration in plasma - mean data

GMFE = 2.374414

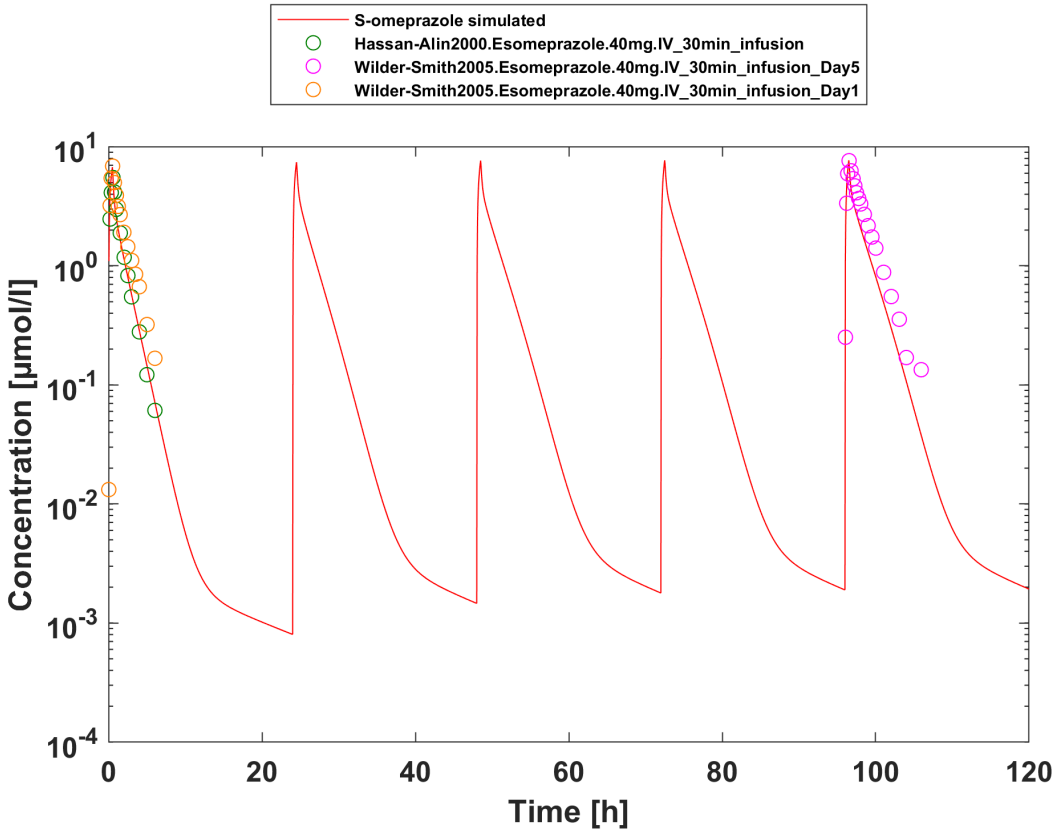
3.3 Concentration-Time Profiles

Simulated versus observed concentration-time profiles of all data listed in Section 2.2.2 are presented below.

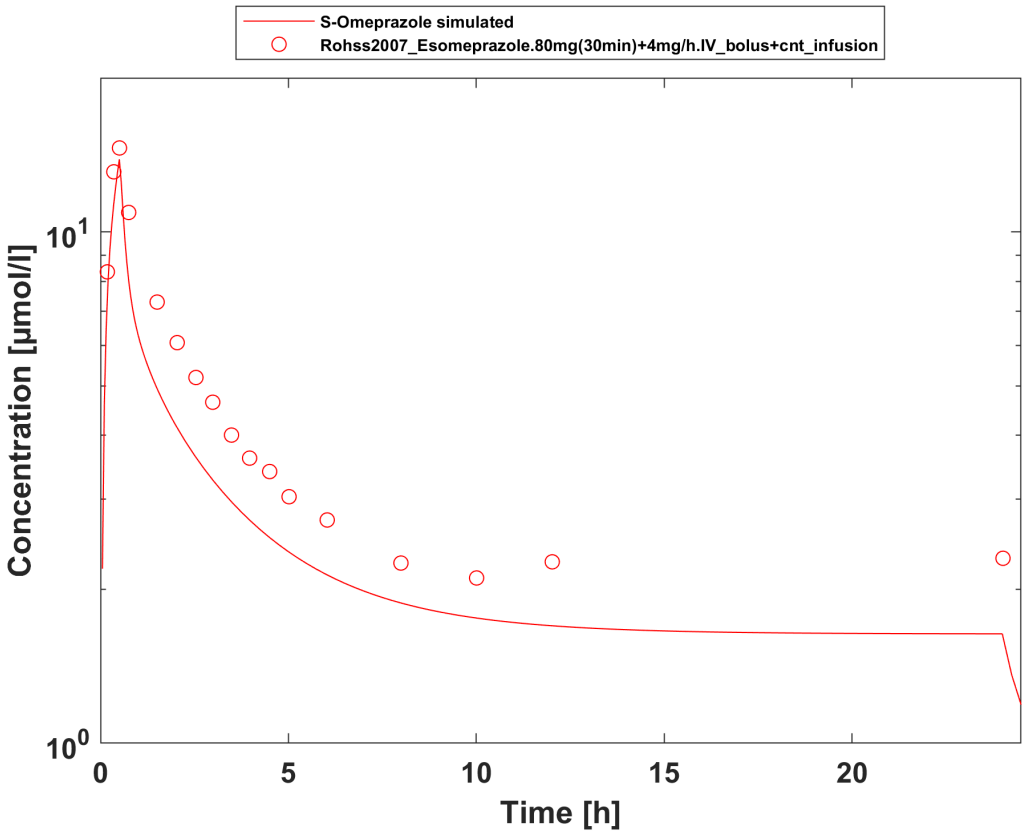
3.3.1 Model Building



20 mg S-omeprazole iv infusion



40 mg S-omeprazole iv infusion



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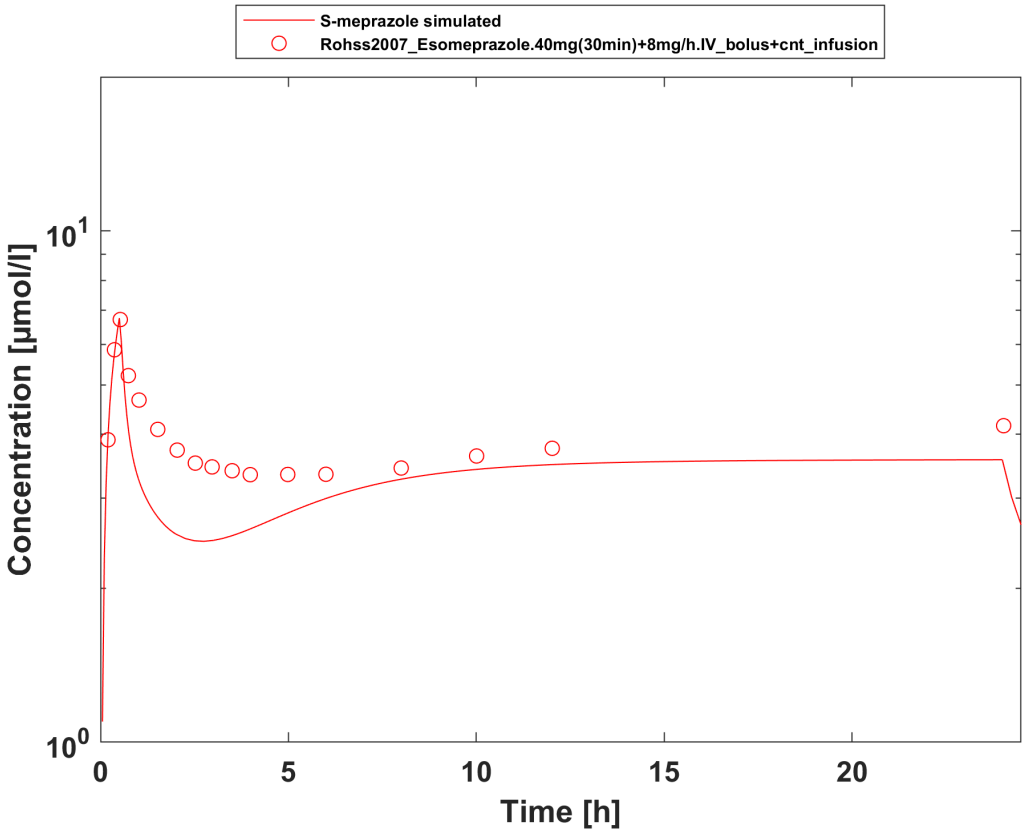

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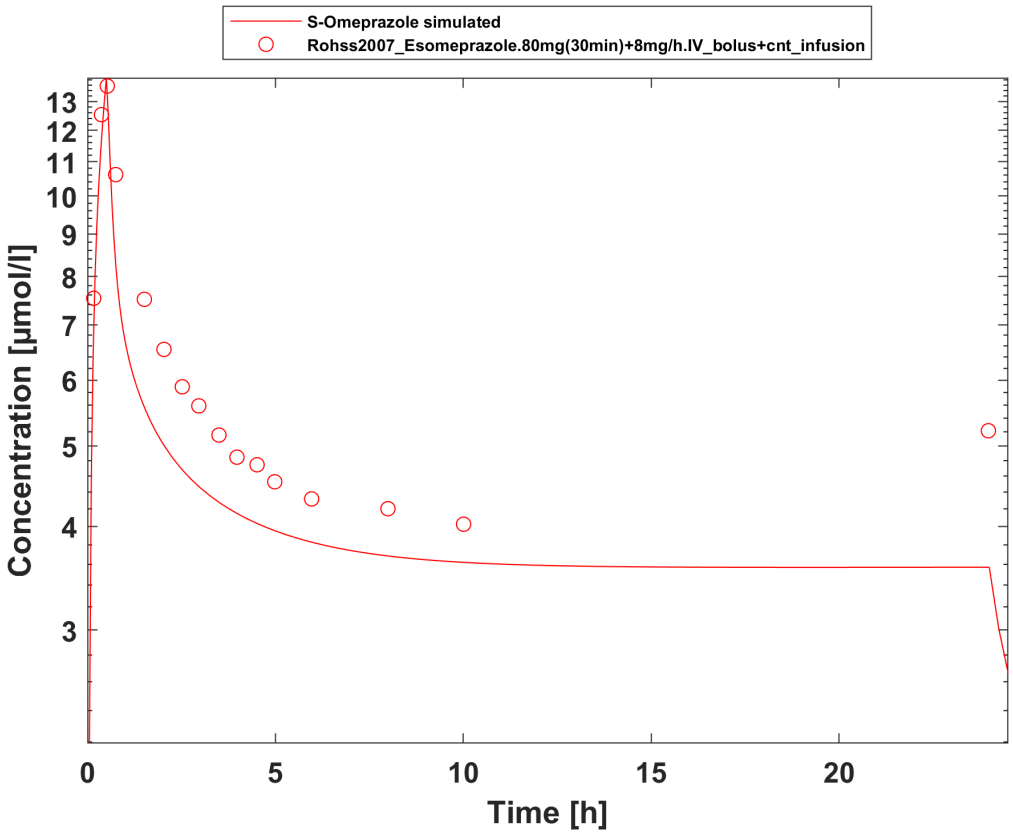

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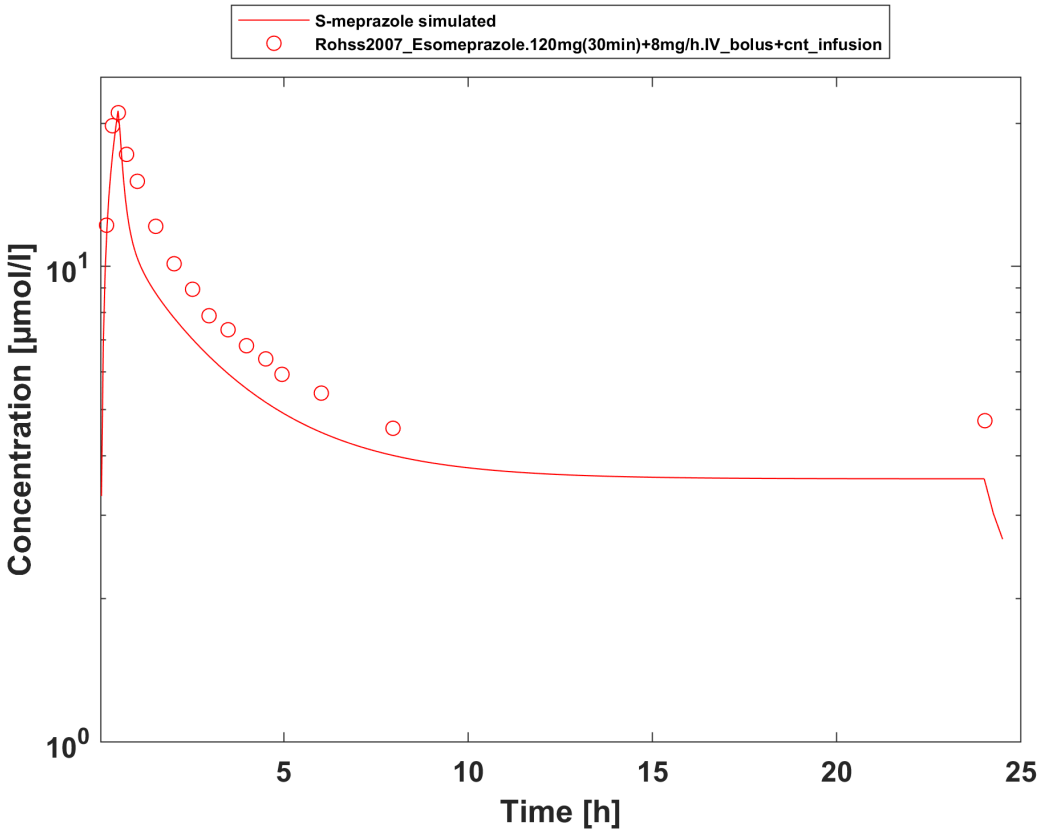

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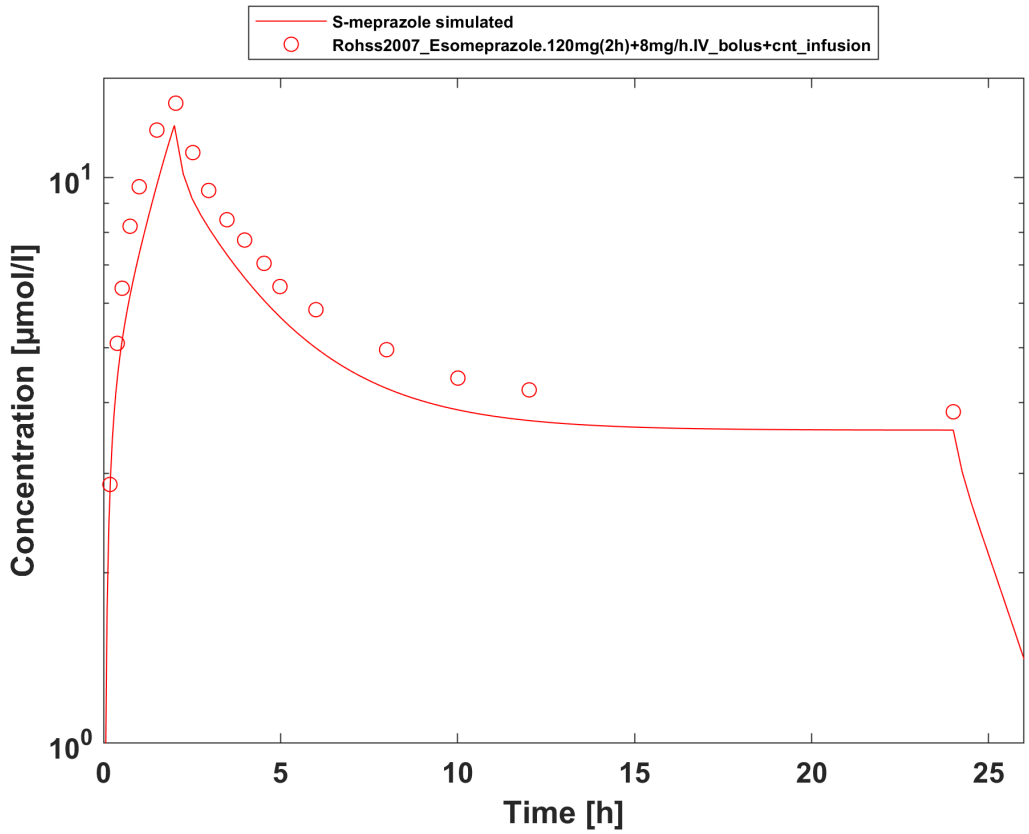

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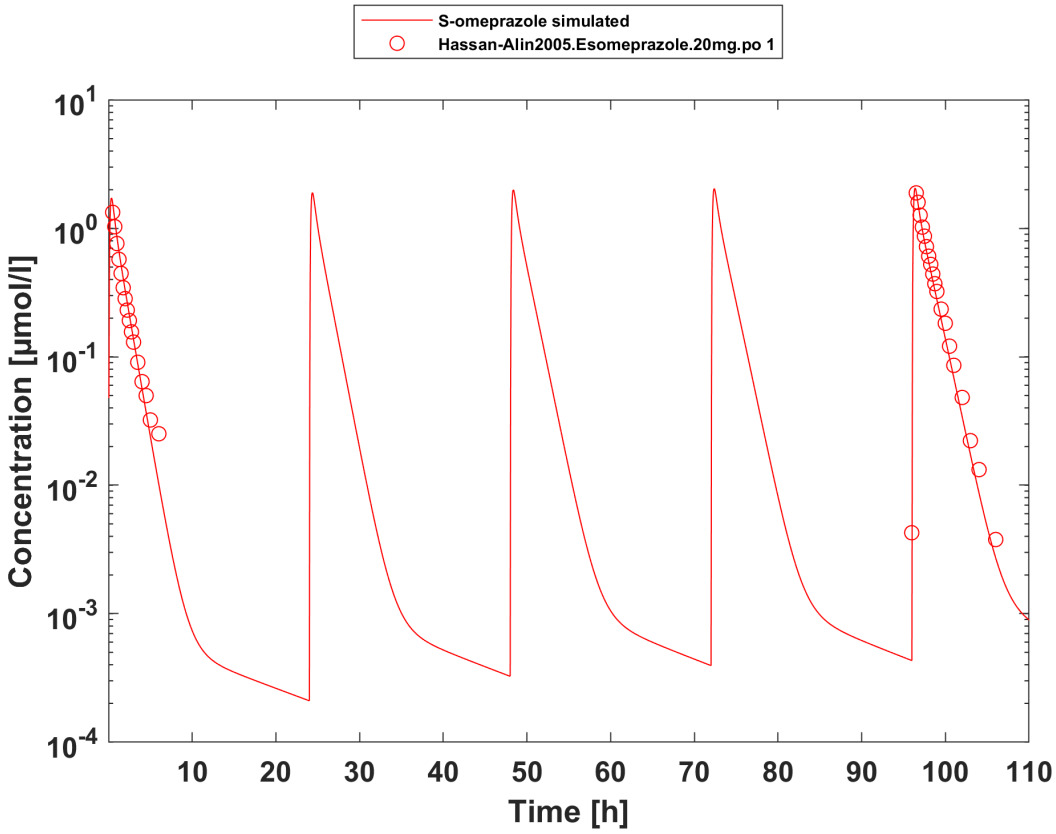

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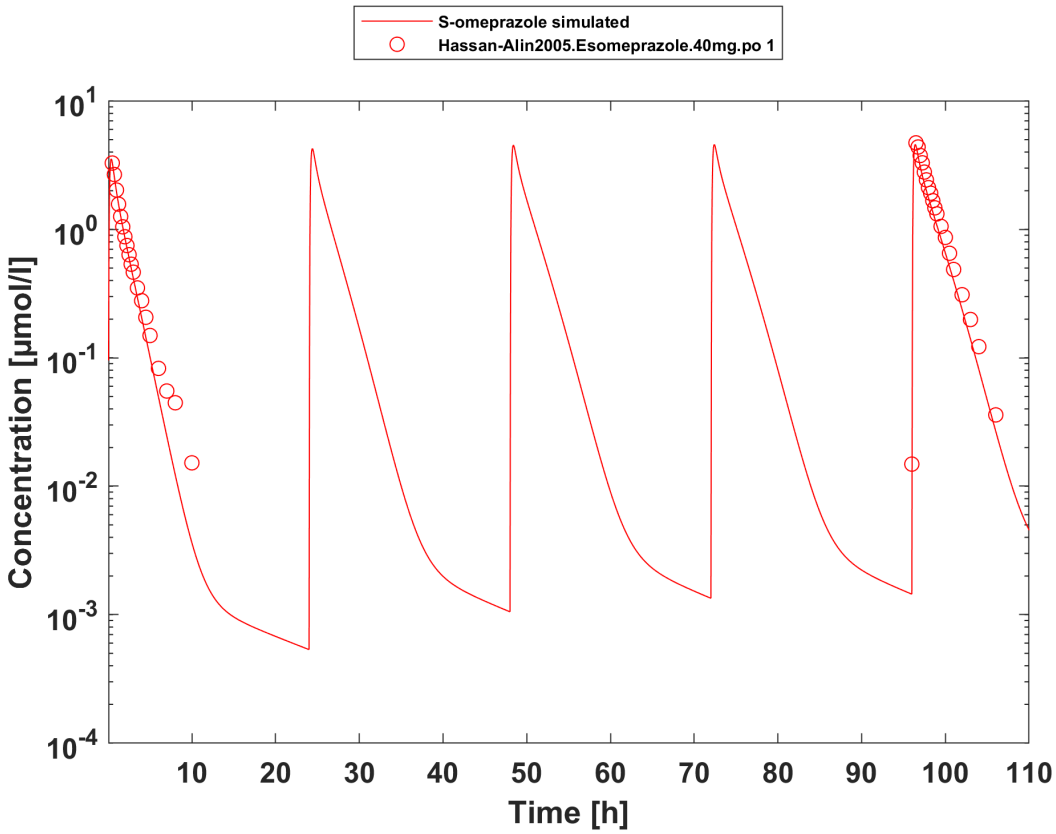

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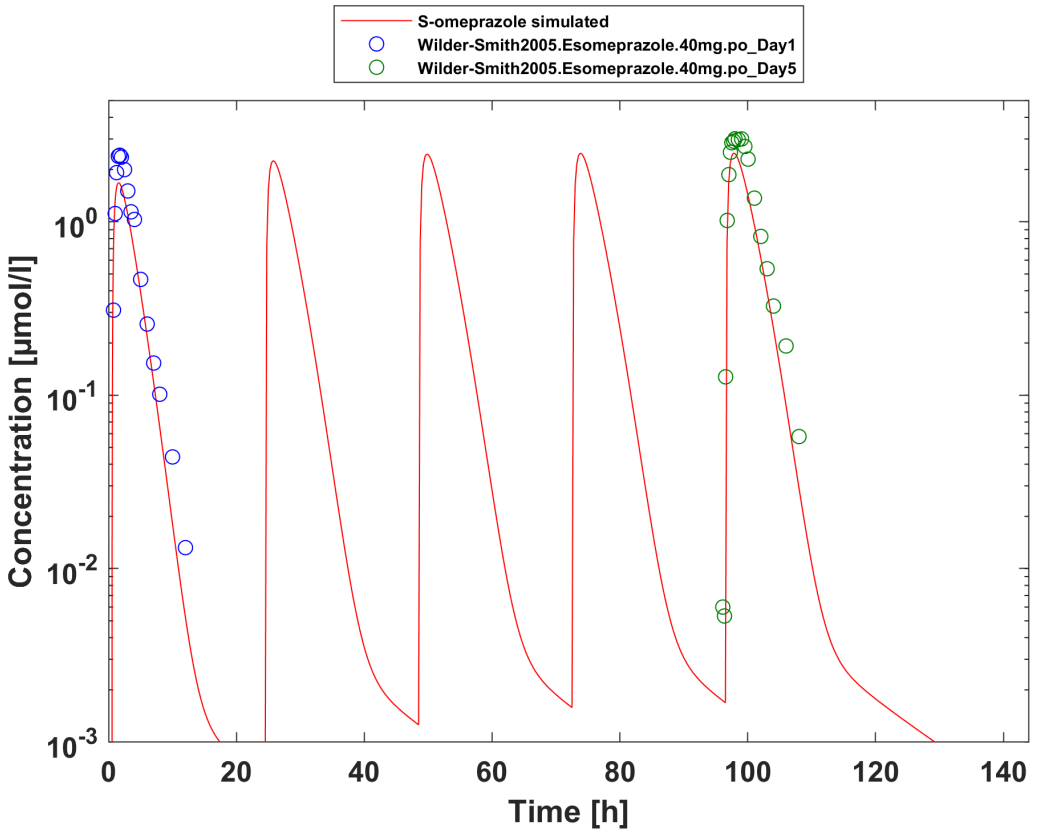

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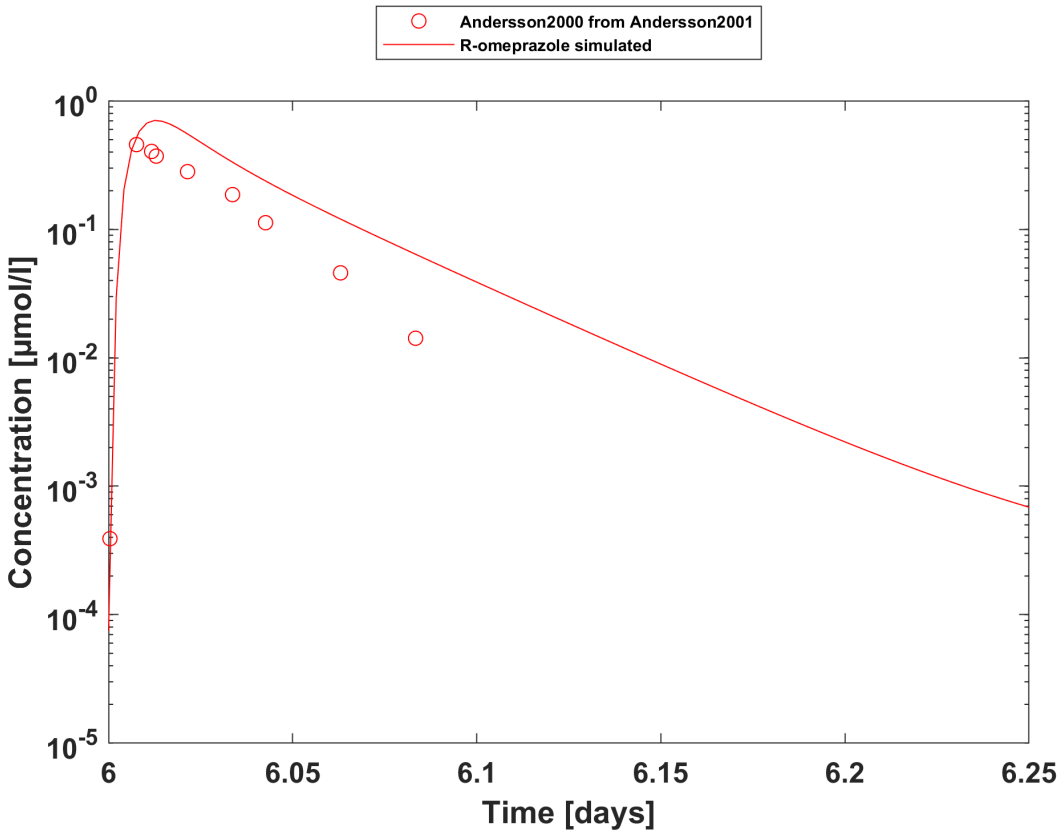
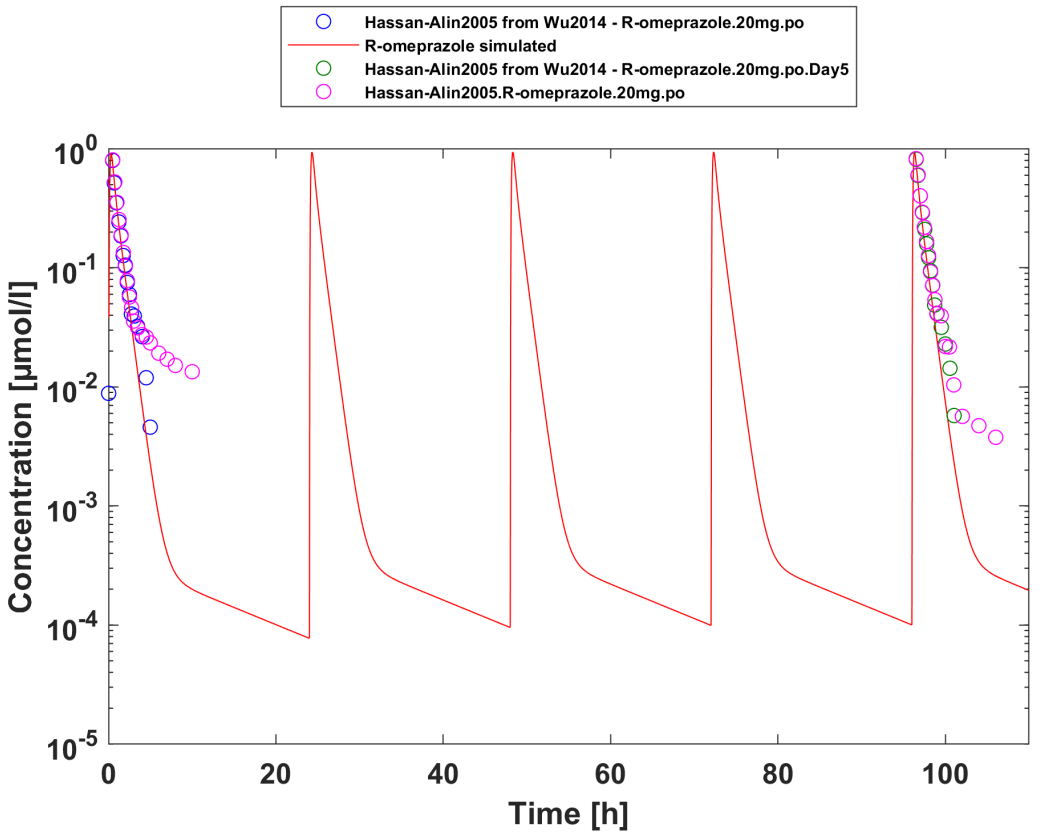


15 mg R-omeprazole oral solution day 6



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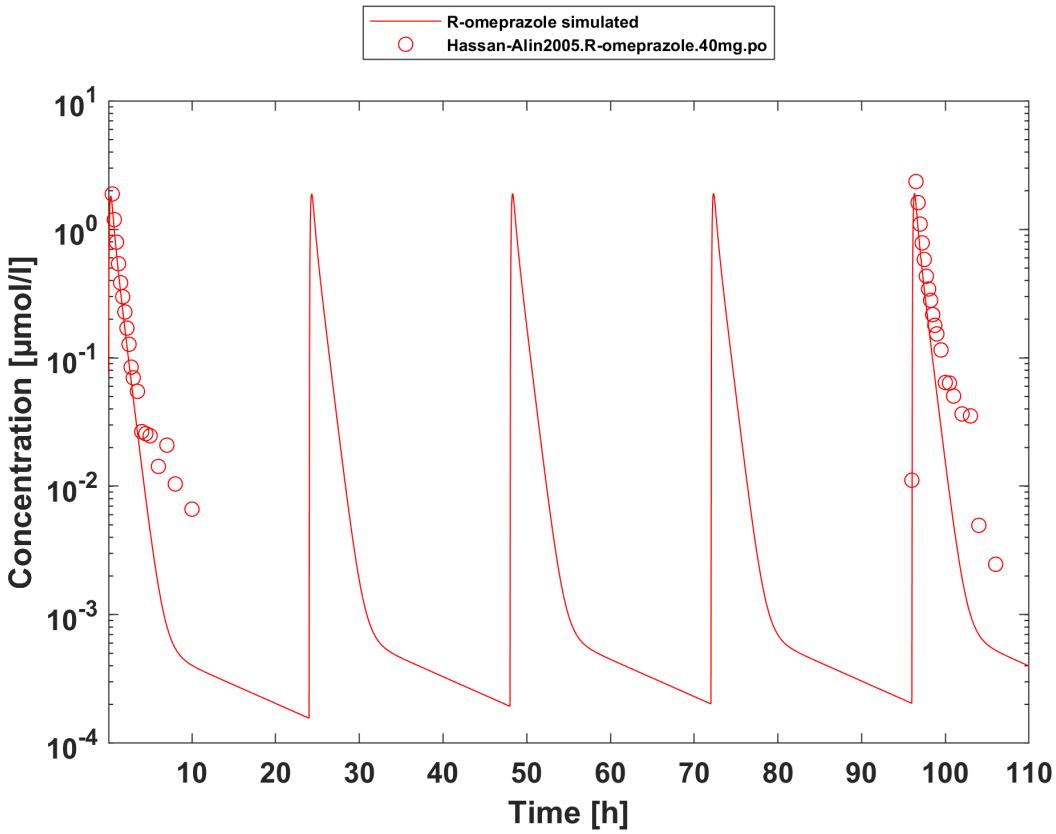

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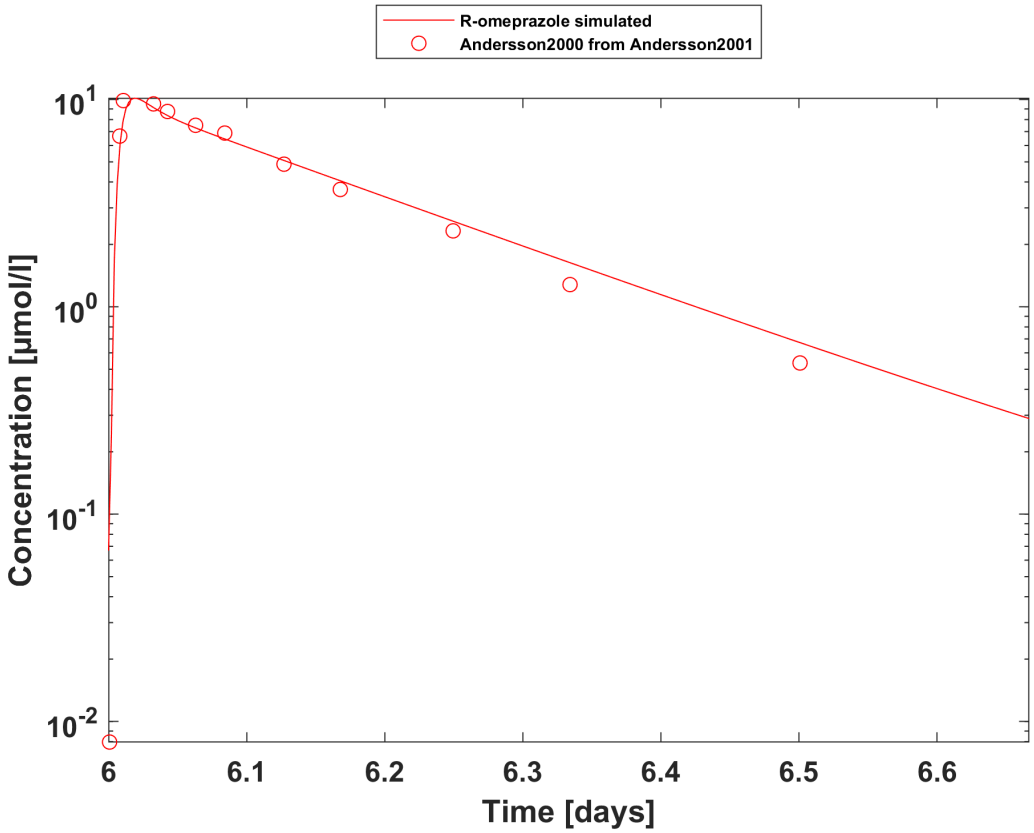

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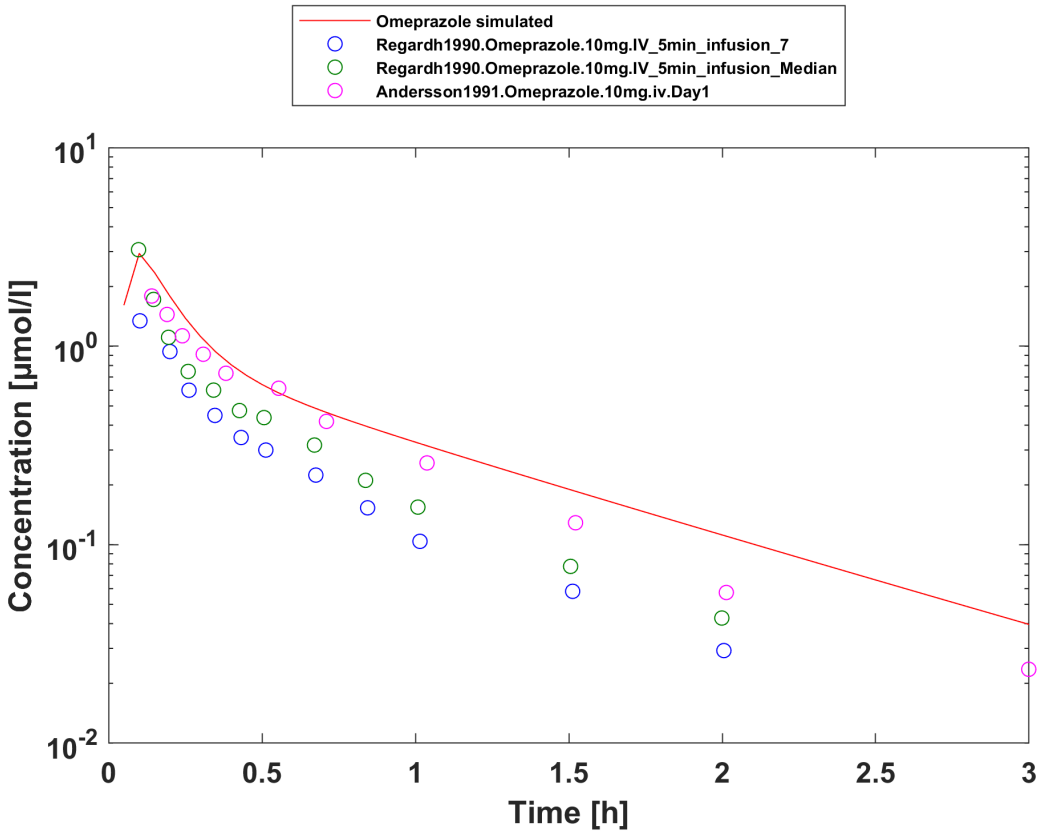
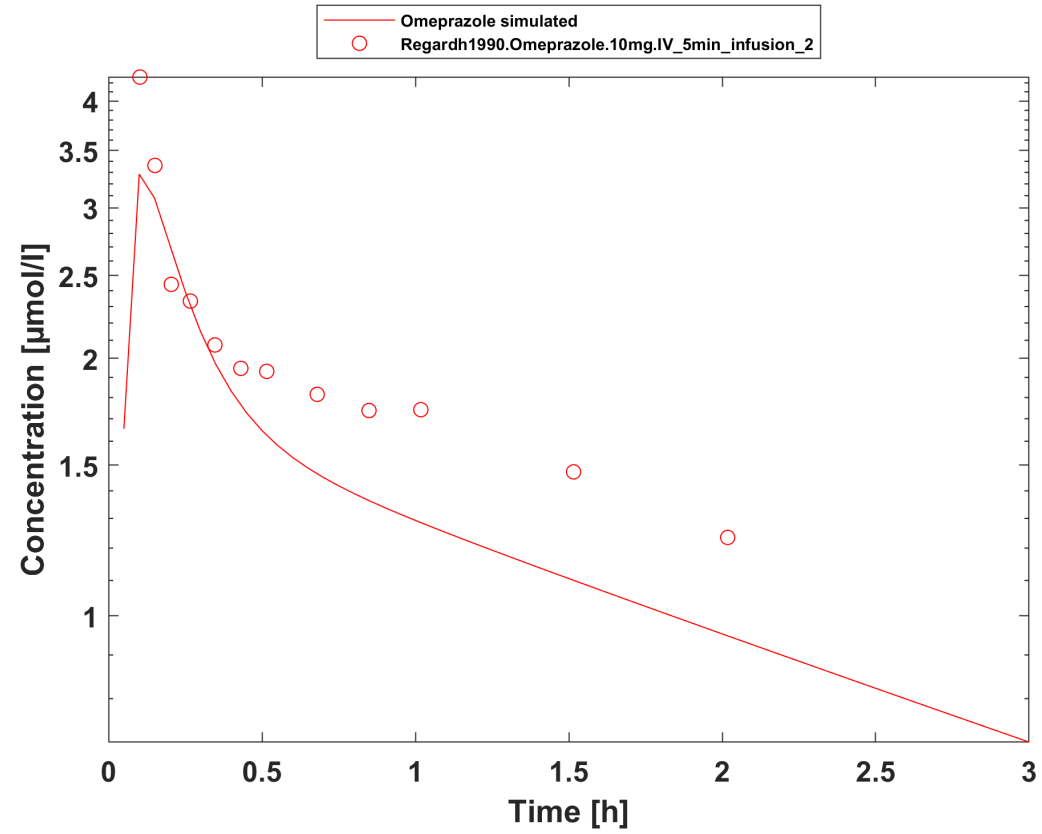


10 mg omeprazole iv



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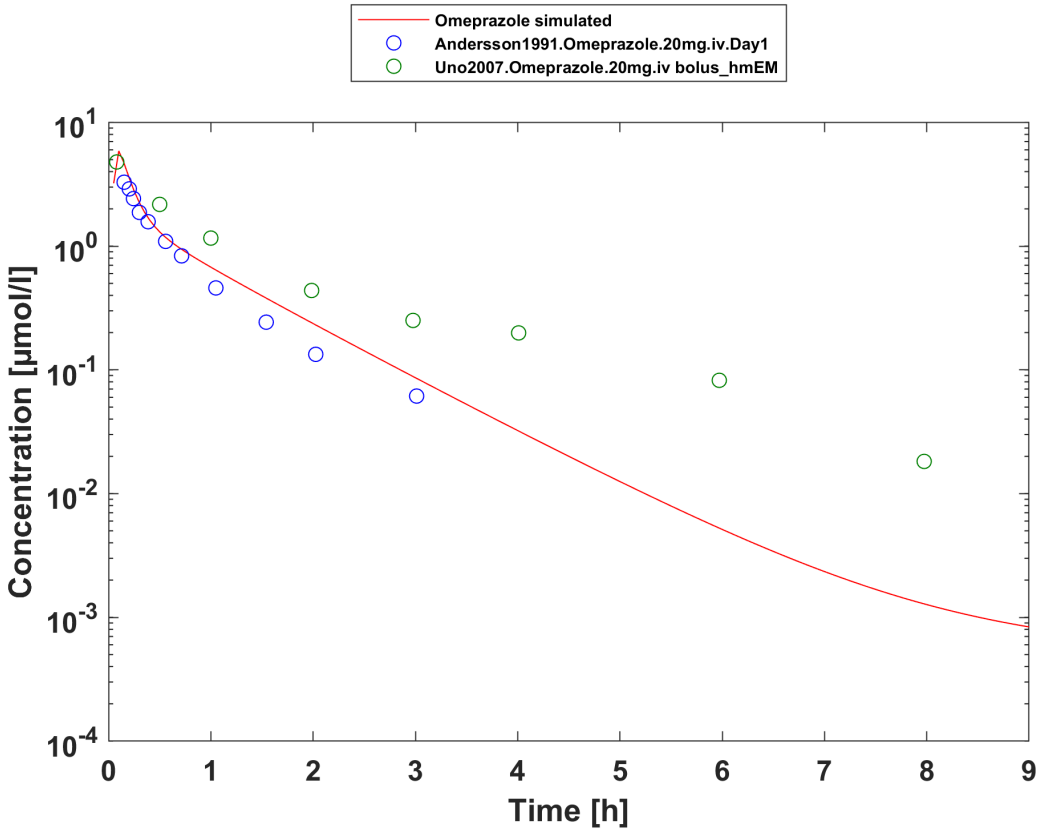

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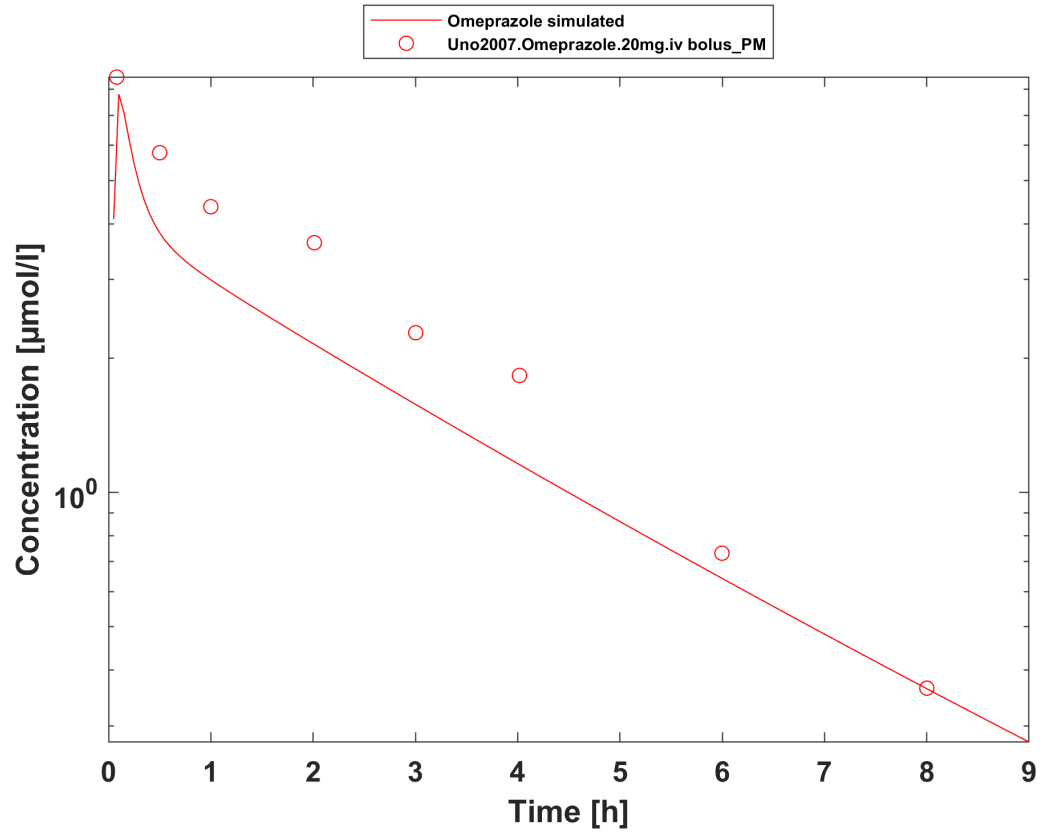

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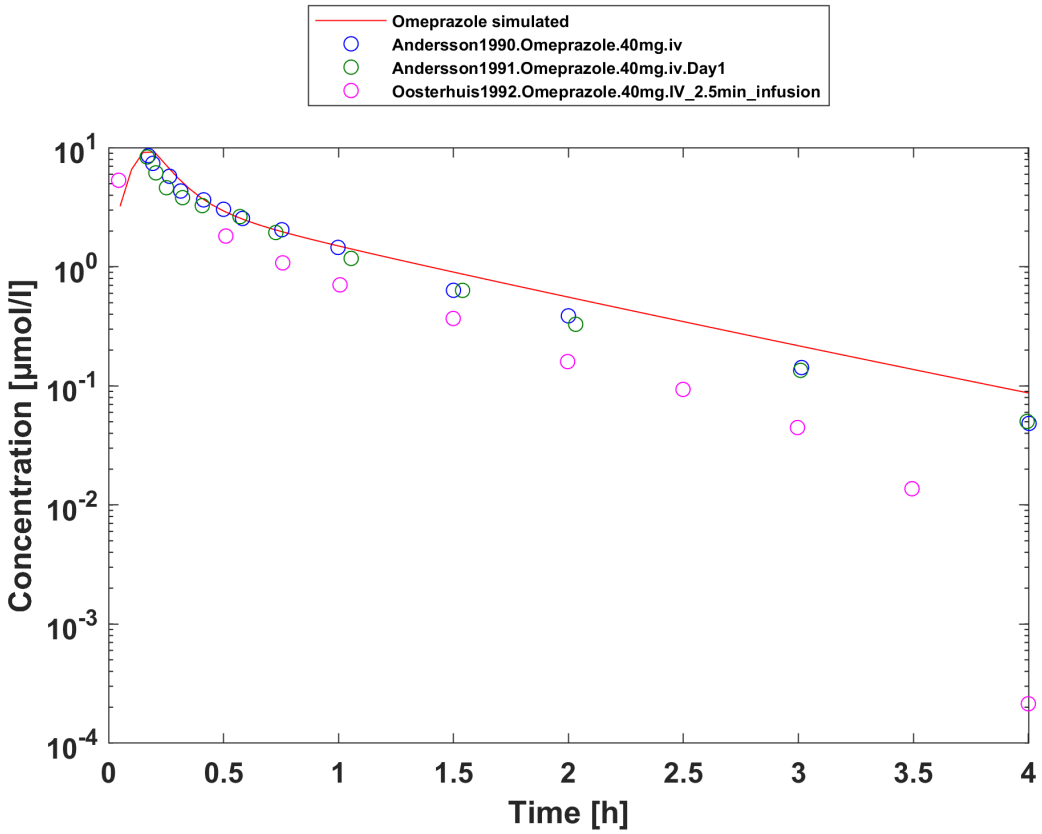

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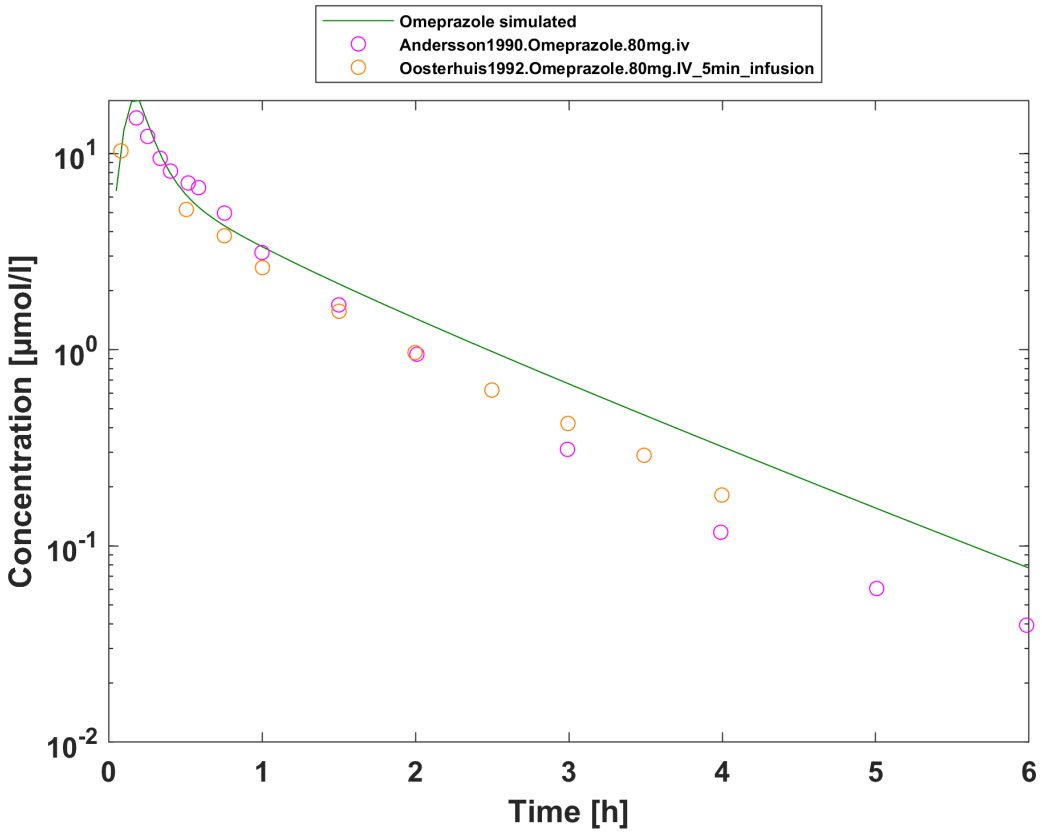

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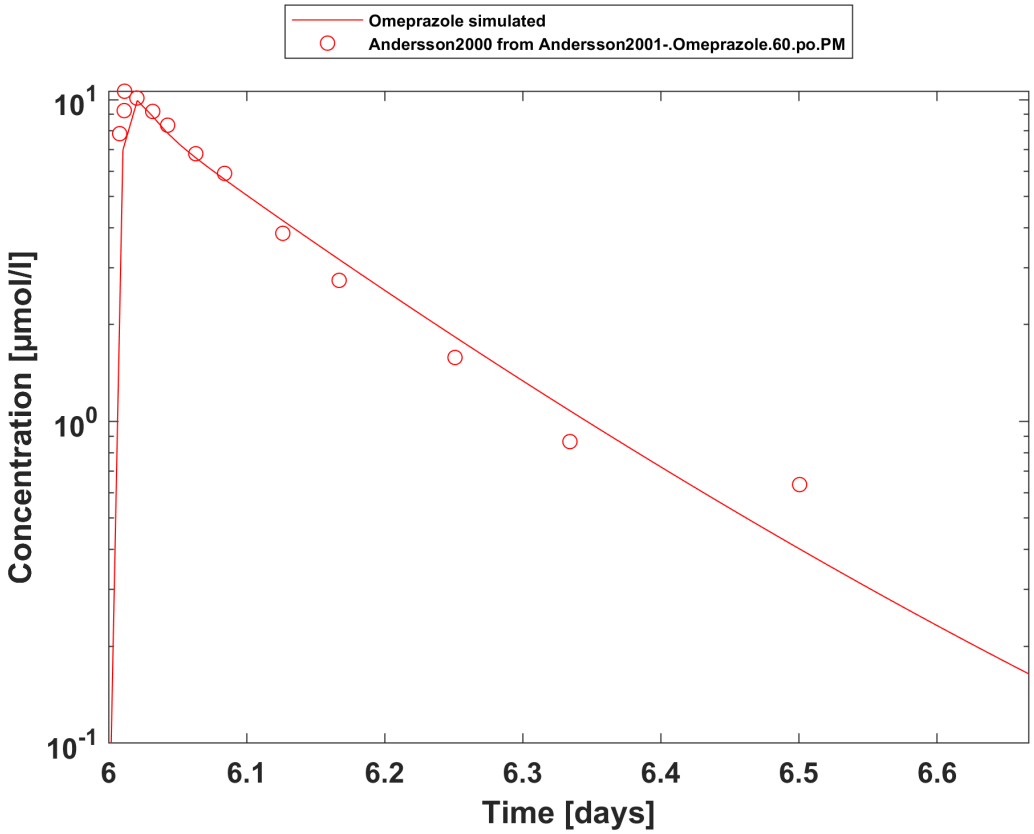
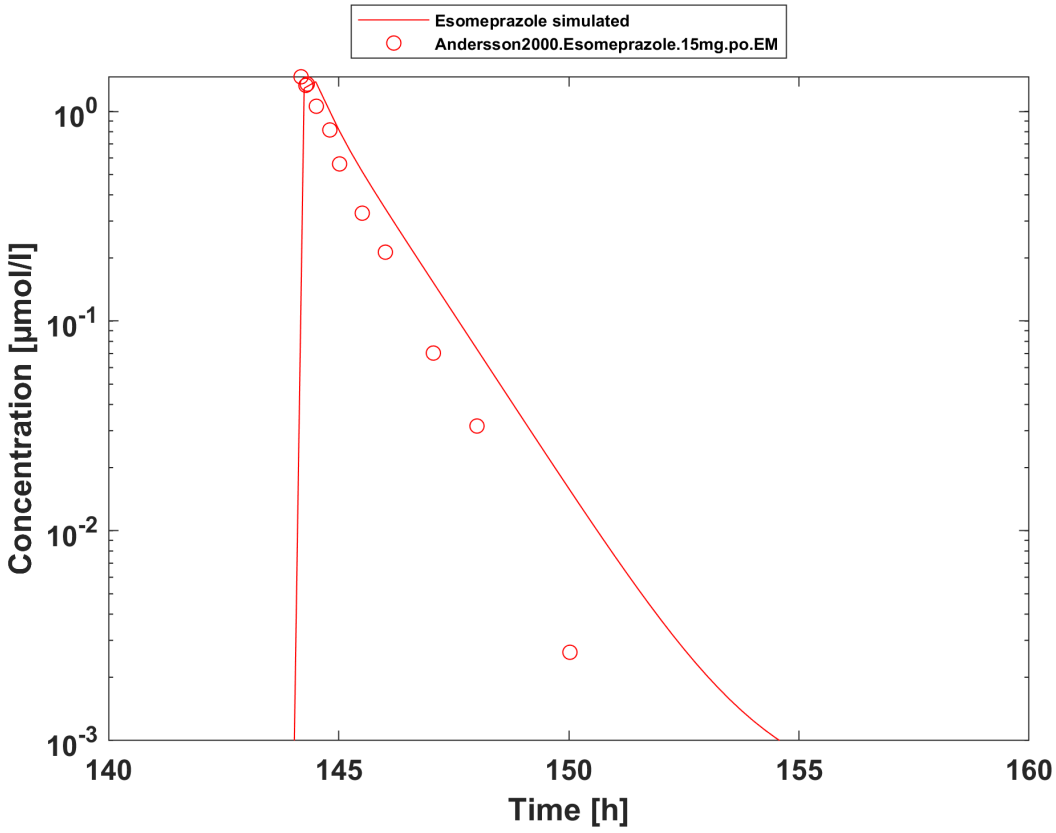


60 mg omeprazole oral solution PM day 6

3.3.2 Model Verification



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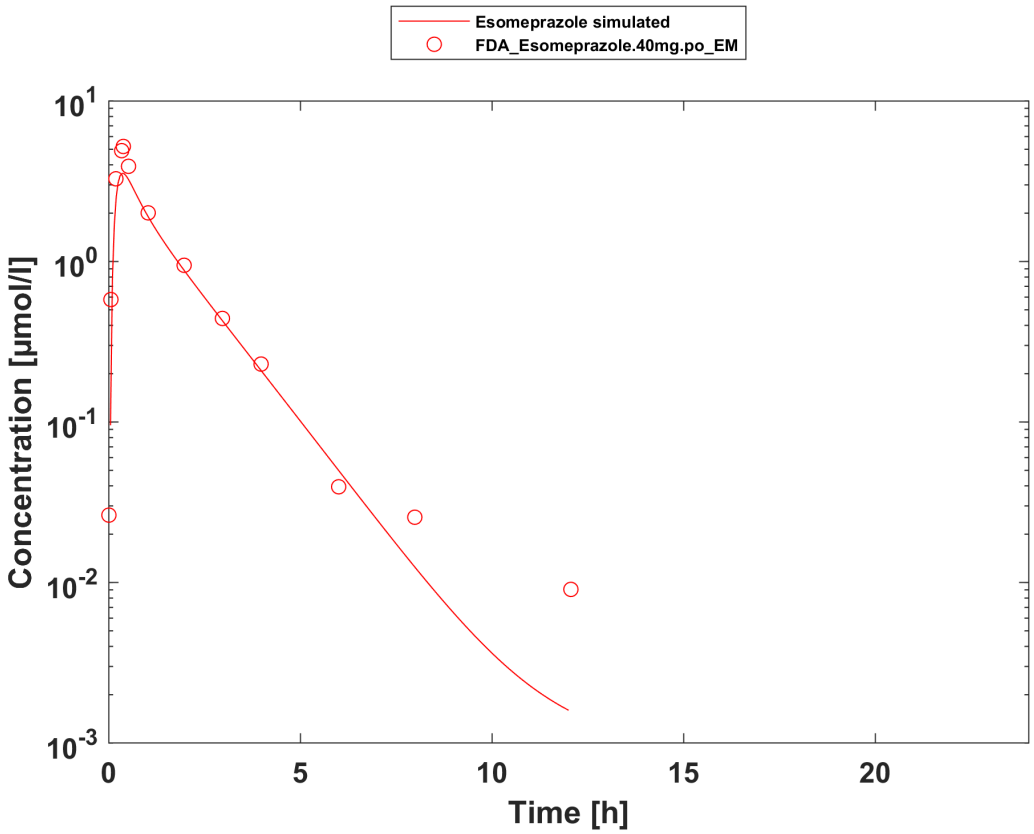

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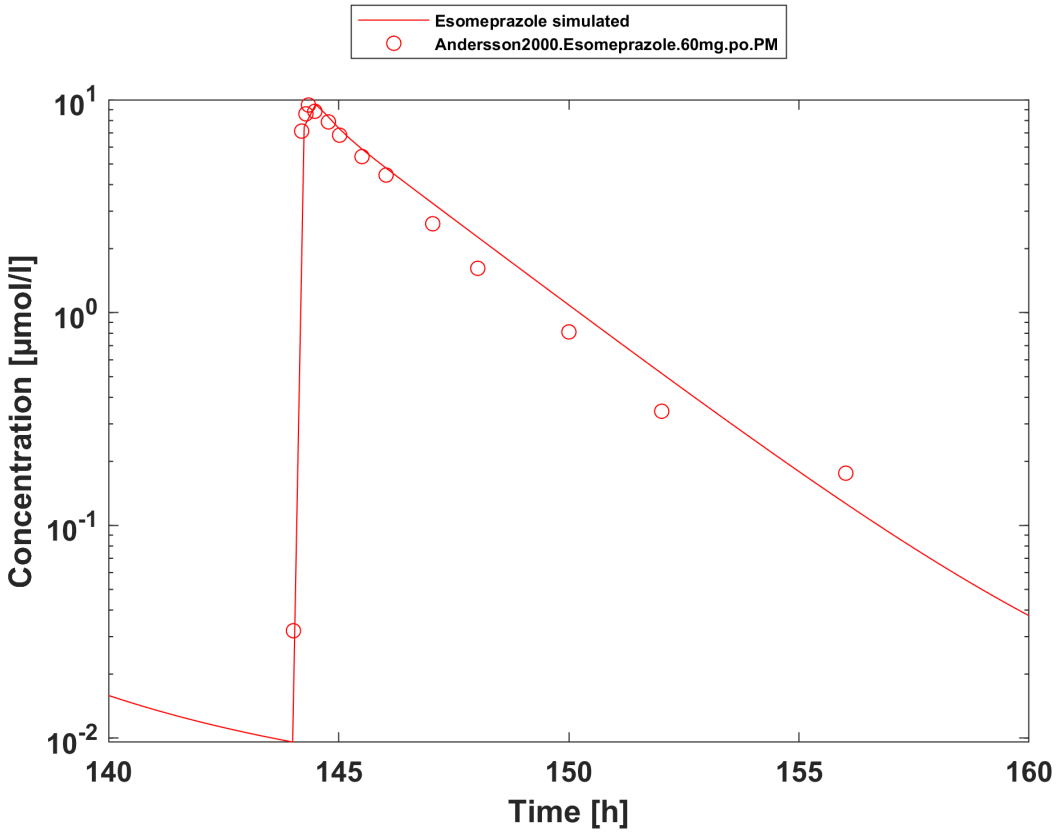

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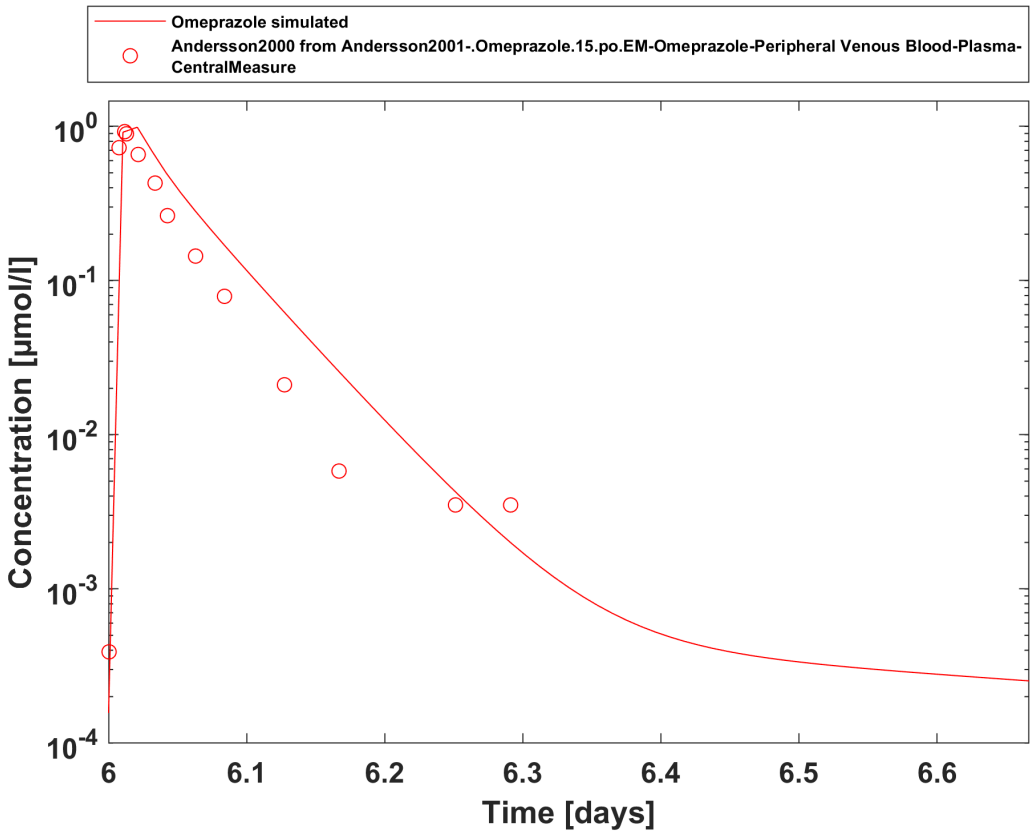
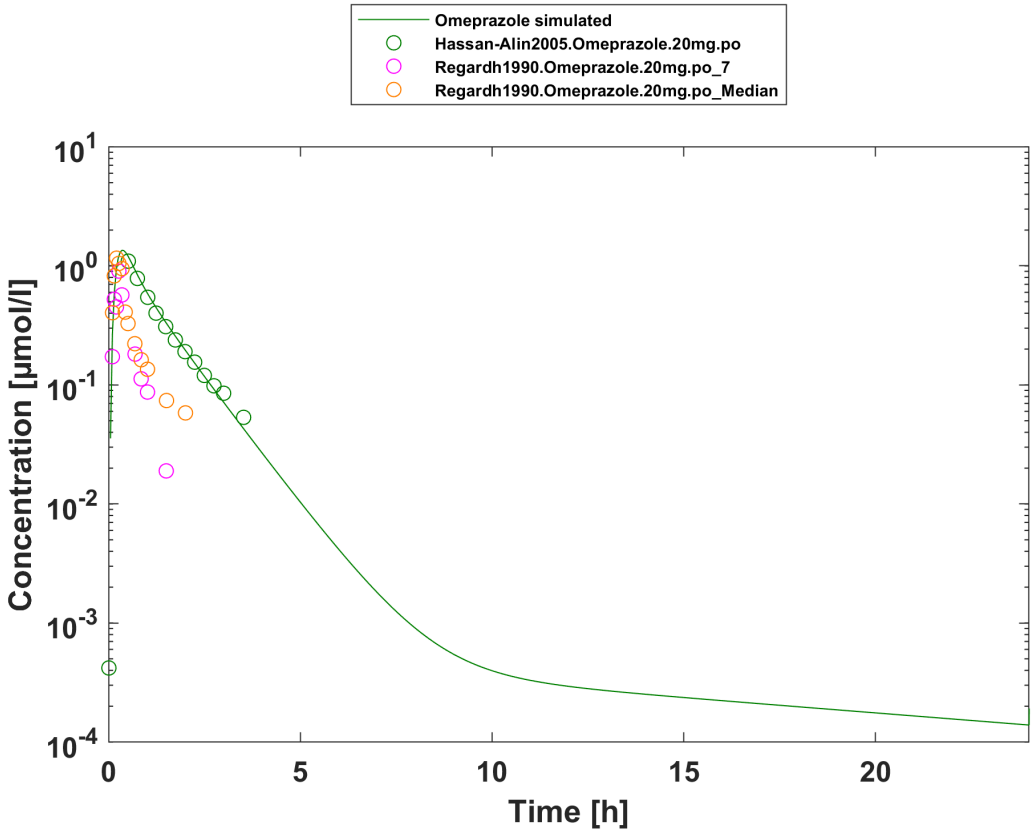
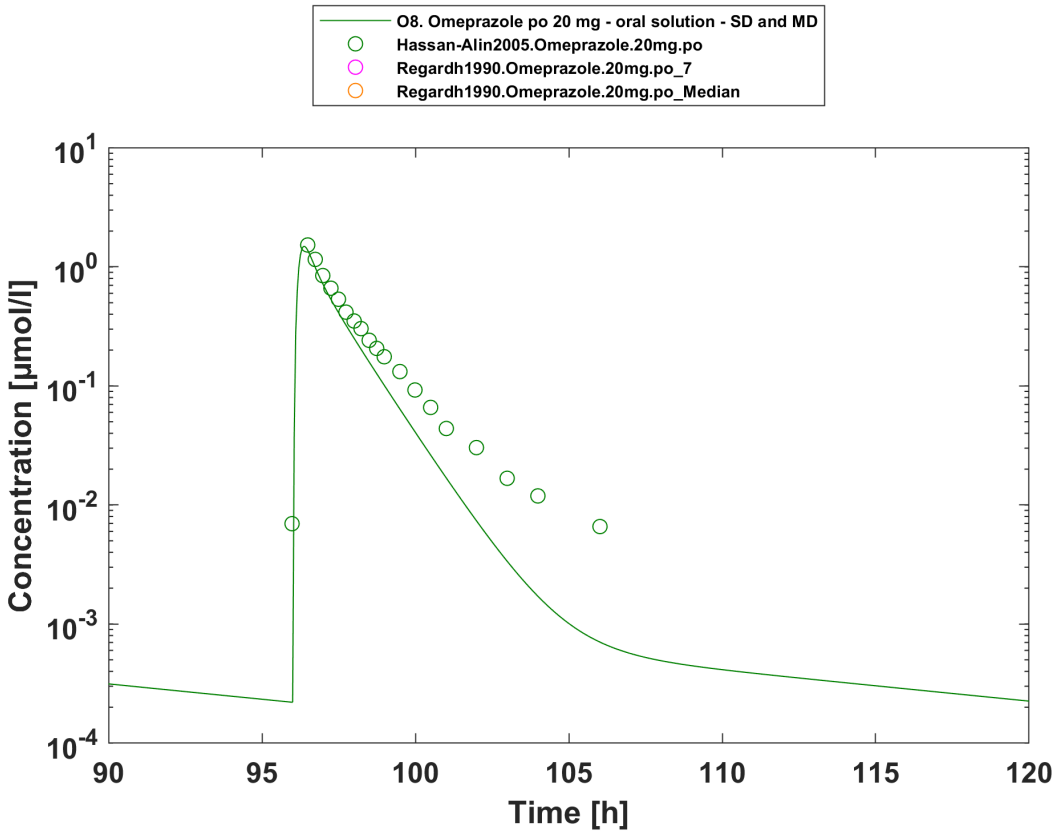


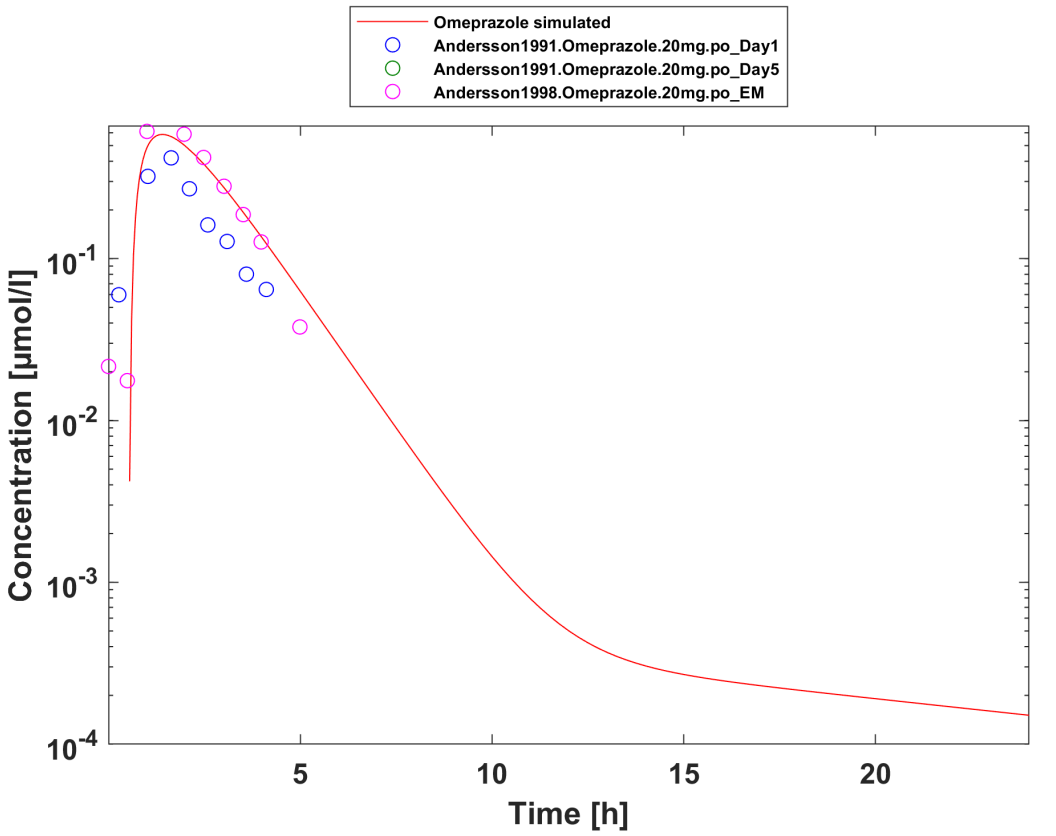
15 mg omeprazole oral solution day 6



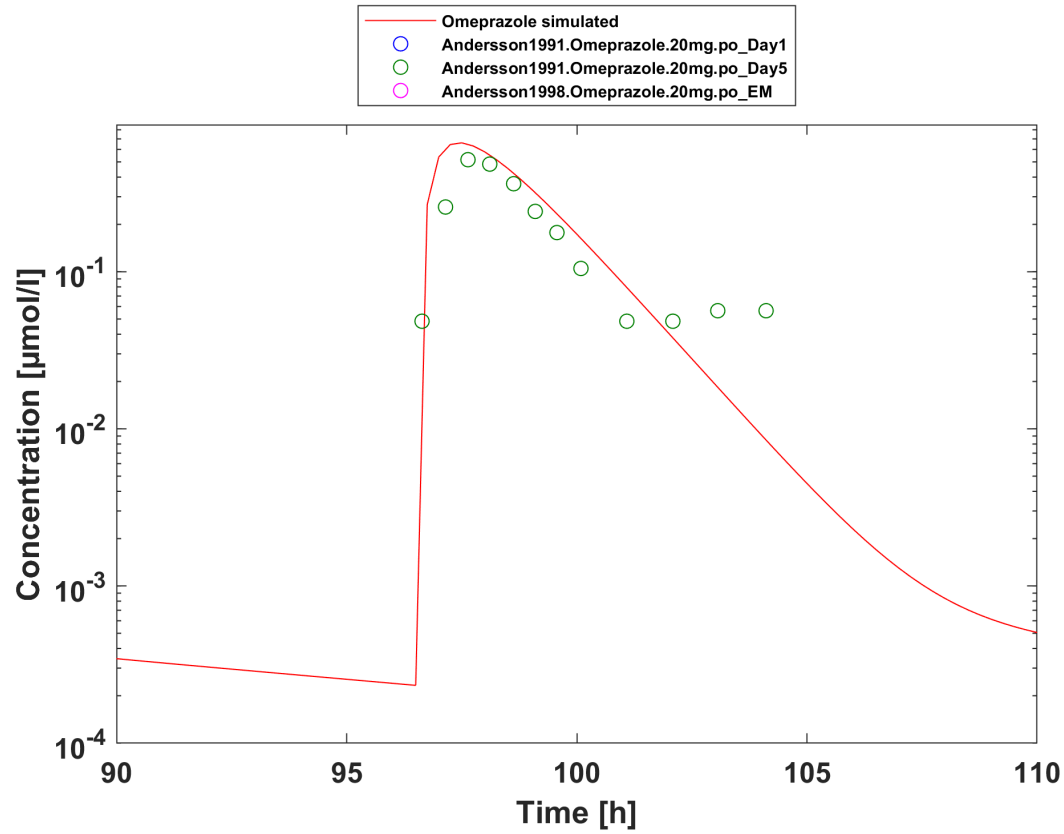
20 mg po solution - day 1



20 mg omeprazole oral solution - day 4



20 mg omeprazole oral capsule - day 1



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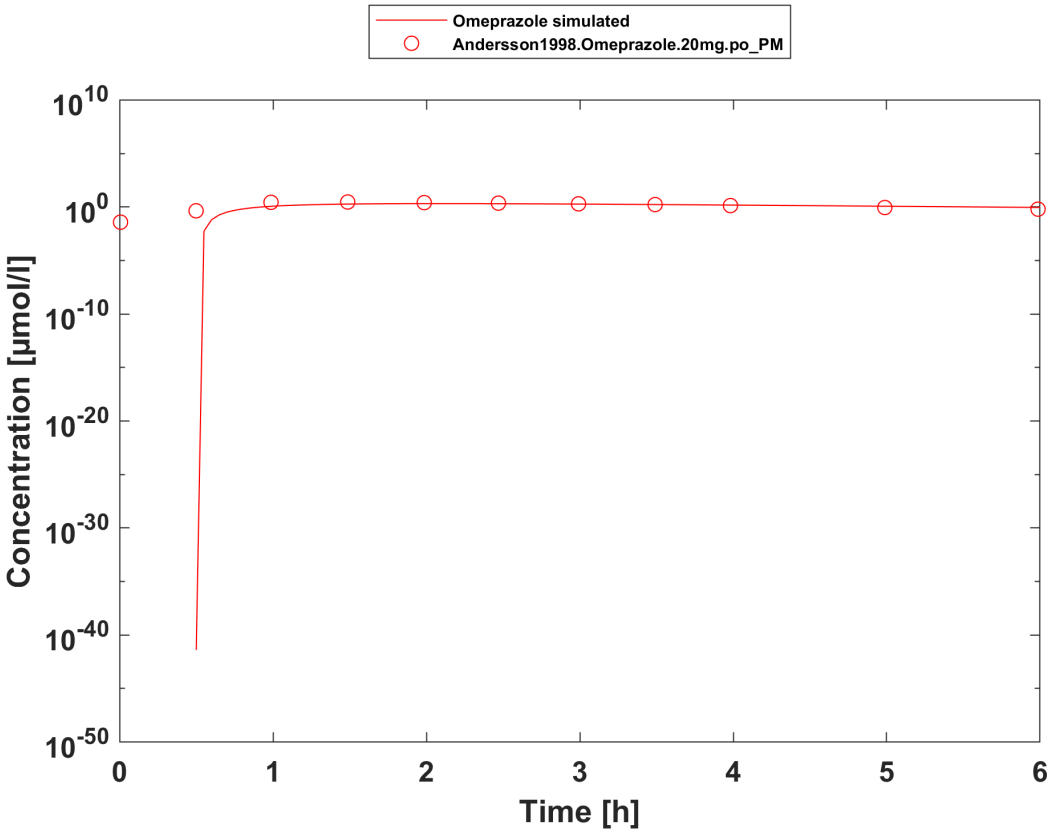
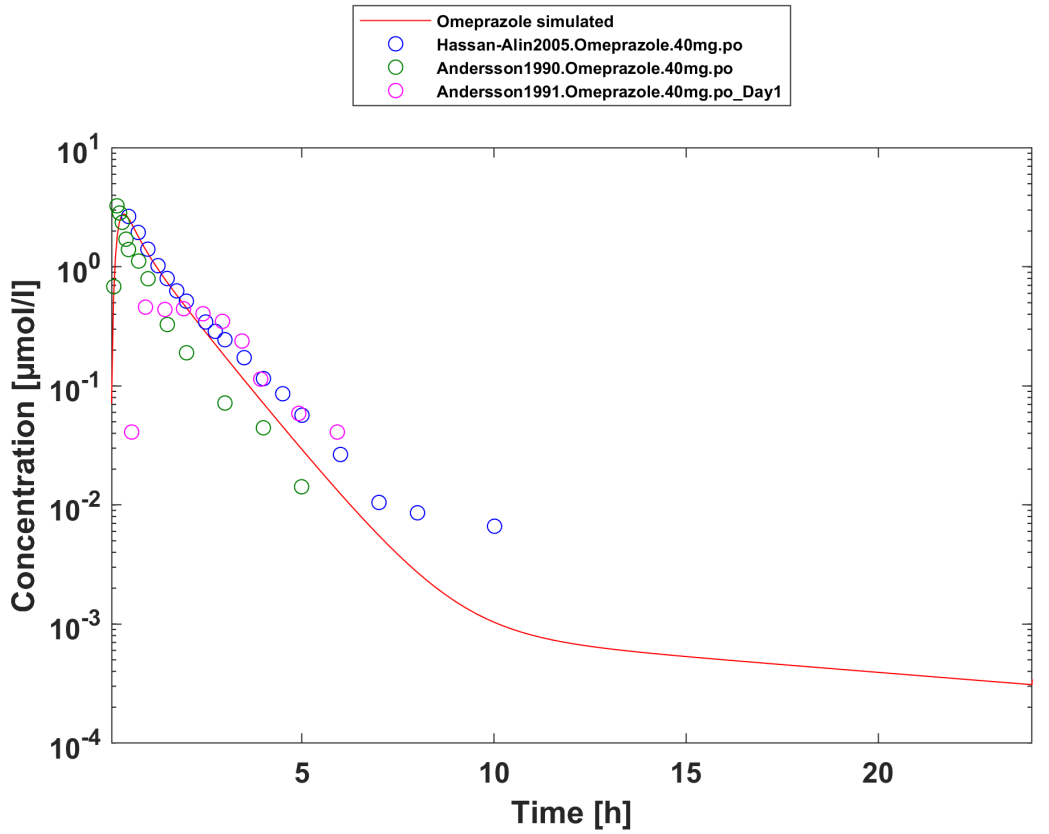


20 mg omeprazole oral capsule PM



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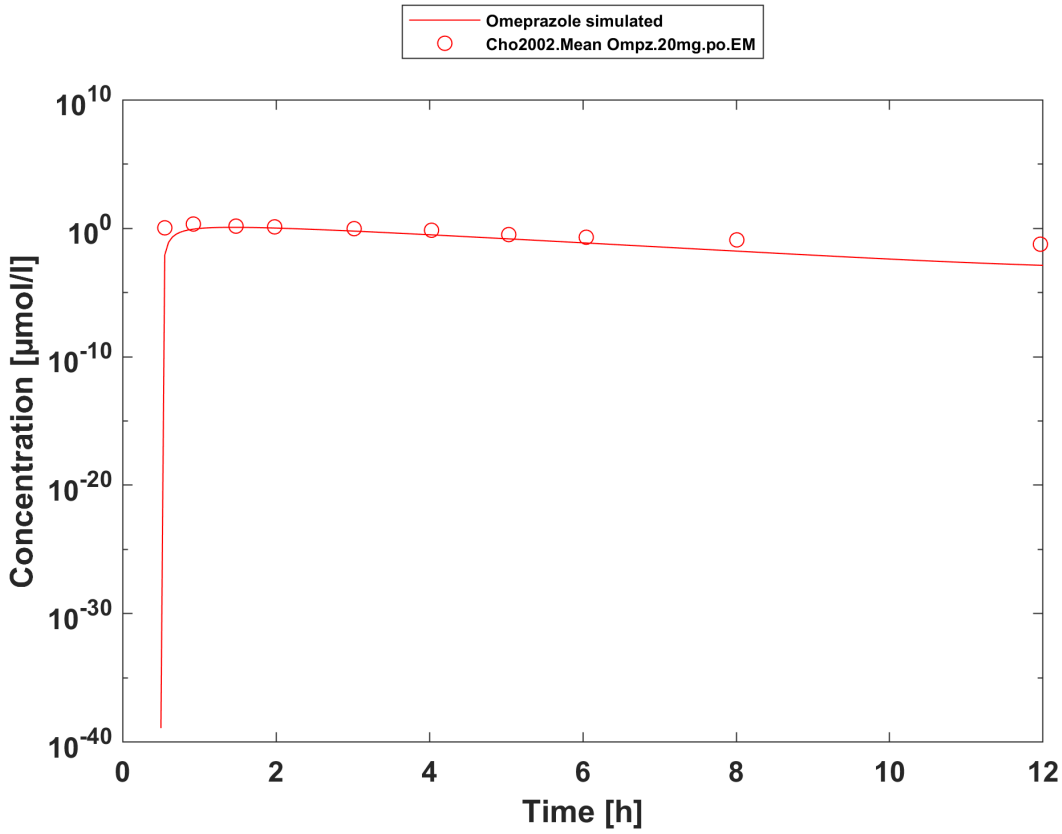

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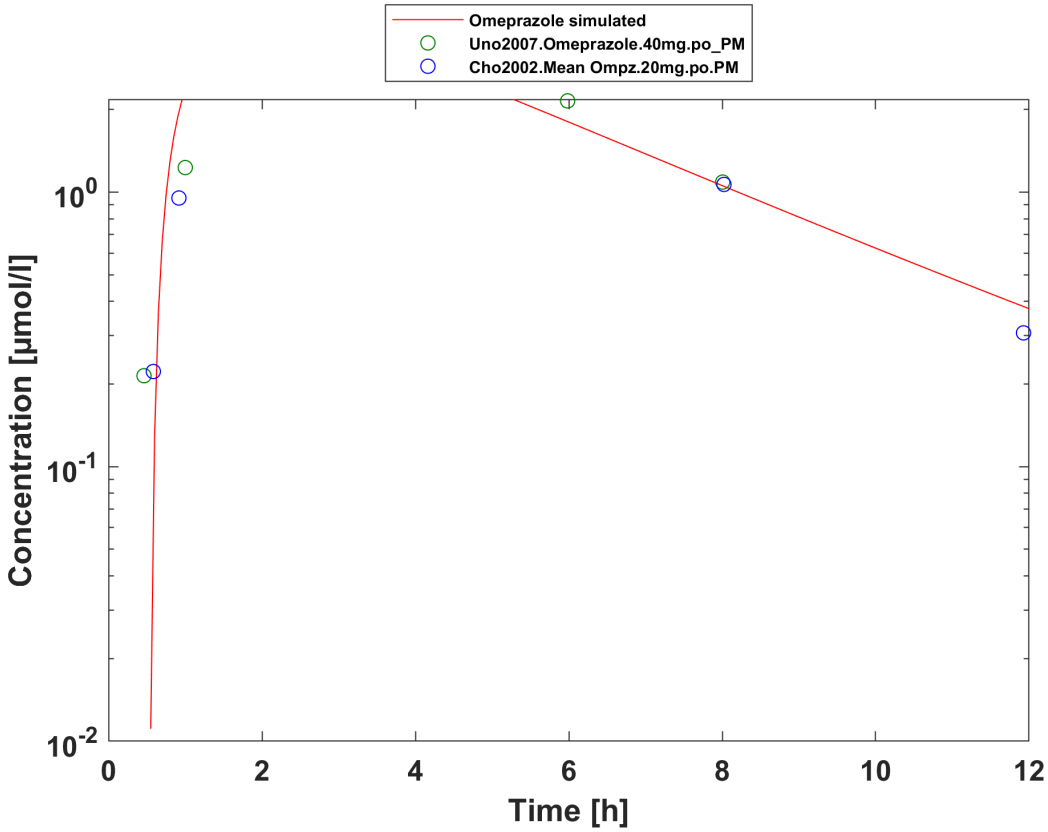

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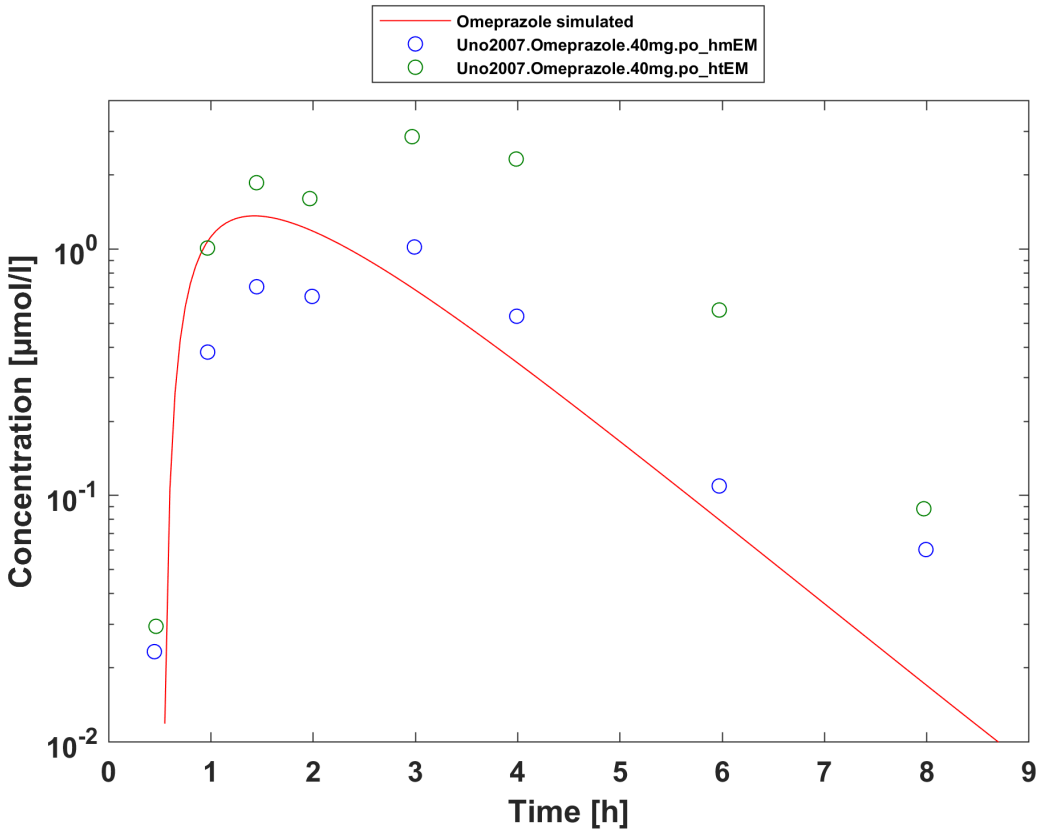
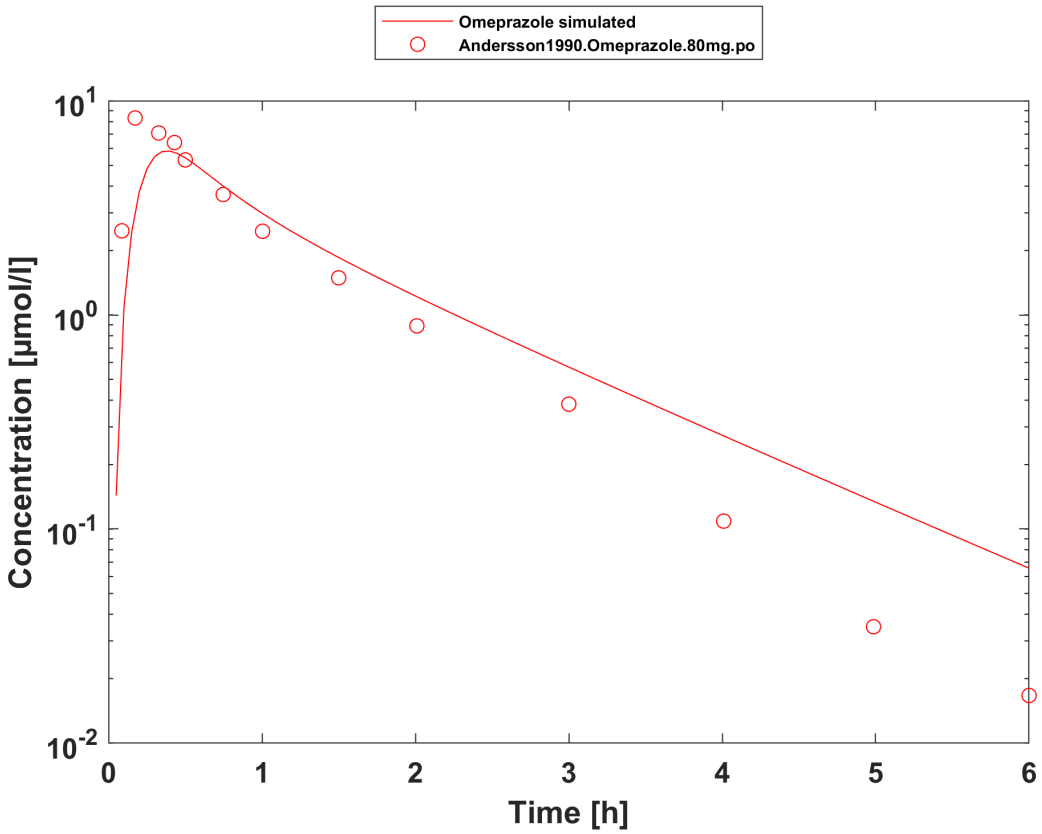
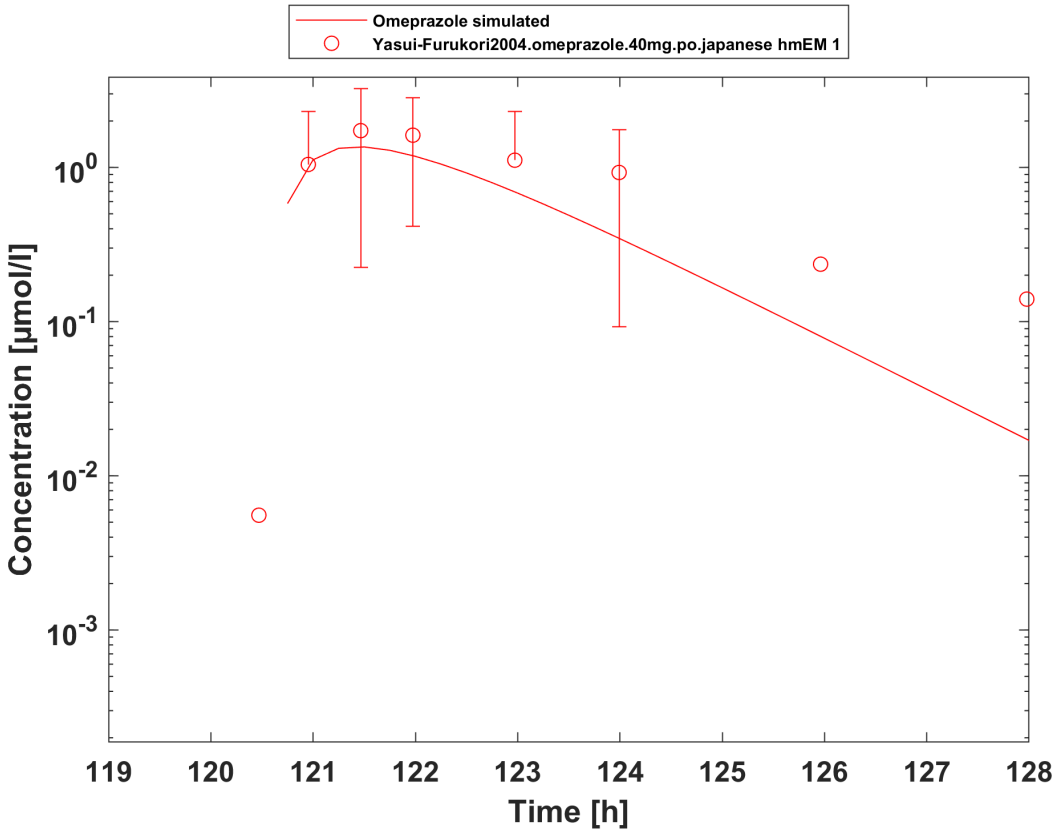


40 mg omeprazole oral capsule Japanese



80 mg omeprazole oral solution



40 mg omeprazole oral capsule

4 Conclusion

The developed PBPK model of omeprazole describes the PK data of S-, R-, and racemat omeprazole in CYP2C19 extensive and poor metabolizers after administrations of single as well as multiple p.o. doses very well.

The assumption for the same distribution model and lipophilicity for R-/S-omeprazole is reasonable, as no i.v. data were available for R-omeprazole.

CYP2C19 expression in gut was reduced according to Olivares-Morales 2016 to better describe R-omeprazole. As CYP2C19 CL and expression are obviously inter-dependent, caution should be used when extrapolating such findings to other CYP2C19 substrates. The impact of the reduced expression of CYP2C19 in gut was therefore investigated for its impact on omeprazole levels.

Comparison of population simulation results with observed data show that the observations were generally within the simulated ranges, both after i.v. and p.o. dosing and for either CYP2C19 EM and PM.

5 References

Andersson 1990 Andersson T, Regårdh CG. Pharmacokinetics of Omeprazole and Metabolites Following Single Intravenous and Oral Doses of 40 and 80mg. *Drug Investig*. 1990;2(4):255-263.

Andersson 1991 Andersson T, Cederberg C, Heggelund A, Lundborg P. The Pharmacokinetics of Single and Repeated Once-Daily Doses of 10, 20 and 40mg Omeprazole as Enteric-Coated Granules. *Drug Investig*. 1991;3(1):45-52.

Andersson 1998 Andersson T, Holmberg J, Röhss K, Walan A. Pharmacokinetics and effect on caffeine metabolism of the proton pump inhibitors, omeprazole, lansoprazole, and pantoprazole. *Br J Clin Pharmacol*. 1998;45(4):369-375.

Andersson 2000 Andersson T, Rohss K, Hassan-alin M, et al. Pharmacokinetics (PK) and effect on pentagastrin stimulated peak acid output (PAO) of omeprazole (O) and its 2 optical isomers, S-omeprazole/esomeprazole (E) and R-omeprazole (R-O). *Gastroenterology*. 118(4):A1210

Äbelö 2000 Äbelö A, Andersson TB, Antonsson M, Naudot AK, Skanberg I, Weidolf L. Stereoselective metabolism of omeprazole by human cytochrome P450 enzymes. *Drug Metab Dispos*. 2000;28(8):966-972.

NCT01983566 Investigation of the effect of food and of increased gastric pH on the relative bioavailability of deleobuvir following single oral administration in healthy Caucasian and Japanese subjects (an open label, randomised, four-way crossover study)

Cho 2002 Cho JY, Yu KS, Jang IJ, Yang BH, Shin SG, Yim DS. Omeprazole hydroxylation is inhibited by a single dose of moclobemide in homozygotic em genotype for CYP2C19. *Br J Clin Pharmacol*. 2002;53(4):393-397.

DrugBank DB00176 (https://www.drugbank.ca/drugs/DB00176)

FDA Nexium Review FDA – Clinical Pharmacology and Biopharmacutics Review – Nexium delayed-Release Capsules – Esomeprazole sodium – Application number 21-153/21-154

FDA SPC FDA_ClinPharmReview LuvoxCR, NDA 22-033, FDADrug_42.pdf, website: digitalcollections.ohsu.edu/downloads/6m311p63g?locale=en

Galetin and Houston 2006 Galetin A, Houston JB. Intestinal and hepatic metabolic activity of five cytochrome P450 enzymes: impact on prediction of first-pass metabolism. *J Pharmacol Exp Ther*. 2006;318(3):1220-1229.

Hassan-Alin 2000 Hassan-Alin M, Andersson T, Bredberg E, Rohss K. Pharmacokinetics of esomeprazole after oral and intravenous administration of single and repeated doses to healthy subjects. *Eur J Clin Pharmacol*. 2000;56(9-10):665-670.

Hassan-Alin 2005 Hassan-Alin M, Andersson T, Niazi M, Röhss K. A pharmacokinetic study comparing single and repeated oral doses of 20 mg and 40 mg omeprazole and its two optical isomers, S-omeprazole (esomeprazole) and R-omeprazole, in healthy subjects. *Eur J Clin Pharmacol*. 2005;60(11):779-784

Nexium prescribing information Website: accessdata.fda.gov/drugsatfda_docs/label/2014/022101s014021957s017021153s050lbl.pdf

Kuepfer 2016 Kuepfer L, Niederalt C, Wendl T, Schlender JF, Willmann S, Lippert J, Block M, Eissing T, Teutonico D. Applied Concepts in PBPK Modeling: How to Build a PBPK/PD Model.CPT Pharmacometrics Syst Pharmacol. 2016 Oct;5(10):516-531.

Liu 2005 Liu KH, Kim MJ, Shon JH, et al. Stereoselective inhibition of cytochrome P450 forms by lansoprazole and omeprazole in vitro. *Xenobiotica*. 2005;35(1):27-38

Ogilvie 2011 Ogilvie BW, Yerino P, Kazmi F, Buckley DB, Rostami-Hodjegan A, Paris BL, et al. The proton pump inhibitor, omeprazole, but not lansoprazole or pantoprazole, is a metabolism-dependent inhibitor of CYP2C19: implications for coadministration with clopidogrel. *Drug Metab Dispos.* 2011;39(11):2020–33.

Olivares-Morales 2016 Olivares-Morales A, Ghosh A, Aarons L, Rostami-Hodjegan A. Development of a Novel Simplified PBPK Absorption Model to Explain the Higher Relative Bioavailability of the OROS(R) Formulation of Oxybutynin. *AAPS J*. 2016;18(6):1532-1549.

Oosterhuis 1992 Oosterhuis B, Jonkman JHG, Andersson T, Zuiderwijk PBM. No influence of single intravenous doses of omeprazole on theophylline elimination kinetics. *J Clin Pharmacol*. 1992;32(5):470-475.

PK-Sim Ontogeny Database Version 7.3 (https://github.com/Open-Systems-Pharmacology/OSPSuite.Documentation/blob/38cf71b384cfc25cfa0ce4d2f3addfd32757e13b/PK-Sim%20Ontogeny%20Database%20Version%207.3.pdf)

Regårdh 1990 Regårdh CG, Andersson T, Lagerstrom PO, Lundborg P, Skanberg I. The pharmacokinetics of omeprazole in humans--a study of single intravenous and oral doses. *Ther Drug Monit*. 1990;12(2):163-172.

Röhss 2007 Röhss, K., Wilder-Smith, C., Kilhamn, J., Fjellman, M. & Lind, T. Suppression of gastric acid with intravenous esomeprazole and omeprazole: results of 3 studies in healthy subjects. *CP* **45**, 345–354 (2007).

Uno 2007 Uno T, Niioka T, Hayakari M, Yasui-Furukori N, Sugawara K, Tateishi T. Absolute bioavailability and metabolism of omeprazole in relation to CYP2C19 genotypes following single intravenous and oral administrations. *Eur J Clin Pharmacol*. 2007;63(2):143-149.

Wilder-Smith 2005 Wilder-Smith CH, Bondarov P, Lundgren M, et al. Intravenous esomeprazole (40 mg and 20 mg) inhibits gastric acid secretion as effectively as oral esomeprazole: Results of two randomized clinical studies. *Eur J Gastroenterol Hepatol*. 2005;17(2):191-197

Willmann 2007 Willmann S, Höhn K, Edginton A, Sevestre M, Solodenko J, Weiss W, Lippert J, Schmitt W. Development of a physiology-based whole-body population model for assessing the influence of individual variability on the pharmacokinetics of drugs. *J Pharmacokinet Pharmacodyn* 2007, 34(3): 401-431.

Wu 2014 Wu F, Gaohua L, Zhao P, Jamei M, Huang S-M, Bashaw ED, et al. Predicting Nonlinear Pharmacokinetics of Omeprazole Enantiomers and Racemic Drug Using Physiologically Based Pharmacokinetic Modeling and Simulation: Application to Predict Drug/Genetic Interactions. *Pharmaceutical Research*. 2014 Aug;31(8):1919–29.

Wu 2016 Wu, J., Gießmann, T., Lang, B., Elgadi, M. & Huang, F. Investigation of the effect of food and omeprazole on the relative bioavailability of a single oral dose of 240 mg faldaprevir, a selective inhibitor of HCV NS3/4 protease, in an open-label, randomized, three-way cross-over trial in healthy participants. *J Pharm Pharmacol* **68**, 459–466 (2016).

Yasui-Furukori 2004 Yasui-Furukori N, Takahata T, Nakagami T, et al. Different inhibitory effect of fluvoxamine on omeprazole metabolism between CYP2C19 genotypes. *Br J Clin Pharmacol*. 2004;57(4):487-494.

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