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Computational modelling of omeprazole - pharmacokinetics and pharmacodynamics

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Abstract

Proton pump inhibitors (PPIs) are one of the most commonly used drugs whose main action is to inhibit the formation of gastric acid. Among the PPIs, omeprazole is one of the most important and most prescribed. Omeprazole is rapidly absorbed by the stomach and has a short half-life of around 1-2 hours in plasma. Omeprazole reduces gastric acid secretion via non-competitive selective inhibition of the H^+/K^+-ATPases in the gastric parietal cells, resulting in an increase in stomach pH. After cessation of omeprazole treatment, it takes a few days until the gastric acid secretion returns to baseline due to protein turnover of the proton pumps. Repeated dosing with omeprazole results in a dose-potentiation due to an increased absorption of omeprazole with increasing pH.

Within this thesis, the pharmacokinetics and pharmacodynamics of omeprazole were studied using a computational modeling approach. Based on extensive curation of clinical data of omeprazole a physiological-based pharmacokinetics/pharmacodynamics model of omeprazole and its effect on stomach pH was developed. The model allowed to simulate the pharmacokinetics of omeprazole under varying doses and treatment regimens and to study the resulting inhibition of the proton pumps and changes in stomach pH. Key questions studied in this thesis were (i) how gastric acid output and pH change with omeprazole dosing and treatment regime, and ii) what the effects of repeated dosing on omeprazole absorption and pH are.

Zusammenfassung

Protonenpumpeninhibitoren (PPI) gehören zu den am häufigsten verwendeten Medikamenten, deren Hauptwirkung darin besteht, die Bildung von Magensäure zu hemmen. Unter den PPIs ist Omeprazol eines der wichtigsten und am häufigsten verschriebenen Medikamente. Omeprazol wird schnell vom Magen absorbiert und hat eine kurze Halbwertszeit von etwa 1-2 Stunden im Plasma. Omeprazol reduziert die Magensäuresekretion durch nicht-kompetitive selektive Hemmung der H^+/K^+-ATPasen in den parietalen Zellen des Magens, was zu einem Anstieg des pH-Wertes im Magen führt. Nach Beendigung der Omeprazol-Behandlung dauert es einige Tage, bis die Magensäuresekretion aufgrund des Proteinumsatzes der Protonenpumpen wieder den Ausgangswert erreicht. Die wiederholte Verabreichung von Omeprazol führt zu einer Dosispotenzierung, da die Absorption von Omeprazol mit steigendem pH-Wert zunimmt.

Im Rahmen dieser Arbeit wurden die Pharmakokinetik und Pharmakodynamik von Omeprazol mit Hilfe eines computergestützten Modellierungsansatzes untersucht. Auf der Grundlage einer umfangreichen Kuration klinischer Daten zu Omeprazol wurde ein physiologisch basiertes Pharmakokinetik-/Pharmakodynamikmodell für Omeprazol und seine Wirkung auf den Magen-pH-Wert entwickelt. Das Modell ermöglichte es, die Pharmakokinetik von Omeprazol unter verschiedenen Dosierungen und Behandlungsregimen zu simulieren und die sich daraus ergebende Hemmung der Protonenpumpen und Veränderungen des Magen-pH zu untersuchen. Die wichtigsten Fragen, die in dieser Arbeit untersucht wurden, waren (i) wie sich die Magensäureproduktion und der pH-Wert mit der Omeprazol-Dosierung und dem Behandlungsregime verändern, und (ii) welche Auswirkungen wiederholte Dosierungen auf die Omeprazol-Resorption und den pH-Wert haben.

1 Introduction

1.1 Omeprazole

Proton pump inhibitors (PPIs) are drugs that inhibit the formation of gastric acid by inhibiting the H^+/K^+-ATPase. Six PPIs exist which are FDA-approved for clinical use: dexlansoprazole, lansoprazole, pantoprazole, esomeprazole, rabeprazole, and omeprazole. Omeprazole was the first PPI on the market and was released in 1989 in the US market [39].

Since the introduction of PPIs in the 1990 many operations related to stomach or duodenal ulcers are no longer necessary due to medication with PPI drugs. PPIs are commonly applied in the treatment of diseases such as Zollinger-Ellison syndrome or gastroesophageal reflux disease (GERD). Zollinger-Ellison syndrome is caused by tumors in the duodenum or pancreas. These neuroendocrine tumors increase the production of the hormone gastrin, which stimulates the production of stomach acid, which leads to over-acidification of the stomach [17]. Another disease that can be treated with PPIs is GERD. GERD is based in the vast majority of cases on a malfunction of the esophageal sphincter, a muscle that lies between the junction of the stomach and the esophagus. In case of dysfunction of the esophageal sphincter, stomach acid can pass into the esophagus because the passage of the connecting piece is not closed. The most common symptoms of GERD include heartburn, chest pain, and the development of Barrett's esophagus, which ultimately leads to a precursor of cancer [8].

In 1960 the pharmaceutical company Hässle started searching for a drug that inhibits gastric acid secretion. The research revealed an antisecretory compound that was effective in rats, but not in humans. Research in the 1970 showed that the last step before gastric acid production was connected to the newly discovered H^+/K^+-ATPase activation. This was followed by the finding that substituted benzimidazole inhibitors of the H^+/K^+-ATPase could be used to inhibit gastric acid secretion [30]. Omeprazole is a substituted benzimidazole (see **Figure 1)**, which reduces gastric acid secretion by selective and non-competitive inhibition of H^+/K^+-ATPases in the parietal cells in gastric cell membrane [29].

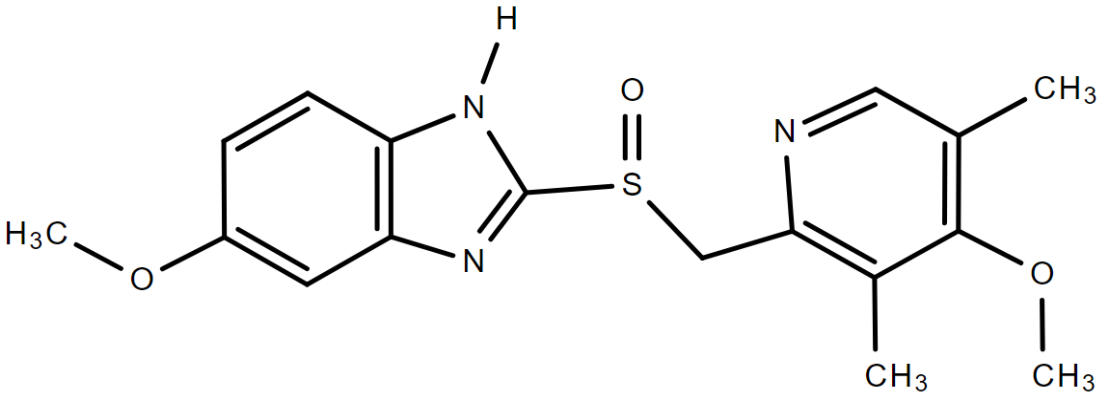

Figure 1: Chemical structure of omeprazole (inchikey: SUBDBMMJDZJVOS-UHFFFAOYSA-N).

1.2 Metabolism

After oral administration of omeprazole (PubChem:4594), it is mainly metabolized by cytochrome P450 (CYP) enzymes in the liver (see **Figure 2**). The cytochrome isoforms CYP2C19 (UniProt:P33261 and CYP3A4 (UniProt:P08684) are responsible for the biotransformation of omeprazole into the two primary metabolites, 5-hydroxy omeprazole (PubChem:119560) and omeprazole sulfone (PubChem:145900). This can be followed by conversion into the end product

5-hydroxy omeprazole sulfone (PubChem:71587531) via the same enzymes [31]. Studies have shown that people with a low activity of the CYP2C19 enzyme have an increased omeprazole effectiveness, i.e., a stronger reduction in stomach pH [31]. In contrast, individuals with increased CYP2C19 activity have a faster metabolization of omeprazole, resulting in a loss of effectiveness. An increased dose of omeprazole is necessary in such individuals [9]. According to in vivo experiments, CYP2C19 accounts for a metabolism of around 70% of S-omeprazole and around 90% of R-omeprazole [1].

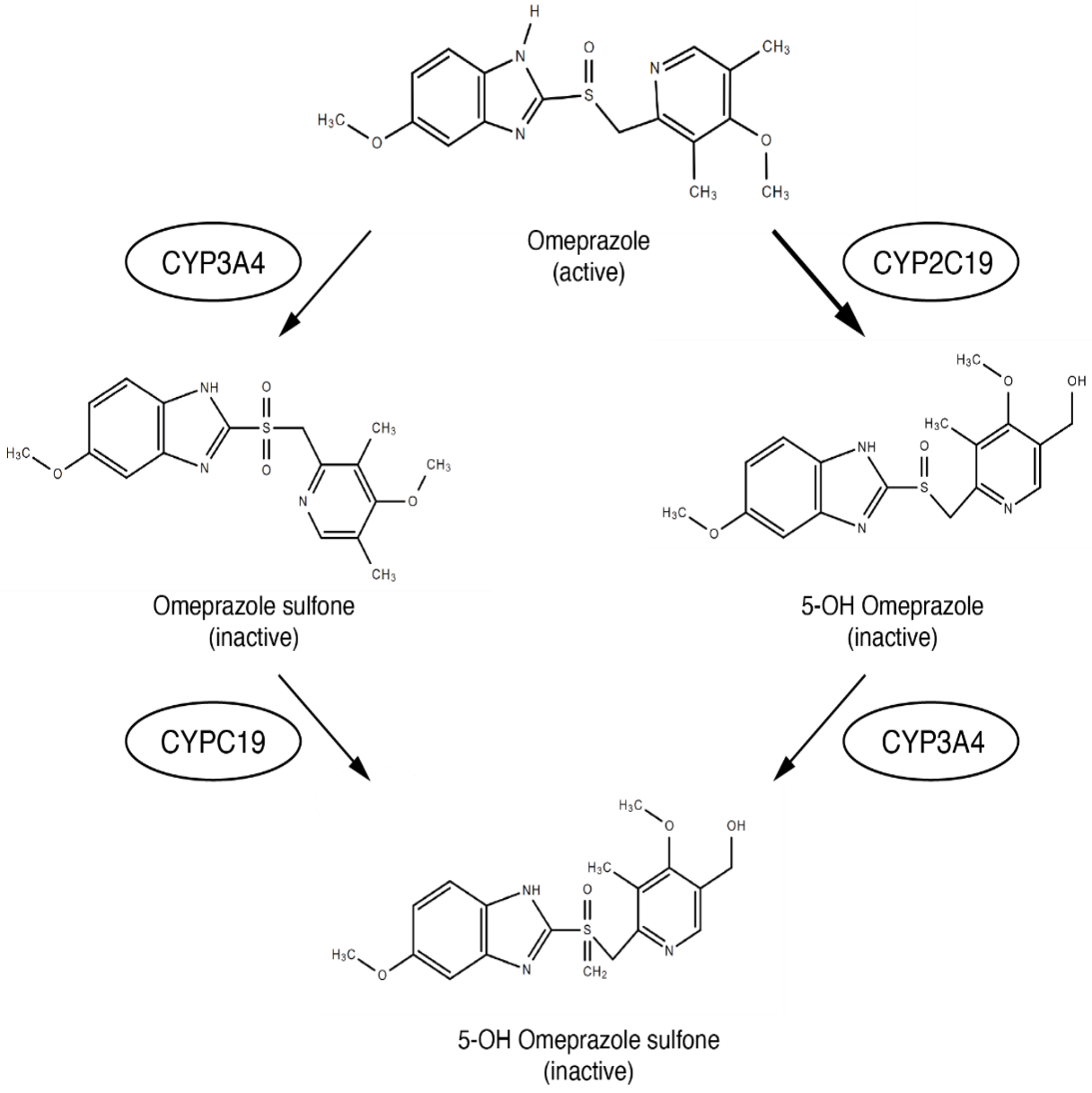

Figure 2: Metabolism of omeprazole.

1.3 Pharmacokinetics

After oral ingestion of omeprazole, it is absorbed very rapidly resulting in an inhibition of approximately 80-95% of gastric activity. After oral ingestion, only 50-70% of the omeprazole dose reaches the systemic circulation (bioavailability), indicating an extensive first-pass metabolism [6]. Omeprazole can be degraded under low pH values as occurring in the stomach. Due to its low stability, omeprazole is very often administered in the form of an enteric-coated capsule to ensure that as much of the drug as possible arrives intact in the intestine [34]. Alternatively, omeprazole is taken in in combination with a base which increases stomach pH and reduces pH-dependent degradation of omeprazole. When omeprazole is taken orally, a correlation exists between the dose and bioavailability, i.e.,with increasing dose, the systemic availability value increases [3]. In contrast to oral application, an intravenous dose is directly available in the systemic circulation after injection and is not affected by degradation in the stomach.

Omeprazole is mainly excreted in the kidney with ~80% of an omeprazole dose being excreted in the urine and the remainder in the feces as omeprazole metabolites. No unchanged omeprazole appears in feces or urine [6]. Omeprazole is almost completely converted into its two main metabolites, hydroxy omeprazole, and omeprazole sulfone in the liver before excretion [6].

Omeprazole has a high degree of clearance, typical clearance values are 30 L/hr [4]. The half-time $t_{½}$ of omeprazole is very fast with around 1-2 hr and an omeprazole dose is almost completely removed from the blood plasma after 3-4 hours. The volume of distribution V_d is around 0.3 l/kg [4].

1.4 Pharmacodynamics

Omeprazole reduces gastric acid secretion by inhibition of H^+/K^+-ATPases in the parietal cells. After omeprazole application, it is transported via the bloodstream to the gastric lining where it can enter the parietal cells of the gastric mucosa. The parietal cells are responsible for secreting protons via proton pumps (PP) on their cell surface which ultimately result in the low pH of the stomach. Within the parietal cells, which have a low pH, omeprazole (pKa value of 4) is converted into its protonated acid form, which can no longer be transported out of the cells. The sulphenamide groups of omeprazole formed as a result of the protonation can bind covalently to the sulfhydryl groups of the cysteine (Cys 813) of the H^+/K^+-ATPases and ultimately lead to an irreversible inhibition of the proton pumps via formation of an enzyme-inhibitor complex [25].

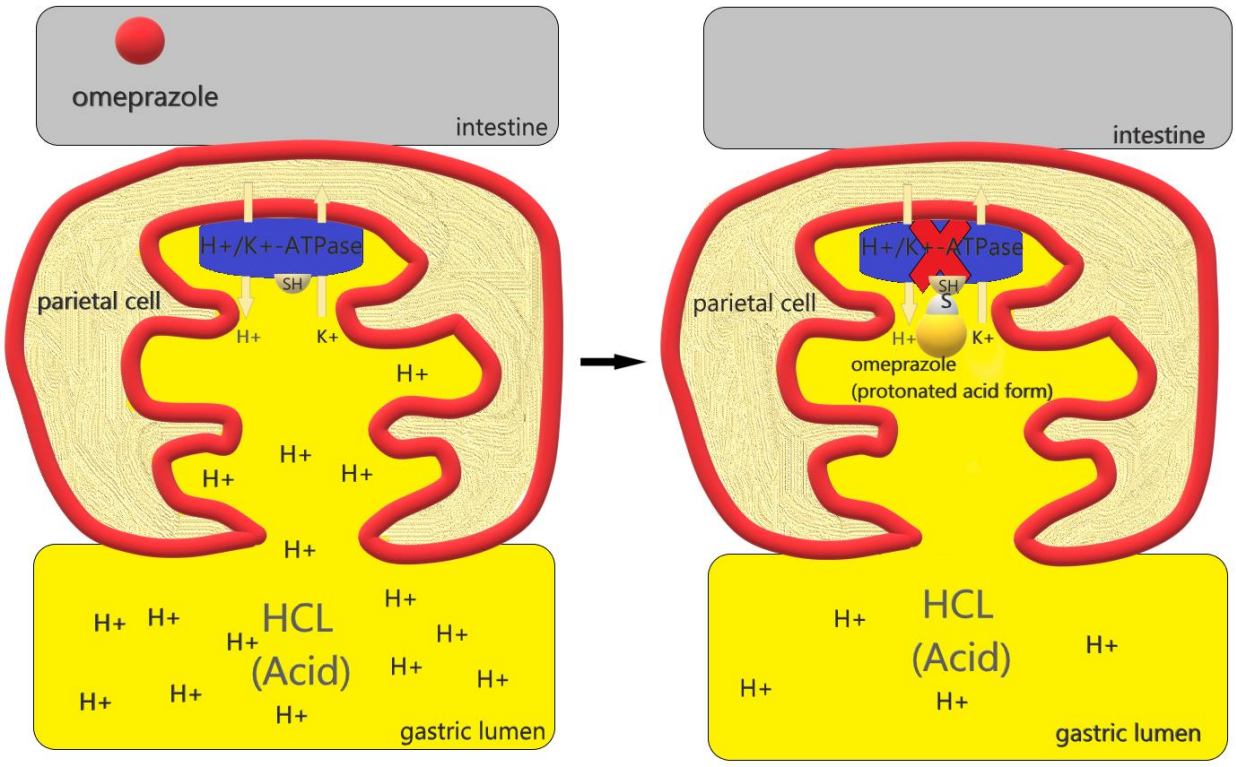

Figure 3: Mechanism of inhibition of proton pumps in the parietal cells by omeprazole. **Left)** In the active state, the gastric acid cells pump protons via the H^+/K^+-ATPase into the gastric lumen, producing gastric acid which results in an acidification of the stomach**. Right)** After omeprazole enters the gastric acid cells it becomes protonated and inhibits the H^+/K^+-ATPase via irreversible, covalent binding. Due to the inhibition less protons are secreted in the gastric lumen resulting in an increased stomach pH.

PPIs have a relatively short half-life due to continuous turnover via protein synthesis and degradation. An inhibited proton pump is thus inhibited for around 24-72 hours, before it is replaced by a newly synthesized PP [28]. Even though omeprazole is metabolized very quickly, due to the covalent inhibition of the PP its antisecretory effect is retained for up to 72 hours after elimination [4]. As a consequence, the steady-state inhibition of acid secretion is only reached after around three days of omeprazole application. The duration of the proton pump inhibition is independent of the omeprazole concentration, but only depends on the turnover of the PP. On the other hand, the degree of PP inhibition is directly linked to the plasma concentration of omeprazole [6] and a direct correlation between the AUC of omeprazole and intragastric pH has been observed [35].

1.5 Multiple dosing and pH dependence of absorption

Studies have shown that repeated dosing with omeprazole increases the AUC and bioavailability. For instance, Andersson *et al.* demonstrated that the multiple dosing effect increased AUC by more than 50% compared to a single dose [3]. Two possible explanations have been proposed to explain this result.

The first explanation is based on the pH-dependent stability of omeprazole. Because the pH value in the stomach increases after ingestion of an omeprazole dose due to PP inhibition, a smaller

fraction of a subsequent oral omeprazole dose is degraded during the passage through the stomach. Consequently, more omeprazole can reach the intestine and systemic circulation after multiple dosing, resulting in an increase of AUC and bioavailability. In summary, since there is less gastric acid, less omeprazole is eliminated, leading to an increased absorption of the drug and thus an augmentation effect with multiple dosing [12].
A second proposed explanation for this phenomenon is that omeprazole could act as an inhibitor of its own metabolism via CYP2A19 and CYP3A4, resulting in a reduced first-pass effect. However, intravenous doses do not show any increased bioavailability or AUC for doses up to 10 mg when comparing single doses to repeated dosing, making this explanation unlikely. Furthermore, despite the impact of the multiple dosing effect on bioavailability and AUC, no change in the elimination rate can be observed [3, 7] providing additional evidence against the second explanation. On the other hand, Cederberg et al., could show a greatly increased AUC (more than 80%) when comparing a 10 mg IV dose and a 40 mg dose of omeprazole [7]. This result would support the second statement presented above. A possible explanation could be that auto-inhibition of omeprazole metabolism by itself only becomes important at large doses.

1.6 Pharmacokinetic/pharmacodynamic model (PK/PD)

Computational models are a unique tool to study complex biological systems *in silico*. Such models allow us to make predictions which can be tested experimentally and allow us to gain insights into underlying mechanisms. One class of such computational models are physiological based pharmacokinetics (PBPK) models which represent the physiology of the human body and allow the simulation of pharmacokinetics time courses and parameters. Such models allow the study of absorption, distribution, metabolization and elimination (ADME) of substances such as omeprazole. Often models describing the pharmacokinetics (PK) are coupled to models describing the pharmacodynamics (PD), i.e., the effect of the drug on the body, resulting in so-called PK/PD models.

1.7 Question, scope and hypothesis

This thesis studied the effect of varying doses and treatment regimes (single dose and multiple doses) on omeprazole metabolism utilizing computational modeling. Specifically, a physiologically-based pharmacokinetic/pharmacodynamic model (PBPK/PD) of omeprazole was developed and applied to study the following questions:

1. How do gastric acid output and stomach pH change with omeprazole dosing?
2. What are the effects of repeated dosing on omeprazole absorption and stomach pH?

Our main hypothesis was:

> Existing pharmacokinetic/pharmacodynamic data can be explained using a PBPK models with the simple assumptions of (i) omeprazole is degraded pH dependent in the stomach; (ii) omeprazole inhibits the H^+/K^+-ATPase irreversibly; and (iii) continuous turnover of the H^+/K^+-ATPase exists.

2 Methods

In this work, the effects of omeprazole were investigated using a physiologically based pharmacokinetics/pharmacodynamics model. The model was created in a data-driven approach using time courses data of omeprazole from published clinical studies to drive model development. Methods applied were: calculation of pharmacokinetic parameters from time course data (Section 2.1), curation of pharmacokinetic data for model building (Section 2.2), development of a physiological-based pharmacokinetic model (Section 2.3) and parameter fitting of model parameters (Section 2.4).

2.1 Pharmacokinetic parameters

From the plasma concentration time courses of omeprazole pharmacokinetic parameters can be calculated using non-compartmental methods. The most important parameters are:

- **C_{max}** is the maximal measured concentration.
- **T_{max}** is the time that is necessary to reach the maximum concentration.
- **Area under the curve (AUC)** describes the area under the concentration-time curve
- **Bioavailability F** describes the percentage of an active ingredient that remains unchanged in the bloodstream
- **Volume of distribution** Vd describes the relative distribution of the drug in the bloodstream and tissue
- **Half-life $t_{1/2}$** means the half-life in which the drug is reduced by half.
- **Clearance** corresponds to the rate at which a substance is eliminated from the plasma.
- **Elimination rate k_{el}** describes how quickly the drug is eliminated from the plasma

AUC is calculated from the sum of all trapezoidal areas plus the triangular area at the end of the curve:

$$AUC_{0-t_n} \approx \frac{1}{2}\sum_{i=1}^{n-1} (t_{i+1} - t_i) \cdot (C_i + C_{i+1})$$

The bioavailability is calculated using the plasma concentrations after an oral and corresponding intravenous dose. The AUC values are required to calculate the absolute bioavailability:

$$F = \frac{AUC_{Oral}/dose_{oral}}{AUC_{i.v}/dose_{i.v}}$$

The volume of distribution is defined as the quotient of the administered dose D of the drug by the plasma concentration c of the drug in the blood:

$$V_d = \frac{D}{c}$$

The half-life can be calculated from the elimination rate k_{el}

$$t_{1/2} = \frac{ln(2)}{k_{el}}$$

The clearance can be calculated from the product of the constant elimination rate and the volume of distribution

$$clearance = k_{el} \cdot V_d$$

2.2 Curation of pharmacokinetics data

PK-DB is an open database for curated pharmacokinetic data from clinical studies [10]. In addition to pharmacokinetic data PK-DB allows the storage of pharmacodynamics information (e.g. gastric acid output). Among other things, data from the studies, such as the specifications of the test subjects, including gender, age, body weight, state of health,, are included in PK-DB. In addition to the characteristics of the subjects, the type of intervention and the reported pharmacokinetic data are included.

Within this work, studies containing omeprazole pharmacokinetic data were curated following established guidelines and added to the PK-DB database. This data set of omeprazole pharmacokinetics information was the basis for the development and validation of the PBPK/PD model developed in this work.

A literature research was performed to retrieve studies that include pharmacokinetic/pharmacodynamic data on omeprazole. Studies were hereby limited to healthy adult human subjects excluding animal data. Most of the studies contained information on i) the studied subjects and groups; ii) the type of intervention (oral or intravenous) and the dosage regime of omeprazole (dose, timing, single vs. multiple application); iii) the study design (substances added, time intervals, type of measurement, and parameters); iv) time curves and tables containing pharmacodynamic and pharmacokinetic data. Data from tables and figures was extracted and curated in a standardized xlsx file format. As part of the curation, a study JSON file was created for the upload of the collected data to PK-DB. The software "Plot digitizer" was used for digitizing numerical data from figures such as time courses. After completing the steps mentioned above and after a thorough review by a second curator, all curated studies were uploaded to PK-DB.

2.3 Physiological-based pharmacokinetics/pharmacodynamics model (PBPK/PD)

The PBPK/PD model consists of a system of coupled ordinary differential equations (ODE) which can be solved numerically using ODE solvers. The model is encoded in a standard format for models in systems biology, the so-called System Biology Markup Language (SBML) [14, 15, 16]. The ODE system can be generated from this standard representation. Meta-data such as annotations to biological and computational ontologies and units were added to the model to enable the sharing and reuse of the model. The model was developed in Python using the sbmlutils package [22], which allows to generate the SBML models programmatically. For ODE simulations, the package sbmlsim was used [23], which allows for ODE simulations with different initial conditions, parameter scans and the fitting of parameters. For the efficient solution of the SBML based ODE systems, sbmlsim uses the high-performance SBML solver roadrunner [37]. Model visualization was performed using cy3sbml [24].

2.4 Parameter fitting

Parameter fitting is a method to adapt parameters *(p_1, …, p_m)* in the model based on experimental data. Parameter fitting is an optimization method which tries to find the best parameters which minimize the cost which depends on the distance between model prediction *$f(x_{i,k})$* and data $y_{i,k}$. The distance was measured via the weighted residuals *$res_{i,k}$ = ($y_{i,k}$ - $f(x_{i,k})$)*. Within this work, SciPy's least-squares method was used.

$$cost(p1, \dots, pm) = 0.5 \cdot \Sigma \, (w_k \cdot w_{i,k} \cdot res_{i,k})^2$$

$res_{i,k}$ is the residue of time i over time k, i.e., the distance between model prediction and data. wi, k is the weighting of the respective data point i over time k based on the error of the data point. wk is the weighting factor of the time course k. An overview over the parameter fitting strategy is provided in the results section with data used in parameter fitting provided in **Table 3** .

3 Results

3.1 Omeprazole data

For this work, a database with omeprazole data was created on the basis of pharmacokinetics. A total of 14 studies were curated as part of this work and uploaded to PK-DB. **Table 1** provides an overview of the curated data, including the core information. In addition to the PMID and the PKDB register number, the application route, dosage, body weight, health condition, information on whether data from the respective study was used for model fitting was used, and a brief description of the respective study are listed.

3.2 Computational model

3.2.1 Whole-body model

A physiologically based computer model was developed to investigate the pharmacokinetic/pharmacodynamic aspects of omeprazole in **Figure 4A**, in the following referred to as PBPK/PD model. The model was established using human *in vivo* data on the pharmacokinetics (omeprazole time courses) and pharmacodynamics (changes in stomach pH and gastric acid output) and *in vitro* information of kinetic parameters. The model is available as SBML [15, 16] under CC-BY 4.0 license from https://github.com/matthiaskoenig/omeprazole-model. Within this work version 0.8.0 of the model was used [21]. A human readable model report documenting all equations, parameters and initial conditions is available from https://sbml4humans.de/model_url?url=https://raw.githubusercontent.com/matthiaskoenig/omeprazole-model/main/models/omeprazole_body_flat.xml.

In the PBPK/PD model the human body was represented via multiple compartments corresponding to organs/tissues which are connected via blood flow in the systemic circulation. The whole-body model allows to simulate the absorption and distribution of omeprazole as well as the distribution of omeprazole metabolites. The whole-body model was coupled to tissue models of the liver, kidney, and stomach. The liver submodel describes the hepatic metabolism of omeprazole (**Figure 4B**), the kidney model the renal excretion of omeprazole metabolites (**Figure 4C**), and the stomach model the proton pump inhibition and gastric acid secretion (**Figure 4D**).

Table 1 - Overview of clinical studies curated in this project. The table lists the name of the studies with the corresponding PK-DB identifiers, the PMID, a brief description of the dosing protocol, the application route (oral or intravenous), the health status of the test subjects, the range of body weights of the test subjects, if the data was used in the modelling of omeprazole and a short description.

Study	PKDB	PMID	Protocol	Route	Healthy	Body weight [kg]	Modelling	Description
Andersson1990a [3]	PKDB00518	2253676	Omeprazole: 10, 40, 90 mg	iv, oral	healthy	70-86		The influence of dose on the kinetics of omeprazole and two of its metabolites, hydroxyomeprazole and the sulfone, has been studied
Cederberg1992 [7]	PKDB00519	1499942	Omeprazole: 10, 20, 40 mg	iv, oral	duodenal ulceration	-	✓	Nine patients with duodenal ulcer were on separate occasions given omeprazole, 20 mg orally, 10 mg intravenously (IV), and 40 mg IV once daily for 5 days.
Howden1984 [13]	PKDB00379	6468483	Omeprazole: 30, 60 mg	oral	healthy	-		The pharmacokinetics of omeprazole were studied in a group of healthy male subjects after single and repeated oral doses of 30 and 60 mg.
Howden1984a [12]	PKDB00520	6428981	Omeprazole: 30, 60 mg	oral	healthy	-		The effects of omeprazole, a substituted benzimidazole, on gastric acid secretion have been studied in twelve healthy subjects.
Landahl1992 [18]	PKDB00521	1458764	Omeprazole: 20, 40 mg	iv, oral	healthy	58 - 88	✓	The pharmacokinetics of omeprazole and its metabolites were studied in 8 healthy elderly volunteers using omeprazole.
Lind1983 [19]	PKDB00522	6832622	Omeprazole: 15, 20, 40, 60, 80 mg	oral	healthy	63 - 88	✓	The effect of oral omeprazole on pentagastrin stimulated gastric acid secretion was studied in 11 healthy subjects.
Prichard1985 [32]	PKDB00523	3880557	Omeprazole: 40 mg	oral	healthy	63 - 116	✓	Pharmacodynamic and pharmacokinetic studies of omeprazole were undertaken in 8 healthy subjects.
Regaardh1986 [33]	PKDB00524	3460172	Omeprazole: 10, 20, 40, 90 mg	iv, oral	healthy	-	✓	Four studies of the pharmacokinetics and metabolism of omeprazole are briefly discussed.
Regaardh1990 [34]	PKDB00525	2315973	Omeprazole: 10, 20 mg	iv, oral	healthy	74.1 ± 5.1	✓	The pharmacokinetic omeprazole, hydroxy omeprazole, omeprazole sulfone, and “remaining metabolites” have been studied in eight young healthy subjects.
Sohn1992 [36]	PKDB00526	1527724	Omeprazole: 20 mg	oral	healthy	55 - 72	✓	Disposition kinetics and metabolism of omeprazole in extensive and poor metabolizers of S-Mephenytoin 4-Hydroxylation recruited from an oriental population.
VazdaSilva2001 [40]	PKDB00527	27517550	Omeprazole: 20 mg	oral	healthy	52 - 87	✓	Study to investigate the relative bioavailability and bioequivalence of two omeprazole enteric-coated formulations following repeated doses (steady state) in healthy male and female adult volunteers.
VazdaSilva2005 [41]	PKDB00380	17532679	Omeprazole: 20 mg	oral	healthy	49 - 88	✓	Study to investigate the relative bioavailability and bioequivalence, in fasting and fed condition, of repeated doses of two omeprazole enteric-coated formulations in healthy volunteers.
Walt1985 [43]	PKDB00528	4029717	Omeprazole: 80 mg	iv, oral	duodenal ulceration	65 - 81	✓	The effects of different dosage regimens of intravenous omeprazole was compared with placebo.

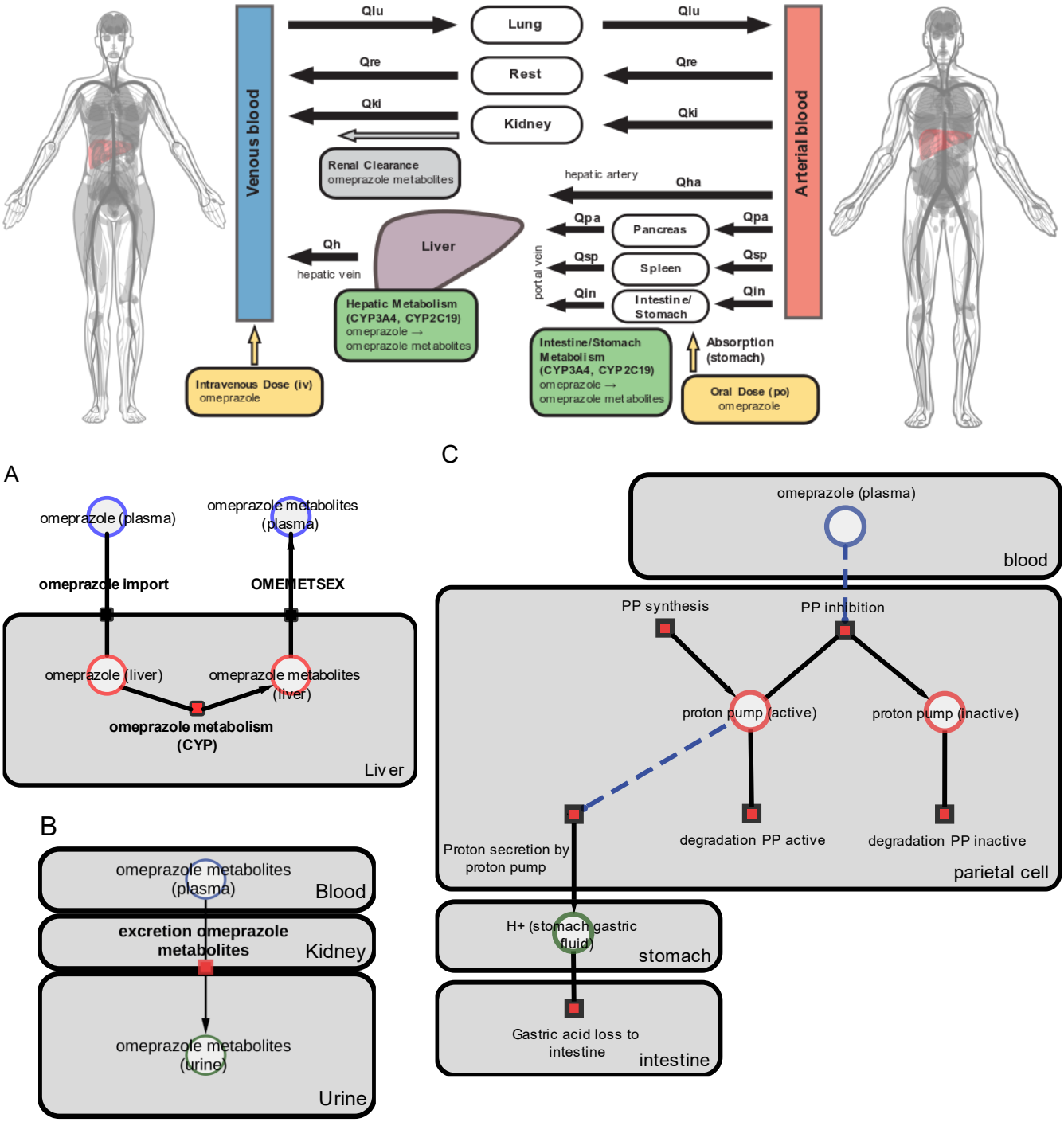

Figure 4 - Overview of developed model. A) Overview of the physiological-based whole-body model. The heart is the pump that drives blood circulation with the bloodstream connecting the organs and tissues. The two main blood compartments are venous blood and arterial blood. Via the systemic circulation blood is transported between arterial and venous blood compartments supplying and draining the various tissue compartments in the process. The blood flow rates to the organs are Qlu, Qre, Qki, Qha, Qpa, Qsp, and Qin. Omeprazole can be administered either intravenously or orally, with absorption in the stomach and intestine. Omeprazole is metabolized in the liver, converting omeprazole into its inactive intermediates by the main enzymes CYP3A4 and CYP2C19 (omeprazole metabolites), which are ultimately excreted mainly via the kidneys and the urine/feces. **B)** The liver model describes the metabolism of omeprazole in the liver consisting of import, conversion to omeprazole metabolites and subsequent export. **C)** The kidney model describes the renal excretion of omeprazole metabolites

in the urine. **D)** The stomach model contains the equations for the turnover of proton pumps, the inactivation of proton pumps via omeprazole and the proton pump dependent secretion of protons in the stomach.

3.2.2 Liver model

The liver submodel describes the uptake of omeprazole from the plasma (OMEIM), the metabolic conversion to inactive omeprazole metabolites by CYP2C19/CYP3A4 (OMECYP) and the export of the omeprazole metabolites back in the plasma (OMEMETSEX). The import, metabolism and export were modelled via irreversible Michaelis-Menten equations

$$OMEIM = \frac{OMEIM\ Vmax \cdot Vli \cdot ome_{ext}}{(OMEIM\_Km\_ome + ome\_ext)}$$

$$OMECYP = \frac{OMECYP\ Vmax \cdot Vli \cdot ome}{(OMECYP\_Km\_ome + ome)}$$

$$OMEMETSEX = \frac{OMEMETSEX\ Vmax \cdot Vli \cdot omemets}{(OMEMETSEX\_Km\_omemets + omemets)}$$

with Vmax being the maximal velocity, Vli the liver volume and Km the Michaelis-Menten constant, and ome_ext the omeprazole concentration in plasma. All tissue reactions were scaled by the respective tissue volumes. The following assumptions were made:
(i)omeprazole is only converted to omeprazole metabolites (combination of 5OH-omeprazole, omeprazole sulfone and 5OH-omeprazole sulfone); (ii) the transport and metabolism are irreversible; (iii) The different CYP isoforms were not modeled individually, but a single reaction was implemented. The cytochrome isoforms CYP2C19 and CYP3A4 are responsible for the biotransformation of omeprazole into the two primary metabolites, 5-hydroxy omeprazole and omeprazole sulfone, these were combined in a single process.

3.2.3 Kidney model

The kidney submodel describes the renal excretion of omeprazole metabolites from the plasma via a first order irreversible mass-action kinetics of the form

$$OMEMETSEX\_k \cdot V_{ki} \cdot omemets\_ext$$

with k being the rate and Vki the kidney volume.
The following assumptions were made: (i) Only omeprazole metabolites can be excreted in the urine, no omeprazole; (ii) the excretion from plasma to urine is direct, i.e., no processes in the kidneys were modeled.

3.2.4 Stomach model

The stomach model describes the activity of proton pumps (H+/ K+ATPase) and the turnover of PP via synthesis and degradation. PP can be irreversibly inhibited via omeprazole. The following assumptions were made: (i) degradation of the active and inhibited PP is identical; (ii) only the active PP can secrete protons in the gastric fluid; (iii) the gastric acid (with protons) is transported in the stomach via gastric acid secretion and changes the stomach pH; (iv) gastric acid can be lost from the stomach to the intestine.

Proton secretion by active PP was modeled via an irreversible kinetic depending on the amount of active PP. A phenomenological equation was implemented resulting in stomach pH changes in line with observed values. pp_rate = pp_rate_k when all proton pumps are active.

$$pp\_rate = pp\_rate\_k \cdot 10^{\frac{-1.1}{pp\_active+0.1}+1}$$

Gastric acid loss was modeled via an irreversible first order kinetic

$$gacid\_loss = Q_{acid} \cdot protons\_stomach$$

Stomach pH was calculated from proton concentration in [mM] in the stomach via

$$pH = -log10\left(\frac{protons\_stomach}{1000mM}\right)$$

Synthesis of active PP was assumed via a constant rate

$$pp\_synthesis = pp\_synthesis\_k$$

Degradation of active and inactive PP was modeled via an irreversible first order kinetic

$$pp\_active\_degradation = pp\_degradation\_k \cdot pp\_active$$
$$pp\_inactive\_degradation = pp\_degradation\_k \cdot pp\_inactive$$

Inhibition of PP, i.e. conversion from the active in the inactive state, was modeled via an irreversible mass action kinetics depending on active PP and omeprazole concentration

$$pp\_inhibition = ppi\_k \cdot pp\_active \cdot ome\_ext$$

3.2.5 Omeprazole absorption

Dissolution of orally applied omeprazole in the stomach was modeled via an irreversible first order kinetics

$$dissolution = Ka\_dis\_ome \cdot PODOSE\_ome$$

with PODOSE_ome corresponding to the amount of orally applied omeprazole.

Absorption of dissolved omeprazole omeprazole was modeled via an irreversible first order kinetics

$$absorption = Ka\_abs\_ome \cdot GUTDOSE\_ome$$

with GUTDOSE_ome corresponding to the amount of dissolved omeprazole in the intestine.

Multiple explanations have been presented for the increase in AUC and bioavailability after multiple dosing of omeprazole (see Section 1.5). Here we assumed a pH dependent fraction absorbed of omeprazole, i.e., assuming a pH dependent degradation of omeprazole in the stomach.

The change in the oral and gut dose are described via the following differential equations

$$\frac{d\,(PODose)}{dt} = -dissolution$$
$$\frac{d\,(GUTDose)}{dt} = F\_ome\_pH \cdot dissolution - absorption$$

with F_ome_pH describing the stomach pH dependent fraction absorbed. I.e. depending on the pH in the stomach either more omeprazole (higher pH) or less omeprazole (lower pH) can reach the gut due to the pH dependent degradation of omeprazole.
The pH dependency of the fraction absorbed F_ome_pH was modeled via a sigmoidal function interpolating between 35% absorption at pH=2 and 84% absorption at pH=6 in case of application as solution

$$F\_ome\_pH = F\_ome\_pH2 + (F\_ome\_pH6 - F\_ome\_pH2)\frac{(pH-2)^{F\_ome\_n}}{(pH-2)^{F\_ome\_n} + F\_ome\_KpH^{F\_ome\_n}}$$

When omeprazole was applied orally as hard capsules, which protect omeprazole from the stomach degradation, it was assumed that the complete omeprazole dose could be absorbed, i.e.,

$$F\_ome = 1$$

3.3 Parameter fitting

Time course data of plasma omeprazole and urinary omeprazole metabolites after intravenous and oral application were used for fitting a subset of model parameters. Parameters were determined in a two step procedure. In a first step the following model parameters were determined using all intravenous data:

- **LI__OMEIM_Vmax,** maximum rate of omeprazole uptake in the liver
- **LI__OMECYP_Vmax,** maximum rate of CYP conversion of omeprazole to omeprazole metabolites in the liver
- **LI__OMEMETSEX_Vmax,** maximum rate of omeprazole matabolite export in the liver
- **KI__OMEMETSEX_k**, rate at which the omeprazole metabolites are excreted in the urine.

In a second step the dissolution and absorption rates were fitted individually for the studies with oral omeprazole application to account for the large interstudy variability in absorption kinetics due to different omeprazole formulations and different study populations. I.e., for every study with oral omeprazole a single combination of the following parameters was fitted:

- **Ka_dis_ome**, rate at which orally administered omeprazole is dissolved.
- **Ka_abs_ome**, rate at which orally administered omeprazole is absorbed

The complete set of model parameters is provided in **Table 2**. An overview over the used data including application type (single or multiple dose), application route (IV or PO), application form, tissue and dose are provided in **Table 3** . If not mentioned otherwise Ka_dis_ome=2 [1/hr] and Ka_abs_ome = 2 [1/hr] were used for model simulations.

Table 2. Overview of main model parameters. The table contains the name of the parameter in the model, a short description of the parameter, the value of the parameter, the unit, and which parameters were fitted.

Parameter	Description	Value	Unit	Fitted
BW	Body weight	75	kg	-
HEIGHT	Height	1.70	m	-
COBW	Cardiac output per bodyweight	1.548	$\frac{ml}{s \cdot kg}$	-
HCT	Hematocrit	0.51	-	-
FVgu	Gut fractional tissue volume	0.0171	$\frac{l}{kg}$	-
FVki	Kidney fractional tissue volume	0.0044	$\frac{l}{kg}$	-
FVli	Liver fractional tissue volume	0.021	$\frac{l}{kg}$	-
FVlu	Lung fractional tissue volume	0.0076	$\frac{l}{kg}$	-
FVsp	Spleen fractional tissue volume	0.0026	$\frac{l}{kg}$	-
FVpa	Pancreas fractional tissue volume	0.01	$\frac{l}{kg}$	-
Mr_ome	Molecular weight ome	345.4	$\frac{g}{mole}$	-
Ftissue_ome	Tissue distribution ome	0	$\frac{l}{min}$	-
fup_ome	Fraction unbound in plasma ome	1	-	-
BP_ome	Blood to plasma ratio ome	1	-	-
ti_ome	Injection time ome	10	s	-
Mr_omemets	Molecular weight omemets	345.4	$\frac{g}{mole}$	-
Ftissue_omemets	Tissue distribution omemets	0	$\frac{l}{min}$	-
fup_omemets	Fraction unbound in plasma omemets	1	-	-
BP_omemets	Blood to plasma ratio omemets	1	-	-
Ka_dis_ome	Dissolution rate ome Cederberg1992 Landahl1992 Lind1983 Prichard1985 Regaardh1986 Regaardh1990 VazdaSilva2001 VazdaSilva2005	2 1.7526 11.742 4.3381 0.8671 10.824 19.993 1.0540 1.2731	$\frac{1}{hr}$	 ✓ (PO) ✓ (PO) ✓ (PO) ✓ (PO) ✓ (PO) ✓ (PO) ✓ (PO)
Ka_abs_ome	Absorption rate ome Cederberg1992 Landahl1992 Lind1983 Prichard1985 Regaardh1986 Regaardh1990 VazdaSilva2001 VazdaSilva2001	2 1.8362 11.481 7.6759 0.8698 10.724 5.0933 1.0590 1.2356	$\frac{1}{hr}$	 ✓ (PO) ✓ (PO) ✓ (PO) ✓ (PO) ✓ (PO) ✓ (PO) ✓ (PO) ✓ (PO)
f_tissue_ome	Tissue distribution ome	0.44948		✓ (IV)
F_ome_pH2	Fraction absorbed at pH2	0.35	-	-
F_ome_pH6	Fraction absorbed at pH6	0.84	-	-
F_ome_KpH	Midpoint of pH absorption effect	4	-	-
F_ome_n	Hill coefficient of pH absorption effect	2	-	-
LI__OMEIM_Vmax	V_{max} omeprazole import	0.010599	$\frac{mmole}{liter \cdot min}$	✓ (IV)
LI__OMEIM_Km_ome	K_m omeprazole import	0.1	$\frac{mmole}{liter}$	-
LI__OMECYP_Vmax	V_{max} omeprazole conversion	0.33805	$\frac{mmole}{liter \cdot min}$	✓ (IV)
LI__OMECYP_Km_ome	K_m omeprazole conversion	0.1	$\frac{mmole}{liter}$	-

LI__OMEMETSEX_Vmax	V_{max} omeprazole metabolite export	0.32125	$\frac{mmole}{liter \cdot min}$	✓ (IV)
LI__OMEMETSEX_Km_omemets	K_m omeprazole metabolite export	0.1	$\frac{mmole}{liter}$	-
KI__OMEMETSEX_k	Rate urinary excretion omemets	0.59741	$\frac{1}{min}$	✓ (IV)
ST__Qgacid	Gastric acid secretion	0.01	$\frac{l}{min}$	-
ST__pp_rate_k	Rate of proton secretion	0.1	$\frac{mmole}{min}$	-
ST__ppi_k	Inhibition rate PP	0.01	$\frac{l}{min}$	-
ST__pp_syntehsis_k	Synthesis rate PP	0.01	$\frac{mmole}{min}$	-
ST__pp_degradation_k	Degradation rate PP	0.01	$\frac{mmole}{min}$	-

Table 3 - Overview of data used in parameter fitting and model evaluation. The table lists the name from the study, the PK-DB identifier and PMID, application route (oral or intravenous), the form in which the drug was administered, tissue, dosage with unit and the name of the fit.

Study	PKDB	PMID	application	dose [mg]	route	form	tissue	data identifier
Cederberg1992 [7]	PKDB00519	1499942	single dose	10	IV	solution	plasma	fm_ome_iv10
Cederberg1992 [7]	PKDB00519	1499942	single dose	40	IV	solution	plasma	fm_iv40
Cederberg1992 [7]	PKDB00519	1499942	multiple dose	10	IV	solution	plasma	fm_iv10_multi
Cederberg1992 [7]	PKDB00519	1499942	multiple dose	40	IV	solution	plasma	fm_iv40_multi
Cederberg1992 [7]	PKDB00519	1499942	single dose	20	PO	hard capsule	plasma	fm_ome_po20
Cederberg1992 [7]	PKDB00519	1499942	multiple dose	20	PO	hard capsule	plasma	fm_ome_po20_multi
Landahl1992 [18]	PKDB00521	1458764	single dose	20	IV	solution	plasma	fm_ome_iv20
Landahl1992 [18]	PKDB00521	1458764	single dose	20	IV	solution	urine	fm_ome_iv20_Fig5
Landahl1992 [18]	PKDB00521	1458764	single dose	40	PO	solution buffered	plasma	fm_ome_po40
Landahl1992 [18]	PKDB00521	1458764	single dose	40	PO	solution buffered	urine	fm_ome_po40_Fig5
Lind1983 [19]	PKDB00522	6832622	single dose	40	PO	solution buffered	plasma	fm_ome_po40
Prichard1985 [32]	PKDB00522	6832622	single dose	40	PO	hard capsule	plasma	fm_ome_po40_am fm_ome_po40_pm
Prichard1985 [32]	PKDB00522	6832622	multiple dose	40	PO	hard capsule	plasma	fm_ome_po40_multi_am fm_ome_po40_multi_pm
Regaardh1986 [33]	PKDB00524	3460172	single dose	10	IV	solution	plasma	fm_ome_iv10
Regaardh1986 [33]	PKDB00524	3460172	single dose	20	PO	solution buffered	plasma	fm_ome_po20
Regaardh1990 [34]	PKDB00525	2315973	single dose	10	IV	solution	plasma	fm_ome_iv10_adult7 fm_ome_iv10
Regaardh1990 [34]	PKDB00525	2315973	single dose	10	IV	solution	urine	fm_KI__omemets_urine_iv10
Regaardh1990 [34]	PKDB00525	2315973	single dose	20	PO	solution buffered	plasma	fm_ome_po20_adult7 fm_ome_po20
Regaardh1990 [34]	PKDB00525	2315973	single dose	20	PO	solution buffered	urine	fm_KI__omemets_urine_po20
VazdaSilva2001 [40]	PKDB00527	27517550	multiple dose	20	PO	hard capsule	plasma	fm_ome_po20_multi_Mopral fm_ome_po20_multi_Ompranyt
VazdaSilva2005 [41]	PKDB00527	27517550	multiple dose	20	PO	hard capsule	plasma	fm_ome_po20_multi_Mopral fm_ome_po20_multi_Ompranyt
Walt1985 [43]	PKDB00528	4029717	single dose	80	PO	powder	plasma	fm_ome_iv80

An overview over the parameter fitting results for the intravenous studies is provided in Figure 5. A large set of heterogeneous IV studies could be fitted with a single parameter set, as can be seen from the comparison of model prediction and experimental data (see **Figure 5A**). All intravenous datasets contributed similar to the parameter fit as can be seen by the comparison of weighted residuals (see **Figure 5B**). On the other hand, the parameter fitting results for the individual oral applications of omeprazole was much more heterogeneous with only a subset of studies fitted very well (data not shown).

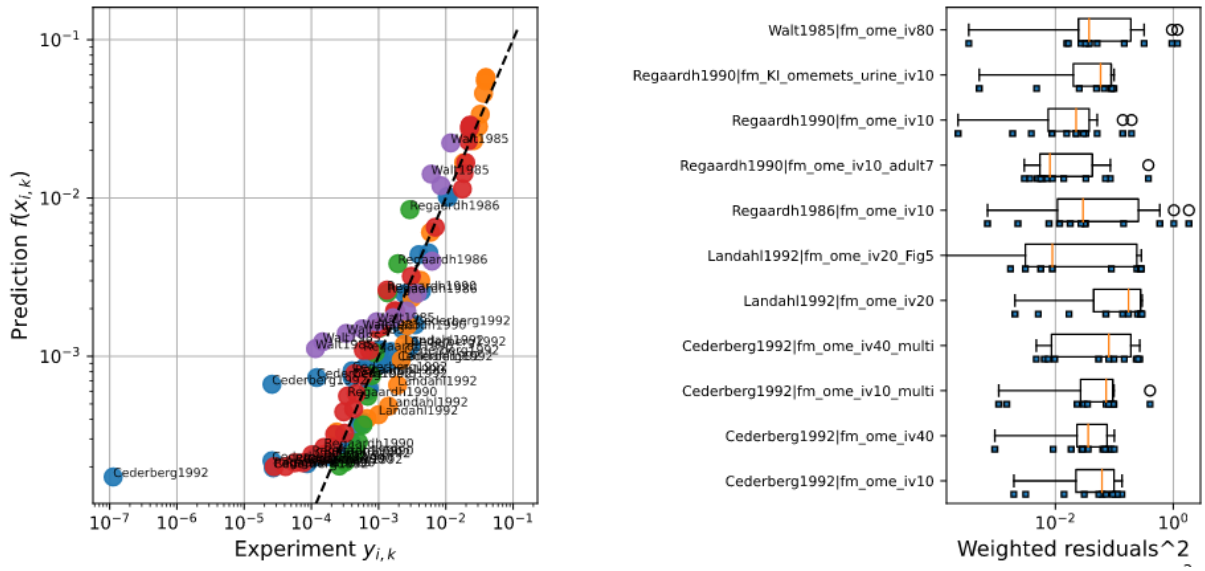

Figure 5: Parameter fitting results of intravenous studies. A) Predicted versus experimental data. A good agreement can be found between experimental data and model predictions. Only outlier is a single data point from Cederberg1992 at very low concentrations. **B)** Weighted residuals of the optimal parameter fit. All intravenous datasets contributed similar to the parameter fit. The resulting fitted intravenous parameters are listed in **Table 2**.

3.4 Model performance

The performance of the model for prediction of omeprazole pharmacokinetics was evaluated by comparing the model simulations with the data. The results for the single doses are reported in Section 3.4.1, the results for multiple doses in Section 3.4.2 and in Section 6 (Supplement).

3.4.1. Model performance single dose

The following studies were used for the evaluation of single dose omeprazole treatment Cederberg1992 (iv10, iv40, po20), Landahl1992 (iv20, po40), Lind1983 (po40), Prichard1985 (po40), Regaardh1986 (iv10, po20), Regaardh1990 (iv10, po20) , Walt1985 (iv80) were selected.

Cederberg1992

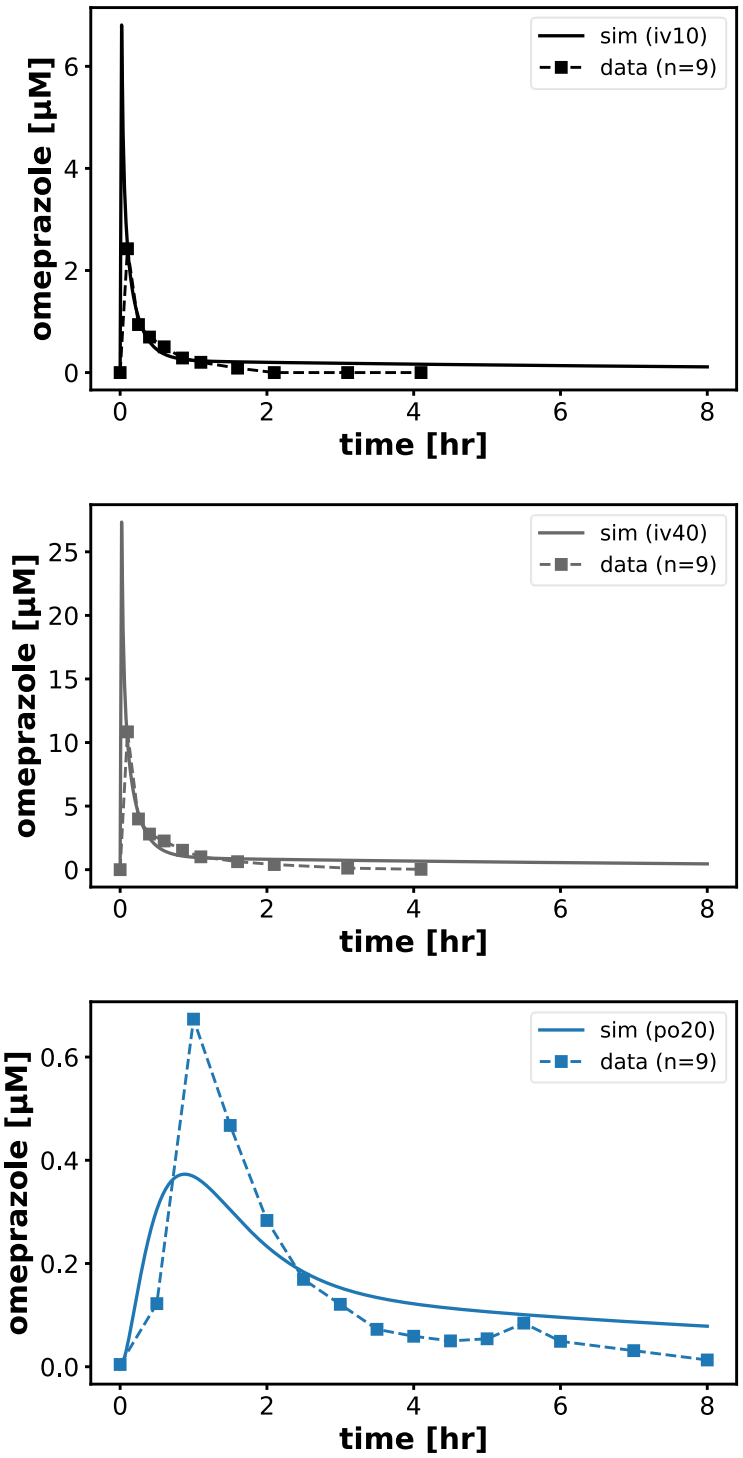

Figure 6: Simulation experiment Cederberg1992. For various dosing protocols the omeprazole plasma concentrations predicted by the developed model and the curated clinical data from Cederberg1992 [7] are compared. The single intravenous administration of omeprazole with 10 mg and 40 mg each and a single administration of 20 mg oral omeprazole are shown. The data come from 9 adult volunteers with duodenal ulcers.

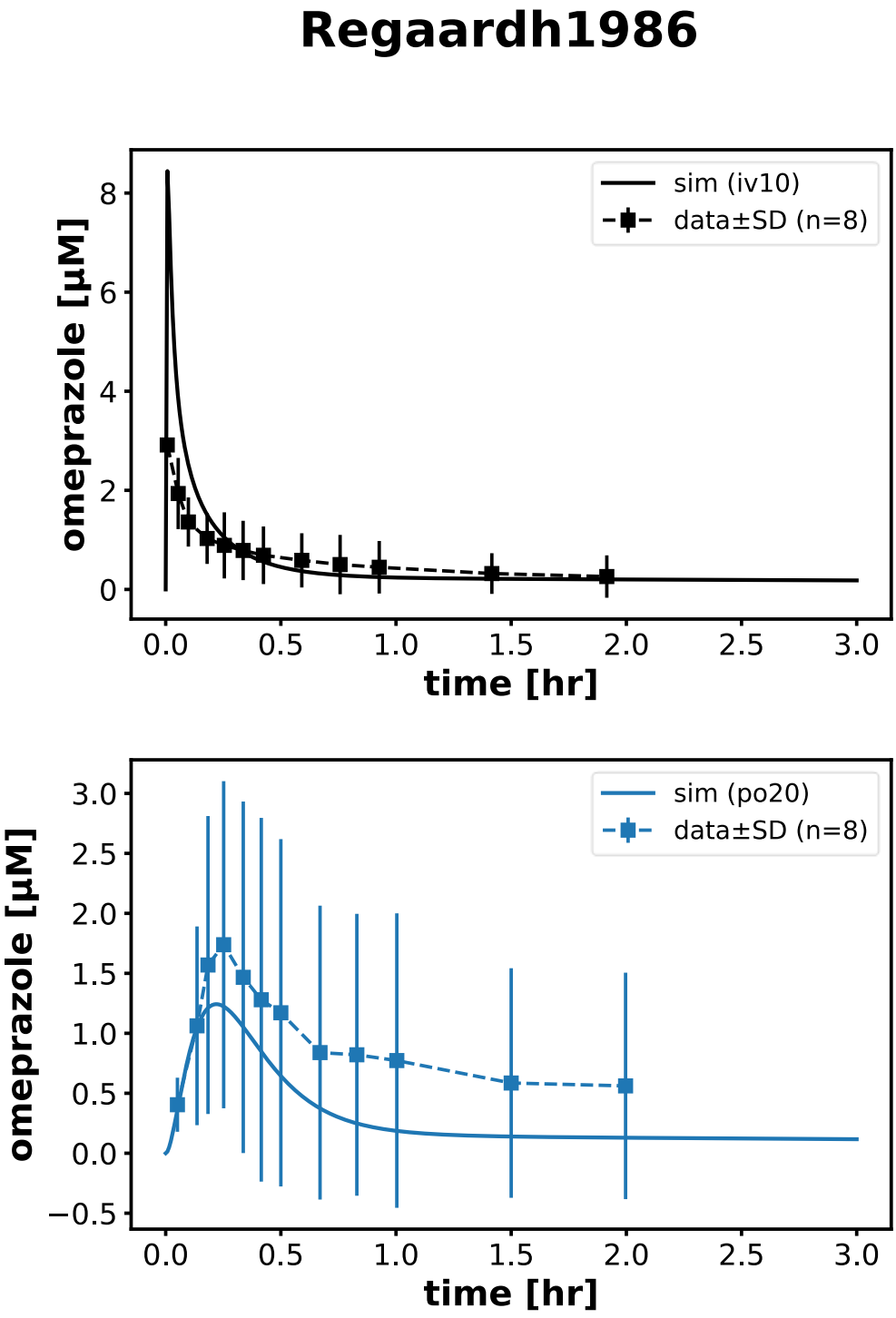

Figure 7: Simulation experiment Regaardh1986. For various dosing protocols the omeprazole plasma concentrations predicted by the developed model and the curated clinical data from Regaardh1986 [33] are compared. The single intravenous administration of omeprazole with 10 mg and 40 mg each and a single administration of 20 mg oral omeprazole are shown. The data come from 8 healthy adult volunteers.

The time course of plasma omeprazole was compared to the respective experimental data in the single application experiments. In addition, the accumulation of omeprazole metabolites in urine was compared in the experiments by Landahl1992 and Regaardh1990. For the simulations, the respective dose and application route of omeprazole and the number (n) of subjects were set in the simulation experiments. In addition, the information on the application form (solution or hard capsule) was used to adapt the fraction absorbed. The results of representative single dose simulations are depicted in **Figure 6** and **Figure 7**, with the remaining simulations in section 6 (Supplement).
The solid line represents the time course prediction by the PBPK/PD model, and the dashed line shows the corresponding data from the curated studies. In general, we see a good agreement between the model prediction and data. When comparing the time curves of intravenous and oral applications, it can be seen that after intravenous application, the plasma omeprazole peak is reached immediately after application and is subsequently eliminated from the blood very rapidly. The oral dose has a delayed start to the increase in concentration and a less pronounced increase until the peak is reached, but higher concentrations of omeprazole can be found even after a few hours. This is due to the relatively slow absorption rate.
Furthermore, the intravenous doses reach much higher maximal concentration values than the oral dose, both in the simulation experiments and studies. The reasons for this have already been mentioned in Section 1.3 since the intravenous dose is not subject to a first-pass effect, whereas the oral dose must first be absorbed in the intestine, and some of the concentration is lost in the process. Also, the maximum peak is not as high as in rapid intravenous application due to the slow absorption rate. The results show that the pharmacokinetics model is in good agreement with experimental data after single dose applications. Whereas all intravenous data could be described very well with a single parameter set and is in very good agreement for all studies with the model predictions, the prediction of oral data was much more challenging (see Supplementary figures). A major challenge was the highly heterogeneous application form of omeprazole in the various studies, which was often not reported in sufficient detail. Depending on the formulation, such as hard capsules, powder, soft capsules or solution, very different absorption kinetics can be expected. Formulations protecting from the stomach acid are not affected by the stomach's pH-dependent degradation, and much larger fractions can be absorbed. Fitting individual dissolution and absorption parameters per study substantially improved the agreement between model prediction and oral data. However, certain studies could not be fitted well, such as Prichard1985.

3.4.2. Model performance multiple dose

In a next step, the effect of multiple dosing was simulated using the following studies: Cederberg1992 (iv10multi, iv40multi, po20multi), Prichard1985 (po40multi), Vazdasilva2001 (po20multi), Vazdasilva2005 (po20multi).
For the model performance of the multiple dosing experiments, analogous to single application experiments, the model predictions were compared to experimental data (representative example in **Figure 8** with all simulations in Section 6). The model predictions are in very good agreement with experimental data in the case of multiple intravenous applications. In the simulation experiment of Cederberg1992, omeprazole was administered every 24 hours for four days, and the plasma concentration in the blood was measured. For the oral application, the same limitations exist as in the single dose application, i.e., highly heterogeneous responses due to the large variability in formulations.

Cederberg1992

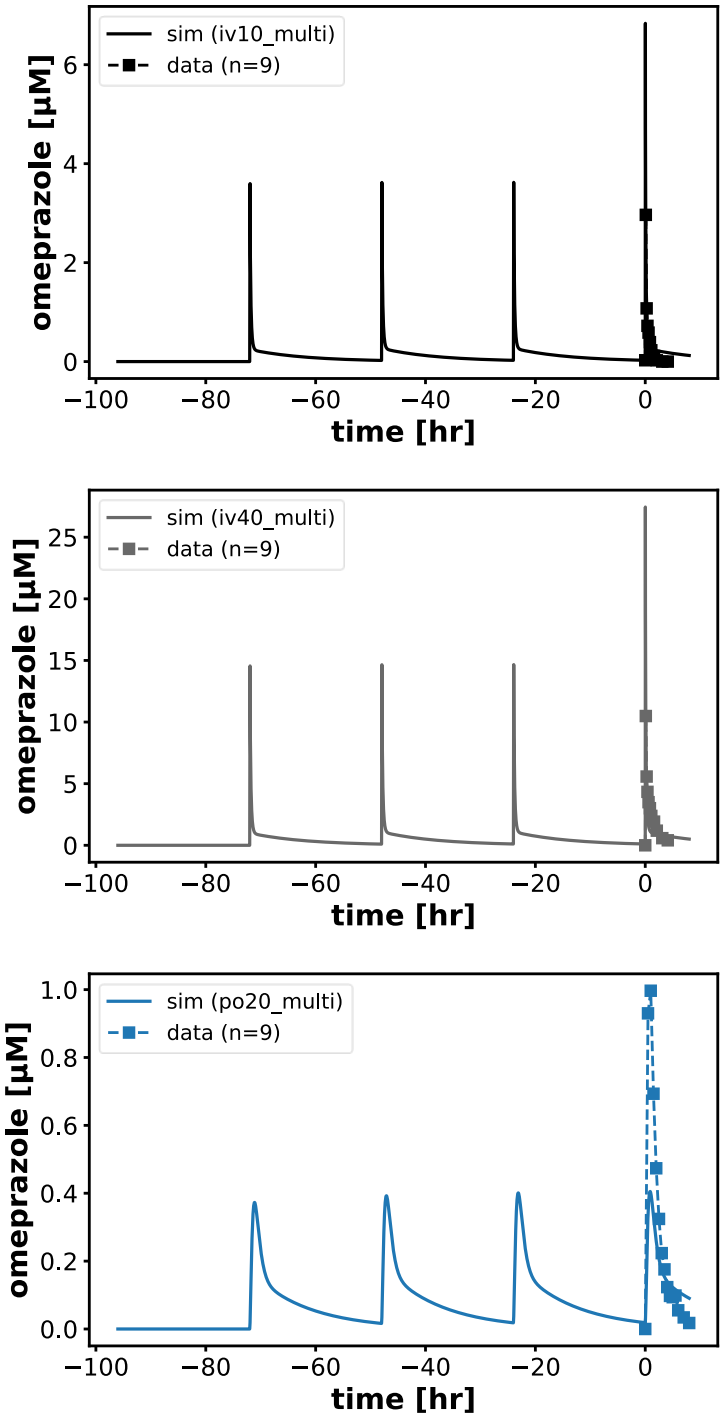

Figure 8: Simulation Experiment Cederberg1992. For various dosing protocols the omeprazole plasma concentrations predicted by the developed model and the curated clinical data from Cederberg1992 [7] are compared. The multiple intravenous administration of omeprazole with 10 mg and 40 mg each and a multiple administration of 20 mg oral omeprazole are shown. The data come from 9 adult volunteers with duodenal ulcers.

3.5 Model application

To evaluate the developed PBPK/PD model, it was tested if the pharmacokinetic and pharmacodynamic properties of omeprazole described in Sections 1.2, 1.3, 1.4, and 1.5 could be correctly represented. For this purpose, three core aspects of the model were checked in the following application experiments: i) Single oral and intravenous applications of omeprazole were compared to study the first path effect, i.e., a reduction in bioavailability due to omeprazole degradation in the stomach, and the difference in increasing stomach pH (Section 3.5.1). ii) Repeated dosing with oral or intravenous omeprazole to evaluate the dose potentiation effect due to changes in stomach pH and the fraction absorbed (Section 3.5.2). iii) Evaluation of the model to reduce stomach pH for different doses, oral and intravenous application, and single and multiple application (Section 3.5.3)

3.5.1 Oral vs. intravenous application

First the effect of oral vs. intravenous application of single doses of omeprazole was tested. The results of the simulation with a single application of 40 mg omeprazole are shown in **Figure 9**:

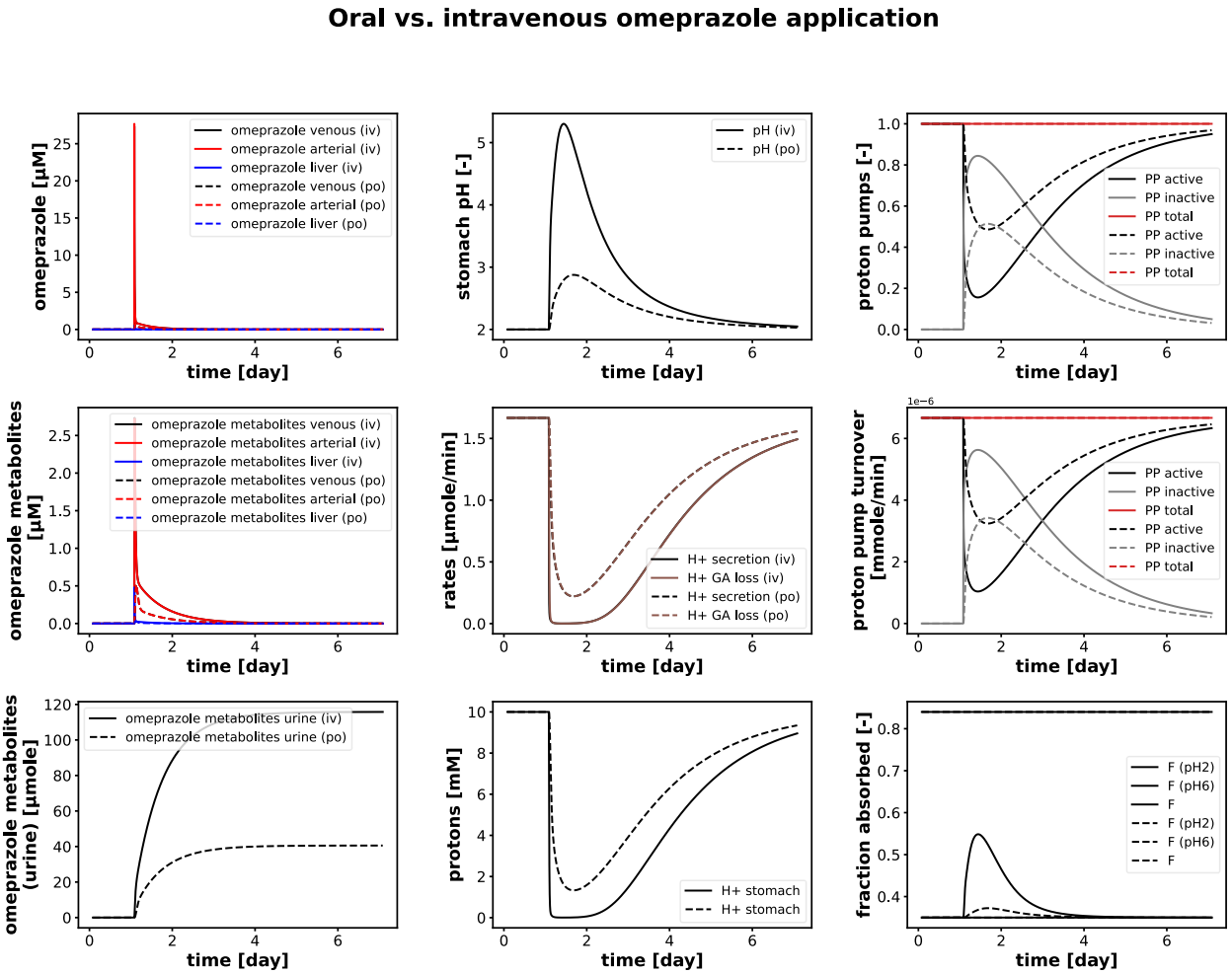

Figure 9: Single oral vs. intravenous dose of omeprazole. Simulations for the intravenous dose (solid) and oral dose (dashed) are compared. The following model readouts are depicted: omeprazole plasma concentration, stomach pH, active and inactive proton pumps, omeprazole metabolites plasma concentration, the rates at which protons are secreted into the gastric lumen, the proton pump turnover, the amount of omeprazole metabolites in urine, the amount of protons in gastric acid, and the fraction of omeprazole absorbed.

Multiple differences can be observed between oral (dashed) and intravenous (solid) single application of omeprazole on day 1. The model shows a steady-state stomach pH of 2 in line with typical observed values of pH 1-3 in healthy subjects. Both after intravenous and oral omeprazole, the pH increases rapidly, with peaks reached within a few hours after application reaching pH 3 in the oral case and > pH 5 in the intravenous case. Despite the fast half-life of omeprazole of a few hours (see **Figure 6, 7, 8**), the pH takes 4-5 days to go back to baseline. The maximal effect on the stomach pH of an oral dose is much smaller than the intravenous dose, mainly due to the reduced fraction absorbed, ranging from losing around one third of the dose in the stomach. The smaller dose reaching the systemic circulation in case of oral application is reflected by the much lower amounts of omeprazole metabolites in the urine. The increase in stomach pH is due to the inactivation of proton pumps reaching up to 80% in case of intravenous omeprazole and up to 50% in case of an oral application. Due to the turnover of the proton pumps the inactive proton pumps are in the cause of a few days replayed with newly synthesized active proton pumps. The change in stomach pH is a direct consequence of the inhibition of the proton pumps, which can secret less protons in the stomach resulting in fewer protons in the stomach and a lower pH. Importantly the change of stomach pH also changes the possible fraction absorbed of future oral omeprazole doses by modifying the pH dependent decay of omeprazole in the stomach. Both iv and oral omeprazole change the fraction absorbed with iv, having a stronger effect, i.e., a larger fraction of an oral dose following an iv dose is decaying than when following an oral dose. A maximum fraction absorbed of 0.85 is assumed for omeprazole at a relatively neutral pH value of 6, and this value is the same for both intravenous and oral dosing. However, if the pH value is in the acidic range, in this case, pH 2, the fraction absorbed rate of omeprazole is strongly reduced in the model, namely to 0.25-0.3. After application of omeprazole this value is increased in the intravenous case to approximately 0.55, or in the case of a single application of an oral dose, a value of a maximum of 0.4 is reached. Only after five days, after the effect of omeprazole on the stomach pH has worn off, the fraction absorbed return to baseline. I.e., a long lasting potentiation effect of omeprazole on future omeprazole doses is predicted by the model in line with reported data.
Because the intravenous dose is not subject to a first-pass effect and the total omeprazole dose reaches the systemic circulation, a more potentiation effect is expected for oral doses following intravenous doses.

3.5.2 Dose potentiation in repeated dosing

Next the dose potentiation effect after repeated dosing was evaluated. Multiple doses of either oral or intravenous omeprazole were applied, and model readouts were compared (**Figure 10**).

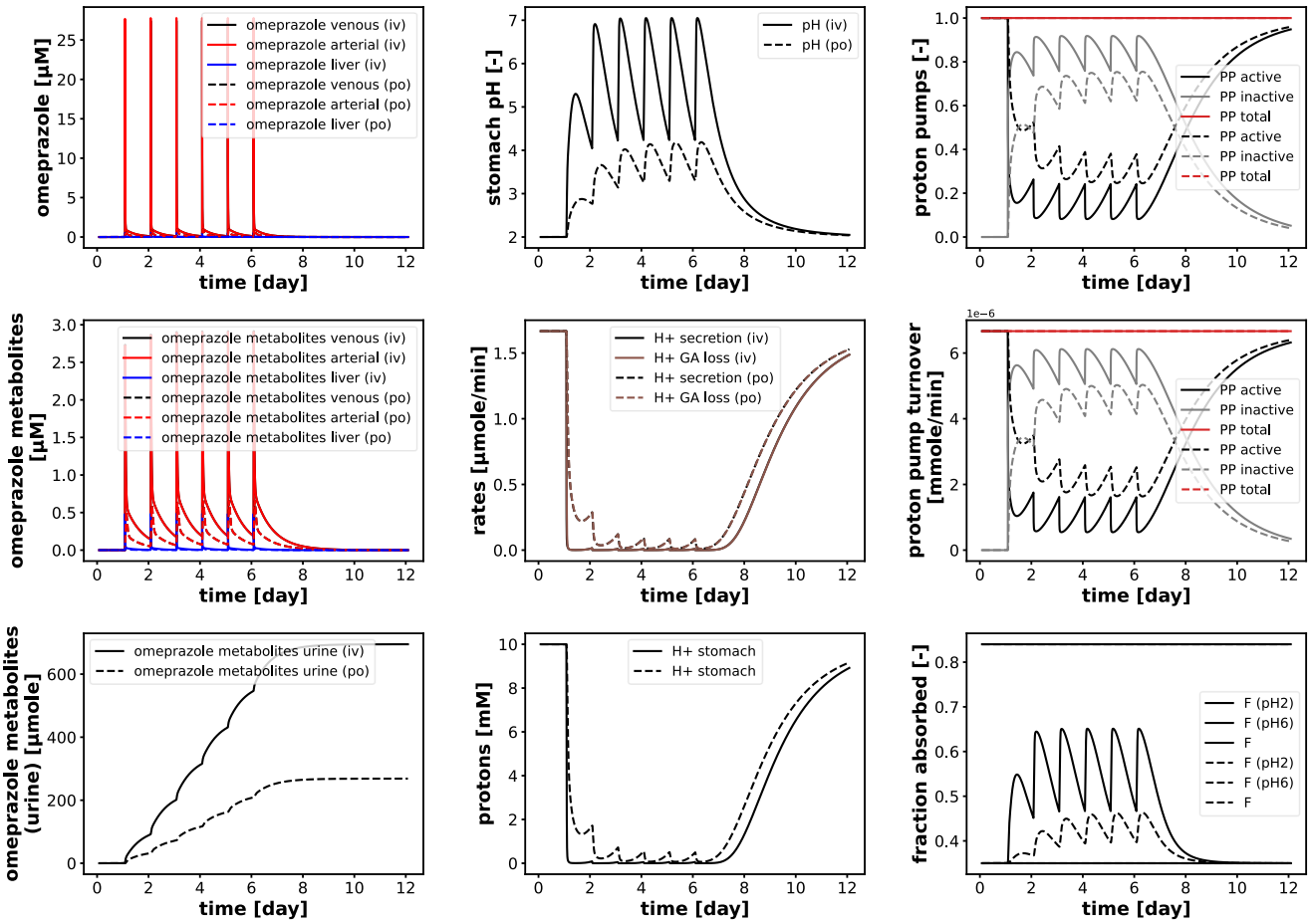

Figure 10 : Single application vs. multiple dose of omeprazole. Simulations for the intravenous dose (solid) and oral dose (dashed) are compared. The following model readouts are depicted: omeprazole plasma concentration, stomach pH, active and inactive proton pumps, omeprazole metabolites plasma concentration, the rates at which protons are secreted into the gastric lumen, the proton pump turnover, the amount of omeprazole metabolites in urine, the amount of protons in gastric acid, and the fraction of omeprazole absorbed.

As in the single application a much higher increase in stomach pH can be observed after intravenous omeprazole compared to oral omeprazole due to reduced fraction of omeprazole reaching the systemic circulation. For both oral and intravenous application a dose potentiation of subsequent doses can be observed with a stabil dosing response reached in the intravenous case after around three applications and in the oral case after around five applications of omeprazole. The slow turnover of the proton pumps results in a dose potentiation because the inactivation effect of subsequent daily doses can add up. The additional dose potentiation in the oral application on top of the turnover effect is due to the increasing fraction absorbed with increasing stomach pH values. A stable fraction absorbed is only reached after a few days. Due to the slow turnover of the proton pumps the effect of omeprazole on stomach pH is long lasting (a few days). Due to the dose potentiation a stomach pH of 7 is reached after multiple iv doses compared to pH 5 after single doses and pH 4 compared to pH 3 after multiple oral doses.

3.5.3 Changes in stomach pH depending on dose and application form

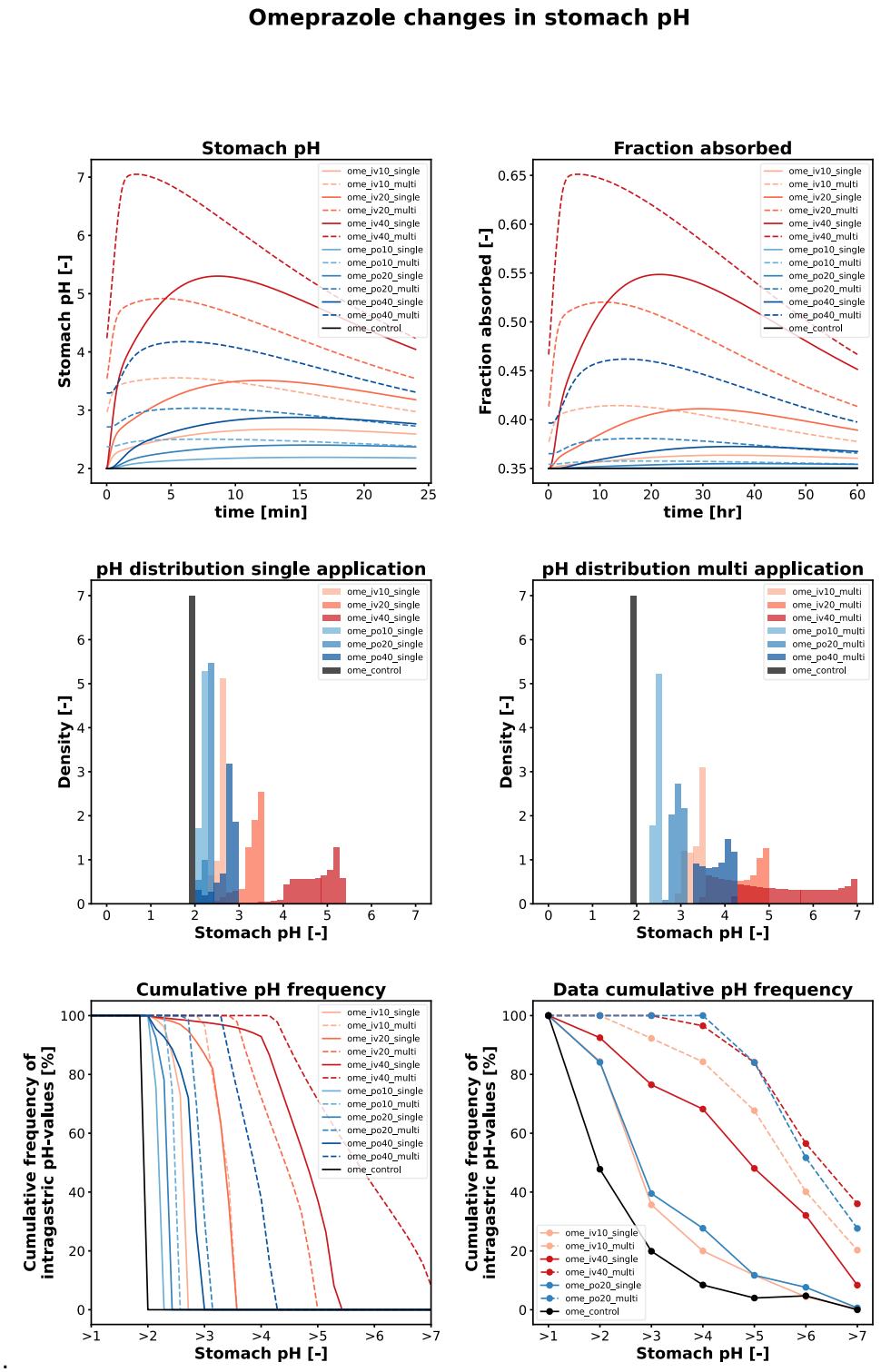

Figure 11 : Changes in stomach pH after various single and multiple oral and intravenous omeprazole doses. Omeprazole iv and po doses of 10, 20 and 40 mg were simulated after single application and on day 5 of multiple application. Simulations were compared against data from Cederberg1992. Different colors represent the three intravenous (red) and oral (blue) doses of omeprazole with single applications as solid lines and multiple applications as dashed lines. Depicted are the simulated time courses of stomach pH and fraction absorbed, a histogram of the stomach pH values under single and multiple applications, and the cumulative pH frequency reported by Cederberg1992.

The following main results can be observed in line with the experimental data: With increasing dose, the stomach pH is increasing for single as well as multiple applications, for oral as well as intravenous application. A strong dose potentiation exists for omeprazole with multiple doses having a stronger increase in pH than single doses for intravenous and oral application. Intravenous application has a stronger effect than the corresponding oral application, mainly due to the loss during absorption. The predicted cumulative pH frequencies are in line with the experimentally observed changes by Cederberg1992. An important difference is much more significant heterogeneity in stomach pH values in the experimental data compared to the model predictions. The main reason is a daily fluctuation in stomach pH values, mainly due to food uptake, which is not considered in the model.

3.6 Summary

Within this thesis, the pharmacokinetics and pharmacodynamics of omeprazole were studied using a computational modeling approach. For this purpose, a detailed analysis of clinical studies was carried out, of which the data from 14 clinical studies were curated and digitized. Based on this data, a PBPK/PD model was developed to study the effect of oral vs. intravenous and single vs. multiple application of omeprazole. The model equations include a pH dependent fraction absorbed of omeprazole and an omeprazole dependent inhibition of proton pumps. The curated time course information of omeprazole in plasma and omeprazole metabolites in urine was used for parameter fitting. The model was applied to investigate the differences between i) oral and intravenous omeprazole application; ii) the effects of a single application of omeprazole and a repeated application on the plasma concentration and the change in stomach pH. The model was applied to study the main questions of this thesis: i) how gastric acid output and pH change with omeprazole dosing and treatment regime, and ii) what the effects of repeated dosing on omeprazole absorption and pH are. In summary, based on the assumptions that omeprazole is degraded pH dependent in the stomach (fraction absorbed), omeprazole inhibits the H^+/K^+-ATPase irreversibly, and that continuous turnover of the H^+/K^+-ATPase exists a multitude of data and phenomena could be explained by the model.

4 Discussion

4.1 Data

In order to build the PBPK/PD model, data from clinical studies were required for model parameterization and evaluation. An important outcome of this work is a high-quality dataset of omeprazole pharmacokinetics freely available for scientific reuse from the pharmacokinetics database PK-DB. Many aspects were important for collecting and curating the omeprazole data set. Most of the curated studies date from the 80s and 90s, as the research on omeprazole was at its peak shortly after its discovery. Many of the key publications characterizing the pharmacokinetics and pharmacodynamics of omeprazole were published in these years. Secondary aspects such as drug-drug interaction were only assessed in later clinical studies. Data curation focused on studies with omeprazole time curves and corresponding pharmacokinetic parameters in healthy human subjects. Liver and kidney disease can strongly influence the pharmacokinetics of substances, so that corresponding studies were excluded from the modeling workflow. Two of the 14 curated studies also examined subjects with duodenal ulcers. Since omeprazole is used for precisely such diseases, these were included in the curation process. The pharmacokinetics should not be altered in these subjects, but pharmacodynamics could be affected. Consequently, only pharmacokinetics data was used from the duodenal ulcers subjects in the modeling process. Another important aspect was the inclusion of studies that report both intravenous and oral administration of omeprazole. In order to assess the influence of the dosage form (solution, hard capsule, powder) on the time curves and finally correct it in the parameter fitting, a heterogeneous selection of application forms was of relevance (see **Table 3**). An additional consideration was the focus on studies in which the test persons had consumed the omeprazole in a fasting state because food consumption can markedly change absorption kinetics (pharmacokinetics) and stomach pH (pharmacodynamics). An essential outcome was observing that the intravenous data were highly consistent between studies and could be described with a single parameter set. In contrast, the oral data was very heterogeneous, mainly due to the large variability in the application form.

4.2 Model validation

The main outcome of this work is a PBPK/PD model of omeprazole able to correctly describe many aspects and phenomena of the pharmacokinetics and pharmacodynamics of omeprazole.
The following key assumptions were made for the model: i) omeprazole can be degraded pH-dependent in the stomach; ii) omeprazole inhibits the H^+/K^+-ATPase irreversibly; and iii) continuous turnover of the H^+/K^+-ATPase, exists. The assumptions were successfully implemented in the model and allowed to recapitulate important aspects of omeprazole pharmacodynamics successfully.
The model predictions (Section 3.4 and 3.5) are in good agreement with the pharmacokinetic and pharmacodynamic data. Intravenous pharmacokinetics of omeprazole can be described very well by the model for single and multiple applications of various doses. In contrast, some of the oral pharmacokinetics are in very good agreement with the data, whereas other studies could not be well predicted. The main limitation was hereby the often missing details on the omeprazole formulation. The formulation of a drug strongly affects its absorption kinetics and determines how much of the substance is already released in the stomach or only later in the intestine. This information is especially relevant for omeprazole with a pH-dependent degradation in the stomach. This work tried to account for the

differences between the oral studies by fitting individual absorption and dissolution parameters per study. This strategy resulted in much better agreement between model predictions and oral data than a single parameter set. An important information is an actual fraction absorbed per formulation, which was not part of the parameter fit but was either assumed to be 1 (completely absorbed) in case of hard capsules or calculated based on the pH dependent fraction absorbed otherwise.
An essential result of this work was that the model could successfully demonstrate the multiple dosing effects. The model performance can be seen in Section 3.5.2 and shows that the stomach pH, as in the clinical studies, increases with subsequent doses and reaches a stable dosing regime after three to five days. Dose potentiation in multiple dosing is due to the slow turnover of the protein pumps in combination with pH dependent fraction absorbed in case of multiple oral dosing. The long-lasting increase in stomach pH over multiple days potentiated in multiple dosing can have important effects on the absorption of other medications. Even days after omeprazole uptake, other pH-labile drugs can be markedly affected in their absorption and bioavailability. Omeprazole can therefore result in important drug-drug interactions (not only based on the cytochrome P450 involved in its metabolism) but also due to alterations of absorption kinetics.
A limitation of the presented work is that no independent validation data was used for model evaluation, but all pharmacokinetics data was used for parameter fitting. Furthermore, the pharmacodynamics effects were only compared qualitatively.

4.3 Model simplifications and assumptions

Various aspects were not included in the presented model, and multiple simplifications and assumptions had to be performed. For instance, no first pass metabolism of omeprazole by CYP3A4 in the intestine was included, whereas, in reality, part of the omeprazole reaching the intestine is already metabolized there. Another aspect, already mentioned in Section 1.5, was that the increased bioavailability of omeprazole after multiple dosing was modeled based on the assumption of acid lability of omeprazole. The second possible explanation that the increased bioavailability is due to an auto-inhibition of omeprazole metabolism by omeprazole was not part of the model. It should be mentioned that the second explanation was the results from the Cederberg1992 study, where a significantly increased AUC value of more than 80% from 10 to 40 mg IV dose could be observed. This result could not be explained by the acid lability, as this only applies to oral and non-intravenous doses. Drugs that exhibit pH instability in the acidic range, as in the case of omeprazole, are often encapsulated in an enteric-coated hard gelatin capsule to increase the bioavailability of the drug. The time of onset of action of the drug is delayed by the coating [38]. For the dose potentiation effect of an oral dose with a hard capsule, no effect is noticeable because, in the model, an absorption of 100% is assumed. This represents a further simplification of the model since the different omeprazole formulations would have to be broken down more precisely. As shown in **Table 3** , hard capsules were used for oral administration in the case of oral dosages. In addition, the inclusion of the application via buffered solution and powder would be helpful for future models in order to obtain more realistic results after oral application.
In addition, the hepatic metabolism of omeprazole (in Section 1.2) was simplified in the model. The conversion of omeprazole in its active form into the primary two forms via the two enzymes CYP2C19 and CYP3A4, omeprazole sulfone, and hydroxyomeprazole, were not modeled in detail. For simplification, these steps were simplified via a single CYP catalyzed conversion of omeprazole to omeprazole metabolites.

Simple irreversible Michaelis Menten equations or mass-action kinetics were used to model transport and metabolic processes. The passive transport of omeprazole in the Parietal cells via diffusion was not included in the model.
An important modulator of stomach pH is food. According to clinical studies, the effectiveness of omeprazole based on the duration of the pH value change in the fasting state is more than twice as high as in non-fasting subjects [11]. Depending on the time of the last food intake and its composition, the pH value strongly fluctuates during the day. These daily fluctuations were not considered in the model, but a constant pH 2 was assumed. As reported in various studies, the daily fluctuation in stomach pH is further complicated due to a circadian rhythm of gastric acid secretion. Typically, acid secretion is more active in the evening than in the morning [26, 27]. Neither food uptake nor circadian rhythmicity was included in the model.

4.4 Future direction of research

Within this thesis, we developed a PBPK/PD model of omeprazole in healthy human subjects and applied it to study essential questions such as dose potentiation in multiple dosing.
Future work could expand the model. One possibility to expand the model would be to include the aspect that omeprazole is a racemate. Omeprazole exists in both its R-form and S-form, with the S-enantiomer having a more significant effect on pharmacokinetics and pharmacodynamics. The S-form (esomeprazole) is even offered as a single PPI and was only discovered a few years later after the development of omeprazole [5]. By including this division of the racemate aspect into S-form and R-form, the results in the model could be specified more precisely.
Another interesting extension would be modeling the effect of food uptake and circadian rhythm on pH to more realistically describe the daily variations in stomach pH. Importantly the metabolism of omeprazole was highly simplified in the model, and a more detailed description of intestinal first pass metabolism and alternative routes and metabolites in the liver could provide important insights. An extended metabolic model could also be applied to test the alternative explanation that omeprazole inhibits its metabolism.
Notably, many aspects of the developed model are not specific for omeprazole but could be directly applied to study other proton pump inhibitors, e.g., the mode of action of drugs such as esomeprazole or pantoprazole). The PPIs all work according to the exact underlying mechanism, which would allow reusing the presented pharmacodynamics model of PP turnover and PP inhibition.
Further possibilities to expand this work would be the modeling of drug-drug interactions. One possibility would be modeling the effectiveness, absorption, activity, and the change in the pH value when taking another drug at the same time which interacts with omeprazole metabolism or studies the effect of altered pH on absorption of other drugs.

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6 Supplement

Single dosing simulation experiments

Regaardh1990

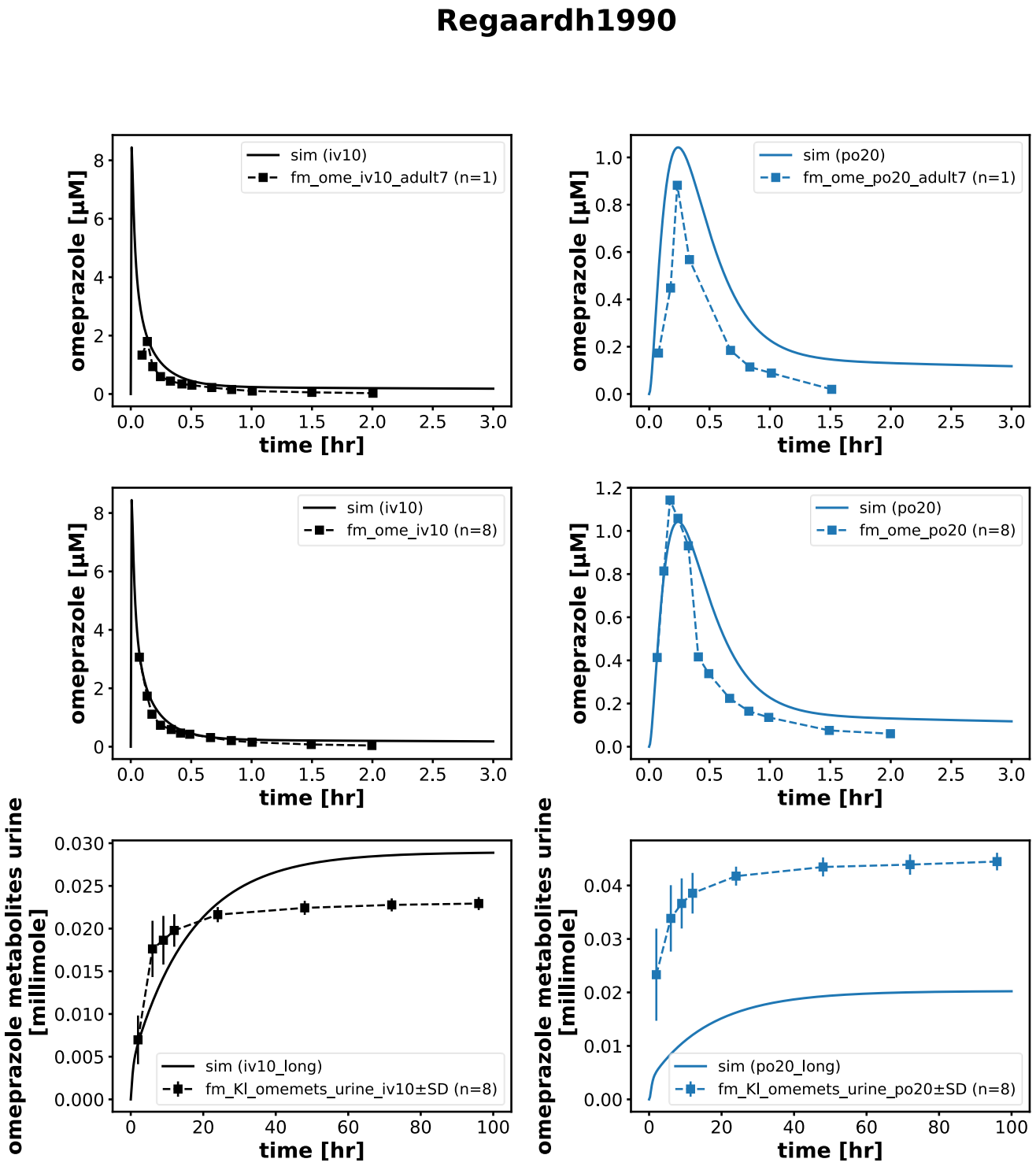

Figure 11: Simulation experiment Regaard1990. The concentration of omeprazole over time and the cumulative excretion of metabolites are shown. Solid line represents the prediction and dashed line the data from the clinical study [34].

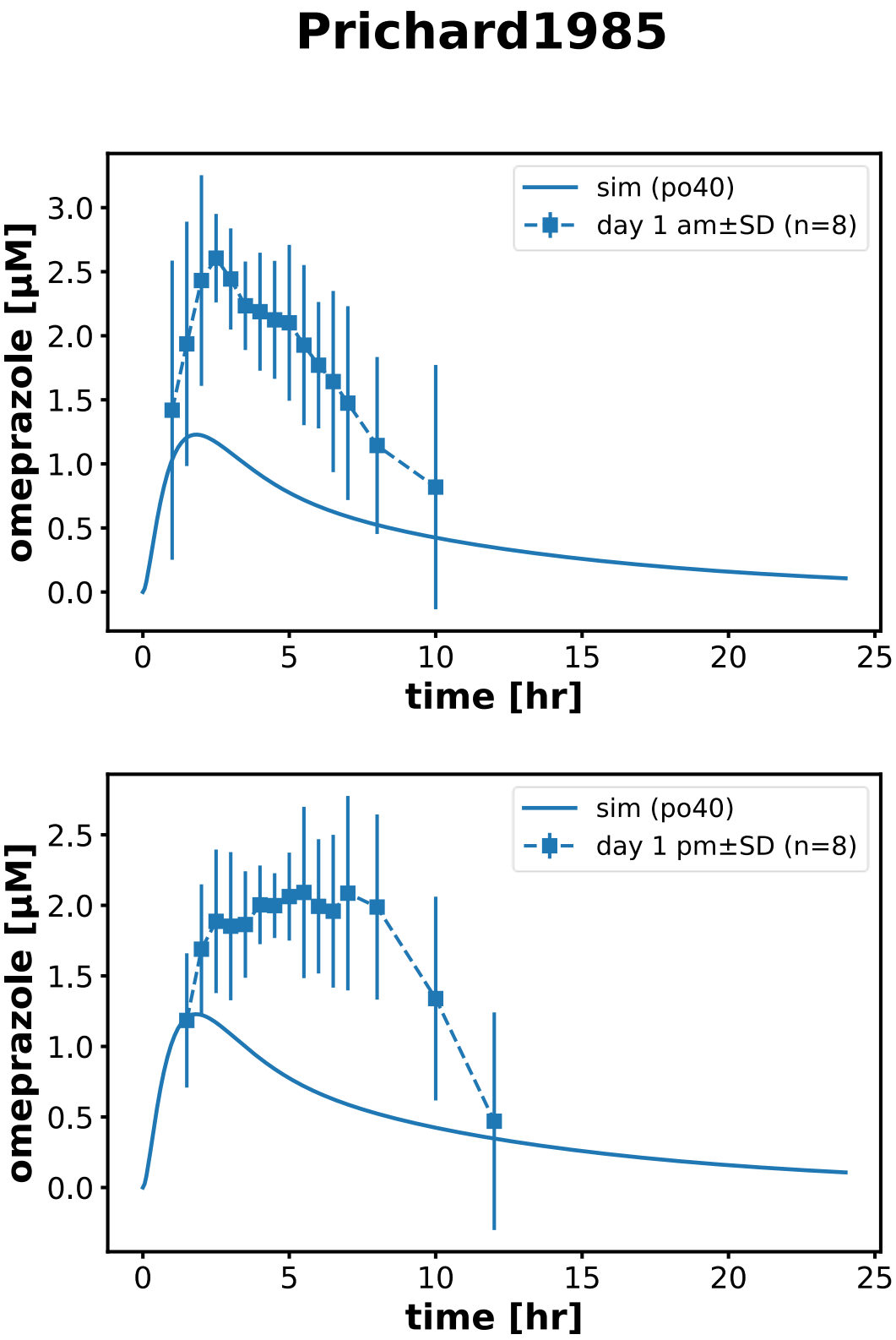

Figure 12: Simulation experiment Prichard1985. The concentration of omeprazole over time is shown in the graph. Solid line represents the prediction and dashed line the data from the clinical study [32].

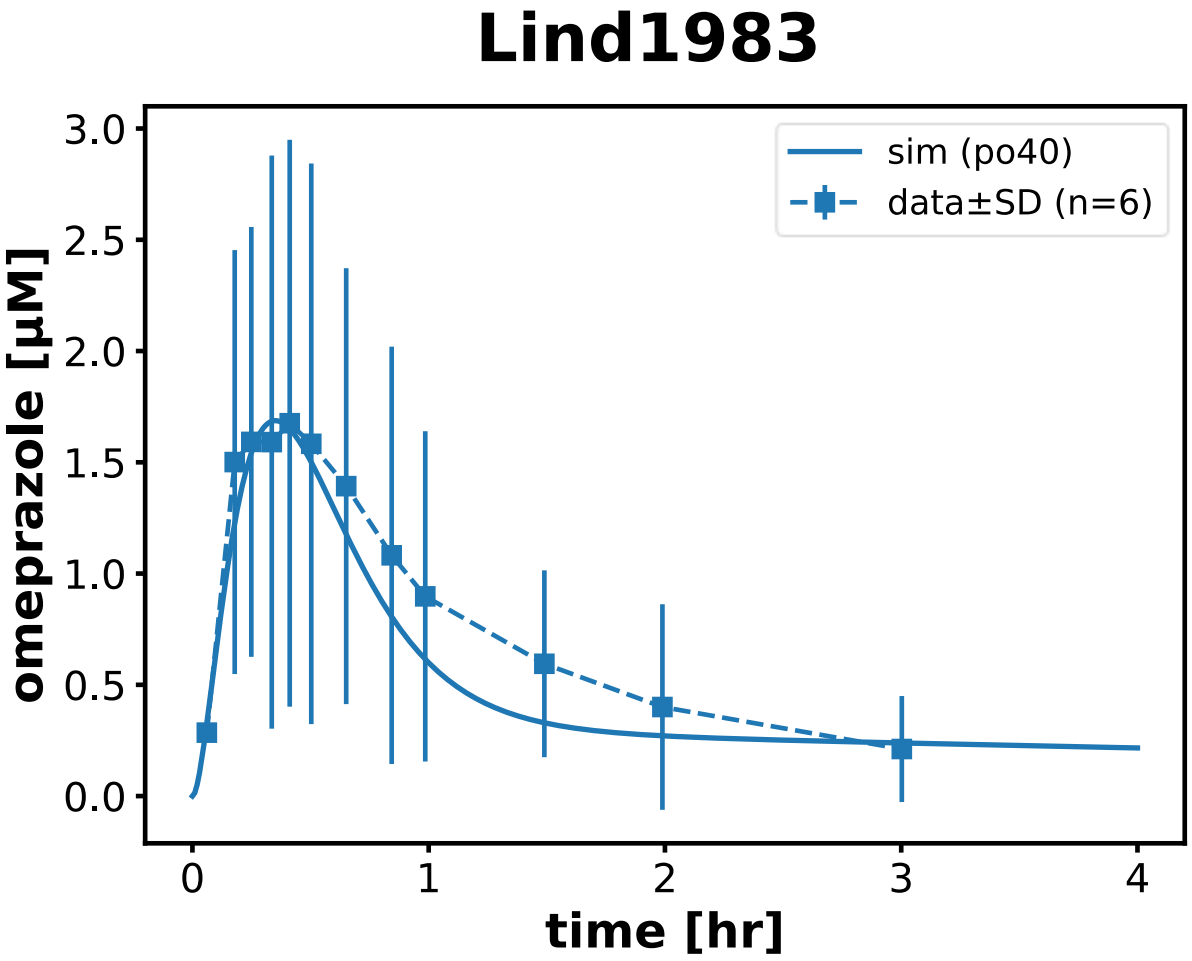

Figure 13: Simulation experiment Lind1983. The concentration of omeprazole over time is shown in the graph. Solid line represents the prediction and dashed line the data from the clinical study [19].

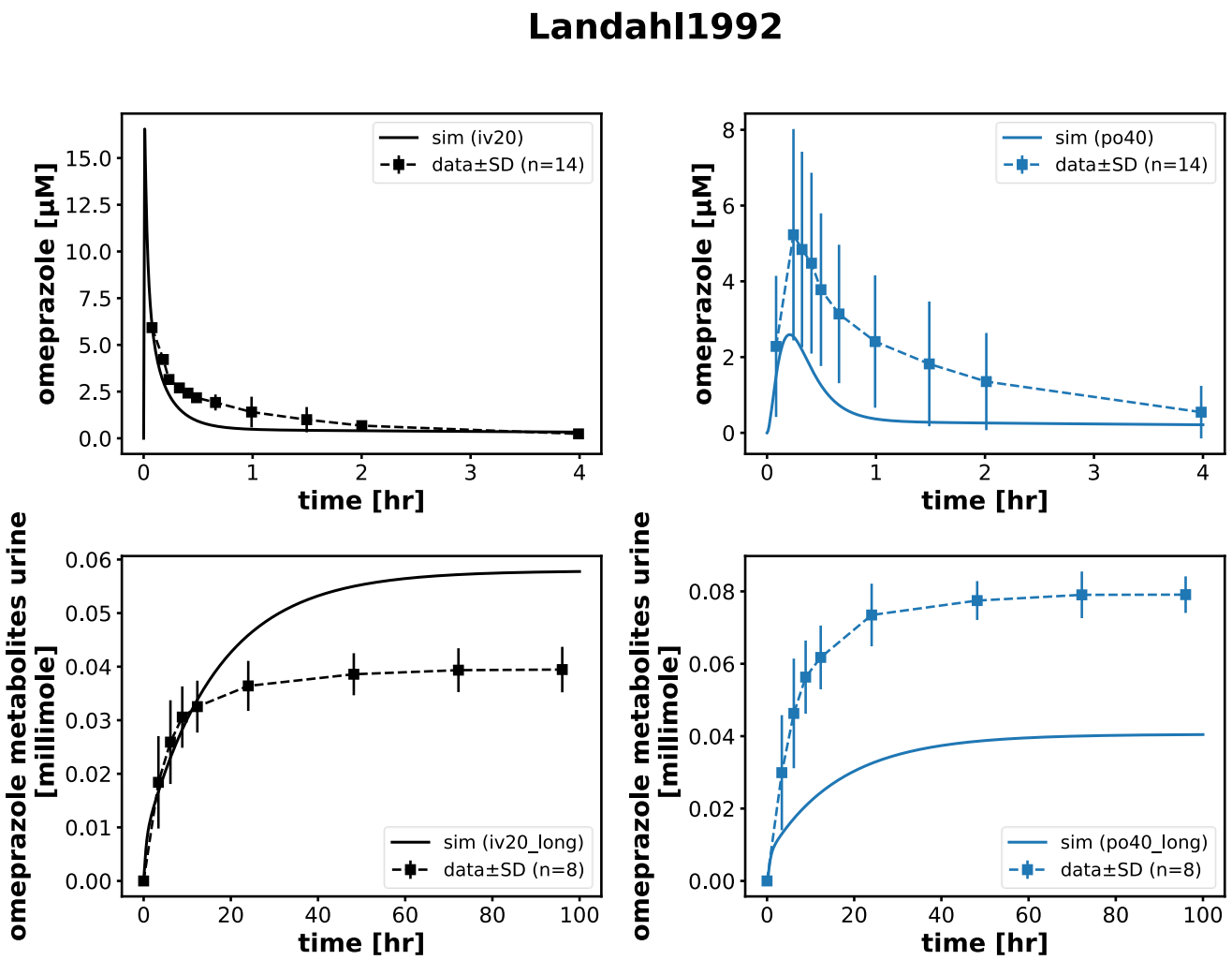

Figure 14: Simulation experiment Landahl1992. The concentration of omeprazole over time and the cumulative excretion of metabolites are shown Solid line represents the prediction and dashed line the data from the clinical study [18].

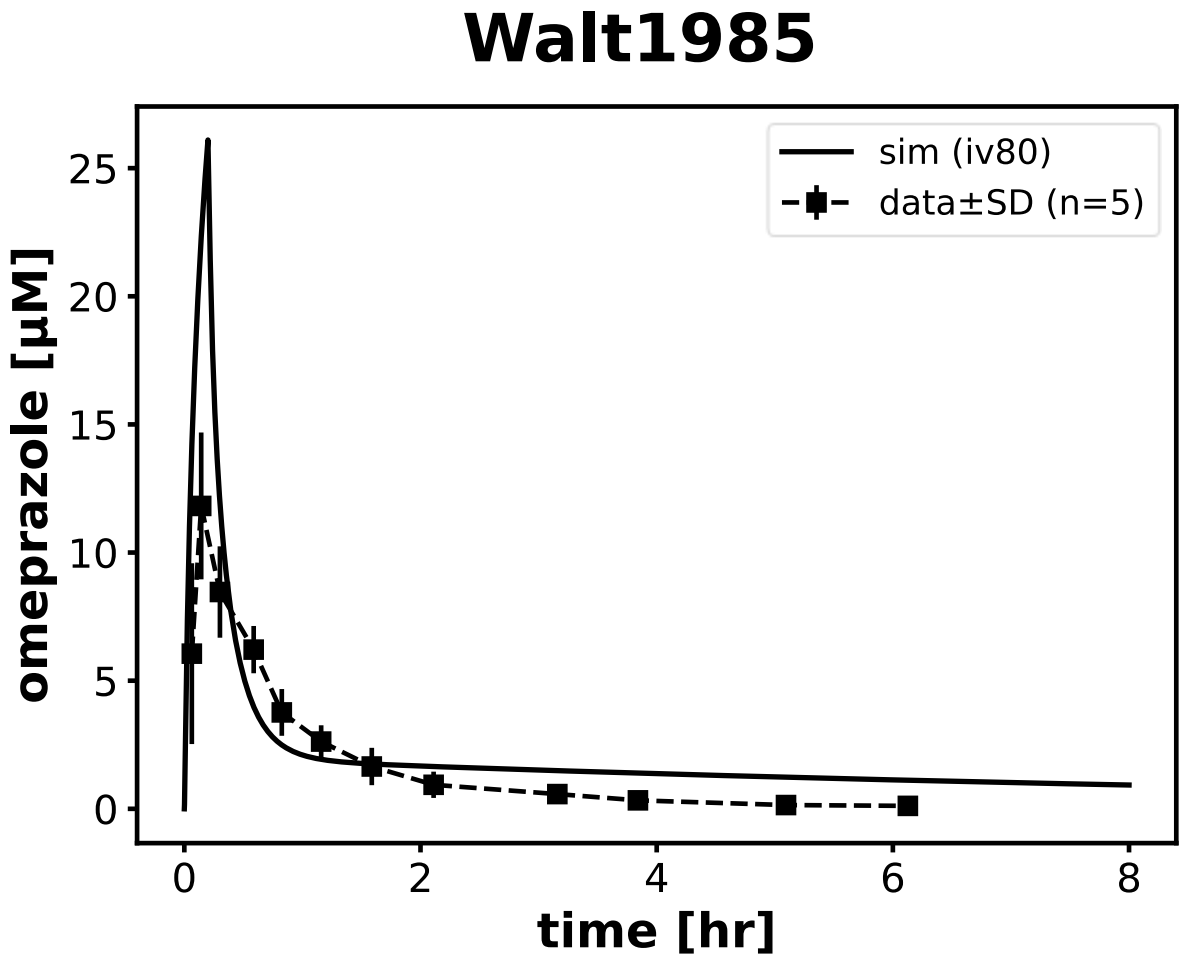

Figure 15: Simulation experiment Walt1985. The concentration of omeprazole over time is shown in the graph. Solid line represents the prediction and dashed line the data from the clinical study [43].

Multiple dosing simulation experiments

Prichard1985

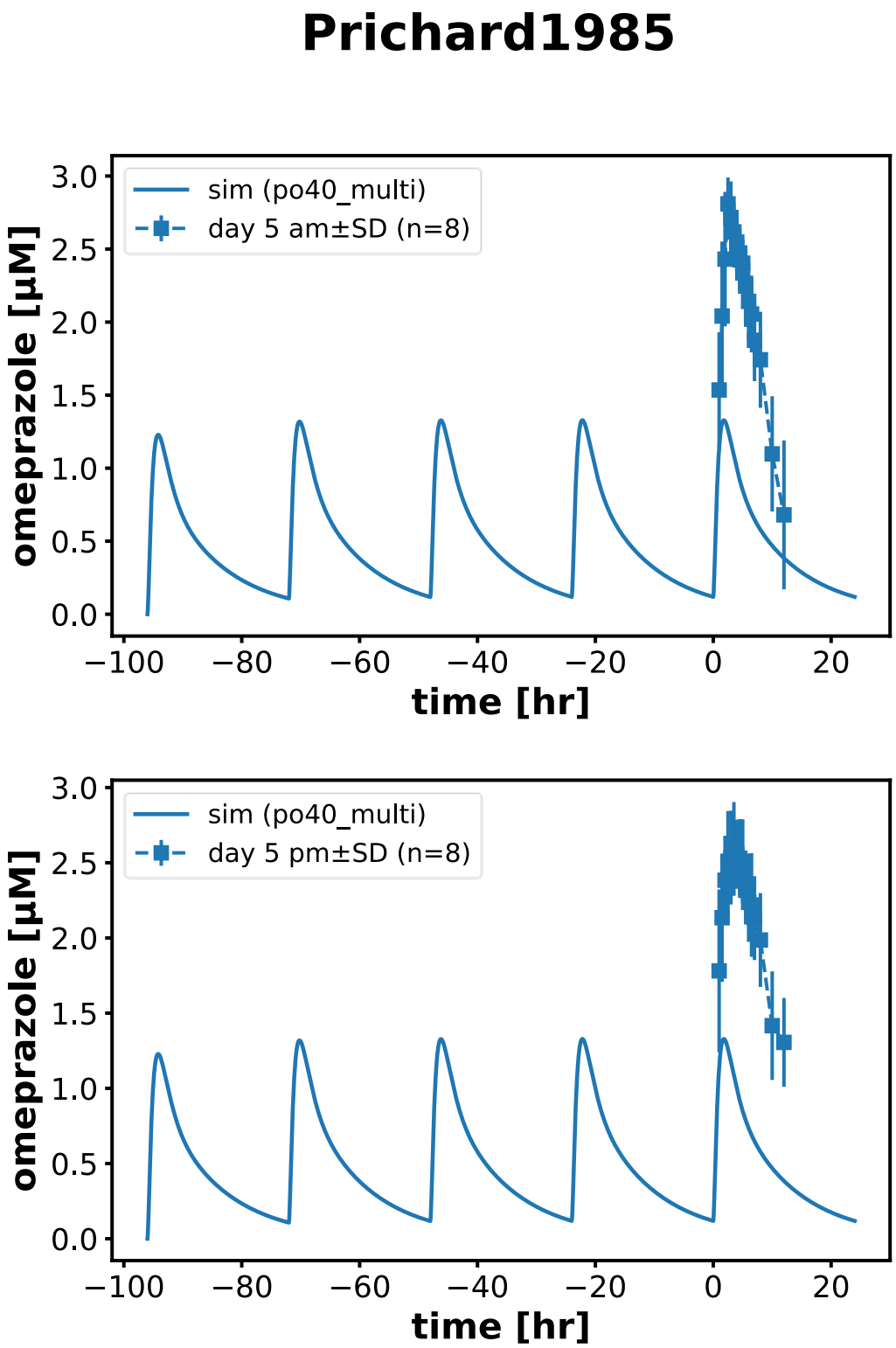

Figure 16: Simulation experiment Prichard1985. The concentration of omeprazole over time is shown in the graph. Solid line represents the prediction and dashed line the data from the clinical study [32].

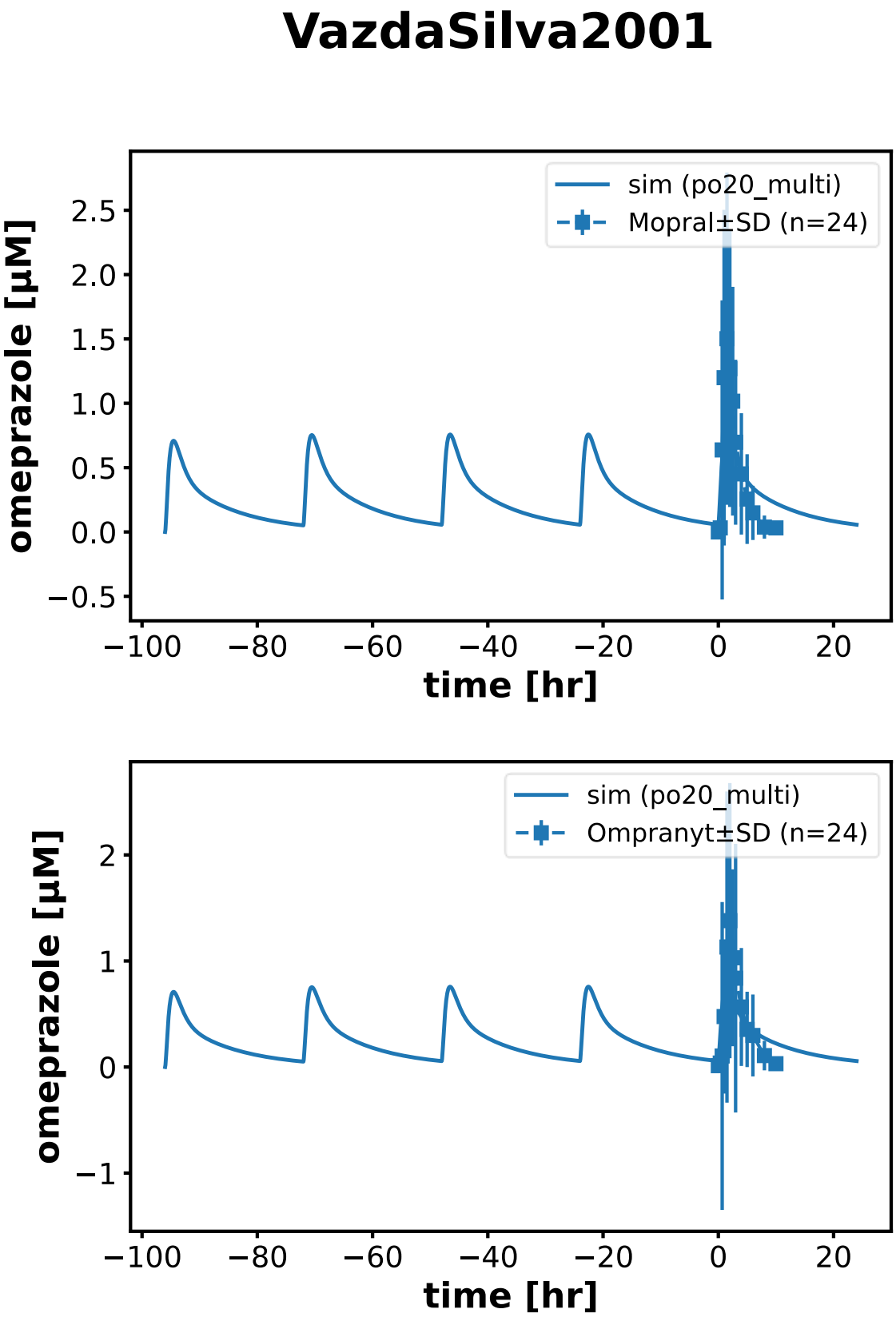

Figure 17: Simulation experiment Vazdasilva2001. The concentration of omeprazole over time is shown in the graph. Solid line represents the prediction and dashed line the data from the clinical study [40].

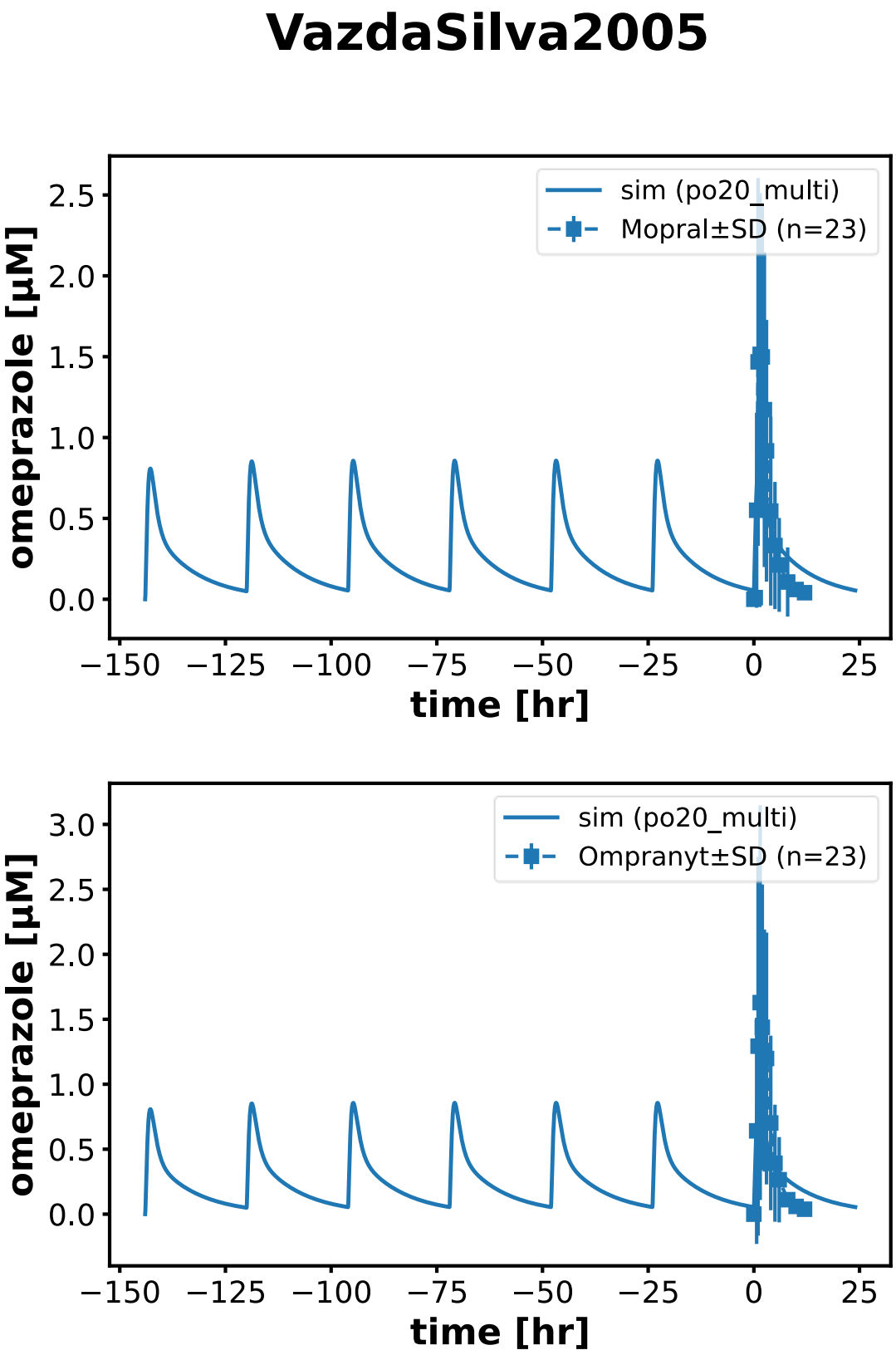

Figure 18: Simulation experiment Vazdasilva2005. The concentration of omeprazole over time is shown in the graph. Solid line represents the prediction and dashed line the data from the clinical study [41].

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Berlin, 15.10.2021, S. Bahn