



Predicting gastric emptying of drug substances taken under postprandial conditions by combination of biorelevant dissolution and mechanistic *in silico* modeling

Fabian Winter^a, Constantin Foja^a, Maximilian Feldmüller^{a,1}, Marie-Luise Kromrey^b, Philipp Schick^a, Mladen Tzvetkov^c, Werner Weitschies^{a,*}

^a University of Greifswald, Institute of Pharmacy, Department of Biopharmaceutics and Pharmaceutical Technology, Felix-Hausdorff-Str. 3, 17489 Greifswald, Germany

^b University Medicine Greifswald, Department of Diagnostic Radiology and Neuroradiology, Ferdinand-Sauerbruch-Straße, 17489 Greifswald, Germany

^c University Medicine Greifswald, Department of General Pharmacology, Felix-Hausdorff-Str. 3, 17489 Greifswald, Germany

ARTICLE INFO

Key words:

PBPK
Gastric emptying
Food effect
Stomach road
Fed state
Magenstrasse
Salivary sampling

ABSTRACT

Physiologically based pharmacokinetic (PBPK) models can help to understand the effects of gastric emptying on pharmacokinetics and in particular also provide a platform for understanding mechanisms of food effects, as well as extrapolation between different postprandial conditions, whether standardized clinical or patient-oriented, non-clinical conditions. By integrating biorelevant dissolution data from the GastroDuo dissolution model into a previously described mechanistic model of fed-state gastric emptying, we simulated the effects of a high-calorie high-fat meal on the pharmacokinetics of sildenafil, febuxostat, acetylsalicylic acid, theobromine and caffeine. The model was able to simulate the variability in C_{max} and t_{max} caused by the presence of the stomach road. The main influences investigated to affect the gastric emptying process were drug solubility (theobromine and caffeine), tablet dissolution rate (acetylsalicylic acid) and sensitivity to gastric motility (sildenafil and febuxostat). Finally, we showed how PBPK models can be used to extrapolate pharmacokinetics between different prandial states using theobromine as an example with results from a clinical study being presented.

1. Introduction

It is a well-known that food can influence the rate and extent of absorption of a drug when the drug is administered shortly after a meal. In fact, 40% of approved oral drugs exhibit a significant effect of food on their pharmacokinetics (PK) with prolonged gastric emptying being one of the main reasons (O'Shea et al., 2019). Regulatory agencies like the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) therefore require food-effect bioavailability (BA) and fed bioequivalence (BE) studies for orally administered drug products as part of investigational new drug applications, new drug applications, abbreviated new drug applications and supplements to these applications.

Their guidance on food effect studies emphasizes a standardized approach using a high-fat, high-calorie meal. This is intended to represent a worst-case scenario of delayed gastric emptying and enhanced drug absorption. When drug administration with a high-fat meal causes

unacceptable toxicity or a loss of drug efficacy, the FDA recommends a low-fat meal that can result in less or no impact on systemic exposures, improved patient compliance, and alleviate localized gastric irritation. In some cases, recommendations between health authorities can even be different. For Imatinib, the FDA requests patients to be tested in a fed-state study after light breakfast, recognizing that cancer patients may experience difficulties with the standard high-fat high-calorie meal. EMA on the other hand prefer fasted state condition or a fed study according to the Guideline on the investigation of bioequivalence. Additionally, volume and time of water administration after the intake of the drug is often decided by the investigators or even allowed as desired by the subject, introducing more variability. Furthermore, the test meals currently recommended by prominent regulatory agencies serve as a standardized approach but present a limited scope of meals in non-clinical conditions where they can vary significantly in terms of calorie content, volume, and nutrient composition, resulting in food effects that vary in intensity and sometimes even point in different directions

* Corresponding author at: Felix-Hausdorff-Str. 3, 17489 Greifswald.

E-mail address: werner.weitschies@uni-greifswald.de (W. Weitschies).

¹ (Present) Bayer AG Pharmaceuticals, Department of Clinical Pharmacology, Müllerstr. 178, 13,353 Berlin, Germany.

(Devriese et al., 2014; Li et al., 2018).

Nonetheless, a clinical food effect study is currently the only data that is accepted by the health authorities, even though, on its own, a clinical study does not provide mechanistic understanding for the food effect. Physiologically based pharmacokinetic (PBPK) models have been shown to be a viable tool to investigate food effects on oral solid dosage forms by combining drug-related properties and physiology-specific data (Pepin et al., 2021; Shono et al., 2009; Back et al., 2018; Lin and Wong, 2017). Several models have been described to investigate the impact postprandial gastric emptying on drug PK, even though their transferability to other drugs or formulations often remains limited (Kiyota et al., 2022; Andreas et al., 2017). In addition, we already highlighted multiple gaps and limitations of commercially available PBPK software when simulating fed state gastric emptying (Winter et al., 2023). It is often described as a simple linear or first order process, contrary to the biphasic pattern observed *in vivo* by Koziolok et al. (2014); Grimm et al. (2017). Furthermore, under postprandial conditions, administered water, together with dissolved or dispersed API, will rapidly pass through the stomach by a mechanism called stomach road or "Magenstraße" (Grimm et al., 2017; Waldemeyer, 1908). This process has been known for a long time but is rarely considered in these models.

To address these challenges, we have previously described the development of a mechanistic gastric emptying model in PK-Sim/MoBi that could simulate the emptying process of semi-solid food based on specific meal characteristics. By separating the gastric emptying process of liquids and solids from the stomach, the effect of the stomach road could be replicated. Input parameters for the gastric model include the time to empty 50% of the meal volume ($t_{50\%}$) as well as the emptying rate k in kcal/min at time point $t = t_{50\%}$. Both parameters can be estimated using the total meal calories and the percent of calories derived from fat (Winter et al., 2023).

Building upon this, we established two main objectives for this current work. First, we tried to simulate the effect of two different meals on the pharmacokinetics of theobromine by combining biorelevant dissolution testing and the previously presented mechanistic *in silico* gastric model. Dissolution testing was done using the GastroDuo, a biorelevant dissolution test device that is able to simulate specific aspects of the human stomach including pH profiles, pressure events and water flow rates (Schick et al., 2020; Schick et al., 2019; Sager et al., 2019). PK parameters of the resulting simulation were compared with an *in vivo* study of theobromine in the postprandial state to demonstrate the viability of the model. Secondly, we used the model to simulate the variability in the onset of drug concentrations of IR-formulations under postprandial conditions in bioequivalence setups caused by the effect of the stomach road. For this, commercial formulations of the high absorption drugs acetylsalicylic acid, sildenafil and febusostat were investigated and compared to *in vivo* pharmacokinetic data.

2. Methods

2.1. *In vivo* studies

2.1.1. Theobromine pharmacokinetic studies

Theobromine pharmacokinetics were investigated in two different studies. Both studies were part of previously published studies. However, the results for theobromine have not previously been published (Sager et al., 2018, 2019). Study 1 compared theobromine pharmacokinetics of 14 healthy volunteers in the fasted and fed state. Every volunteer received each treatment 4 times in repeated single doses for a total of 56 observations per treatment. All 14 participants completed the fasted treatment. However, due to dietary restrictions, one participant did not complete the high calorie treatment. Another person was excluded for base contamination of the salivary samples with theobromine. The fed state conditions met the criteria of the FDA guidance for food-effect bioavailability and fed bioequivalence studies (Cooper and Voelker, 2012). In short, subjects were asked to eat a high-caloric, high

fat meal consisting of 2 eggs, 2 strips of bacon, 2 slices of toast with butter, 4 oz of hash browns potatoes, and 8 oz of whole milk within 15 min. 35 mg theobromine in form of the ice capsule was taken 30 min after beginning of the meal or after a 10 h fast together with 240 mL of water. Total caloric intake was 964 kcal with 55% of the calories derived from fat. In study 2, 75 mg theobromine were taken together with 240 mL of water 30 min after the intake of a light meal consisting of 2 slices of toast, 30 g of strawberry jam, 250 g of yoghurt and 120 mL orange juice (Light-meal). Total caloric content of the meal was 466 kcal with 55 kcal derived from fat. 16 healthy volunteers participated in study 2. Detailed meal composition and sampling scheme are reported in the supplemental material.

Salivary theobromine concentrations were determined at fixed timepoints in both studies using LC-MS/MS. Theobromine was obtained from Sigma-Aldrich Chemie GmbH, Schnellendorf Germany. Theobromine was administered in form of an ice capsule. Ice capsules are shells made of frozen water filled with liquid solutions of theobromine. The purpose of this is to prevent the oral cavity from being contaminated with the drug substances prior to salivary sampling. The ice capsules melt immediately after ingestion with minimal lag time. Preparation of the ice capsule was the same as described by Sager et al. (2016). Written informed consent was obtained from all participants and the studies were conducted in compliance with the Declaration of Helsinki. The study protocols were approved by the ethics committee of the University Medicine Greifswald (registration numbers: BB116/15 and BB 172/17).

Calculation of the main PK parameters was performed using Stata (Release 18, StataCorp, College Station, TX). PK parameters included C_{max} , t_{max} and $AUC_{0-tlast}$.

2.1.2. Caffeine, acetylsalicylic acid, febusostat and sildenafil

Pharmacokinetic data for caffeine, acetylsalicylic acid, febusostat and sildenafil were taken from previously published studies where individual data for each patient was on hand (Schick et al., 2019, 2020; Sager et al., 2018). Similar to theobromine, caffeine concentrations measurements for caffeine represent salivary concentrations while pharmacokinetic samples for all other drugs were taken from the peripheral venous blood. The study protocol for all studies was identical to the one described above for food-effect bioavailability and fed bioequivalence studies. The number of participants were 6, 30, 14 and 34 for caffeine, acetylsalicylic acid, febusostat and sildenafil respectively.

Except for caffeine, which was in form of an ice capsule, all tested formulations were marketed immediate release tablets. Doses, brand names manufacturers and batch numbers are shown in Table 1. Dissolution profiles in compendial devices can be found in the respective publications. In the case of Acetylsalicylic acid, two different formulations were investigated. One was a regular tablet containing only cornstarch and Cellulose (Elcema G250) as fillers and binders. The other one was a recently developed fast disintegrating and dissolving (FDDT) Aspirin tablet that, by micronizing the drug and using sodium carbonate as a superdisintegrant in acidic conditions of the stomach, achieves an earlier action of onset due to rapid disintegration (Cooper and Voelker, 2012; M et al., 2016).

Table 1

Formulations of caffeine, acetylsalicylic acid, febusostat and sildenafil used for *in vivo* and *in vitro* investigations.

Drug	Formulation	Dose	Manufacturer
Caffeine	Ice Capsule	35 mg	(developed and produced in house (Sager et al., 2018))
Acetylsalicylic acid	Aspirin RT	500 mg	Bayer AG, Leverkusen, Germany
Acetylsalicylic acid	Aspirin FDDT	500 mg	Bayer AG, Leverkusen, Germany
Febuxostat	Adenuric	80 mg	Berlin-Chemie AG, Berlin, Germany
Sildenafil citrate	Viagra	100 mg	Pfizer Pharma GmbH, Berlin, Germany

2.2. *In vitro* experiments using GastroDuo

2.2.1. Theobromine

The GastroDuo is a biorelevant dissolution test device. It simulates physiological aspects of the stomach and the small intestine. This includes gastric emptying kinetics, luminal pH, and temperature profiles as well as a realistic simulation of pressures arising during GI transit due to motility. The test programs used in this work have been described previously by Schick et al. (2020). They are designed to investigate the impact of the stomach road and gastric stress conditions on the drug release kinetics of IR dosage forms. In program I, the stomach road was simulated directly at the beginning by a first-order like perfusion profile completed within 30 min, followed by a basal perfusion rate of 2 mL/min. In program II, the same profile was applied, but only after 60 min. This program was based on the assumption that the stomach road may not have been of relevance directly after drug intake, for instance due to the location of the dosage form away from the stomach road or mixing of the drug into the gastric contents. Schematic presentations of the test programs are shown in Fig. 1. These 2 programs represent the different scenarios which are likely to occur if an IR formulation is taken together with a glass of water under postprandial conditions as proposed by Koziolok et al. (2016) The medium composition changes over time to simulate a pH gradient in the postprandial stomach and is a 1:1 mixture of 50 mM phosphate buffer pH 4.5 and 50 mM citrate buffer pH 4.5 where an increasing fraction of SGFsp (pH 1.2) is added.

Drug concentrations in the acceptor vessel and at the outlet of the gastric cells were measured by the use of a Cary® 50 UV-Vis spectrophotometer (Varian Inc., Mulgrave, Australia) equipped with fiber optics. Theobromine absorption was measured at 270 nm and a second measurement at 500 nm was performed to enable baseline correction. For the measurements in the acceptor vessels, the fiber optics were equipped with 2 mm tips whereas for the measurements at the outlet 1 mm tips were used. The calibrated range for the 2 mm tips was between 0.002 mg/mL and 0.2 mg/mL and for the 1 mm tips between 0.001 mg/mL and 0.1 mg/mL.

2.2.2. Caffeine acetylsalicylic acid, febuxostat and sildenafil

In vitro results for caffeine, acetylsalicylic acid (Aspirin®), febuxostat (Adenuric®) and sildenafil (Viagra®) have been reported previously (Schick et al., 2019, 2020). Setup and test programs were identical to the ones described above for theobromine.

2.2. PBPK-Modeling

2.2.1. General structure

The general model for all simulations was built in MoBi (www.open-systems-pharmacology.org). It consisted of 3 segments: the gastric segment, an intestinal segment and a distribution/elimination segment.

A schematic picture of the model is shown in Fig. 1. The development of the gastric model used in this study has been reported previously (Winter et al., 2023). In Short, the gastric segment consists of 2 compartment which represent the liquid gastric contents and chyme respectively. Drug from the liquid compartment can be emptied rapidly via a first order process. Drug from the chyme compartment empties according to the observations from MRI imaging studies as describes previously. The equation used to describe the gastric emptying process is given by Eq. (1) and is the derivative of the function that describes the overall gastric content volume. The calculated rate represents the emptying rate of the chyme compartment (k_{es} , Fig. 2). The input parameters for the gastric segment were $k = 3.16$ kcal/min and $t_{50\%} = 211.82$ min for the high fat meal and $k = 1.27$ kcal/min and $t_{50\%} = 133.44$ min light meal respectively. The effect of secretion can be incorporated as the sum of volume change given by Eq. (1) and the secretion rate. The amount of drug emptied via each route is determined by the *in vitro* dissolution results as described below. Since all tested drugs in this study are highly permeable and absorption is mainly influenced by gastric emptying, a simple first order process was used to describe absorption from the intestine. Depending on the drug characteristics, the distribution/elimination segment was in case of caffeine and theobromine represented by one compartment models and for sildenafil, febuxostat and acetylsalicylic acid by two compartment models. Parameters for absorption, distribution and elimination were estimated using on hand individual data that have been published previously (Schick et al., 2019, 2020; Sager et al., 2018). The applied compartment model parameters for each drug are given in Table 2.

$$\frac{d(w)}{d(t)} = w \cdot \frac{k \cdot t_{50\%} \cdot \left(\frac{t}{t_{50\%}}\right)^{\frac{2 \cdot k \cdot t_{50\%}}{\ln(2) \cdot V_0}} \cdot 2 \cdot \left(1 - \left(\frac{t}{t_{50\%}}\right)^{\frac{2 \cdot k \cdot t_{50\%}}{\ln(2) \cdot V_0}}\right)}{t \cdot V_0} \quad (1)$$

2.2.2. Integration of *in vitro* results into the pharmacokinetic model

In vitro results from the GastroDuo can be incorporated into the *in silico* model by adjusting the amount of drug that can be emptied from the stomach during the occurrence of a simulated stomach road. This percentage of the total drug amount is placed into the liquid compartment of the stomach and emptying follows the emptying pattern obtained with the GastroDuo. The remaining drug is placed into the chyme compartment of the stomach. It is assumed that drug in the chyme compartment is equally distributed within the chyme and is emptied according to the emptying pattern simulated by the model for each meal. To replicate *in vivo* conditions, drug intake was simulated 30 min after the simulated start of the meal intake. A second occurrence of the stomach road can be simulated with the same amount of drug but only if the drug has not been completely emptied from the stomach up until this point.

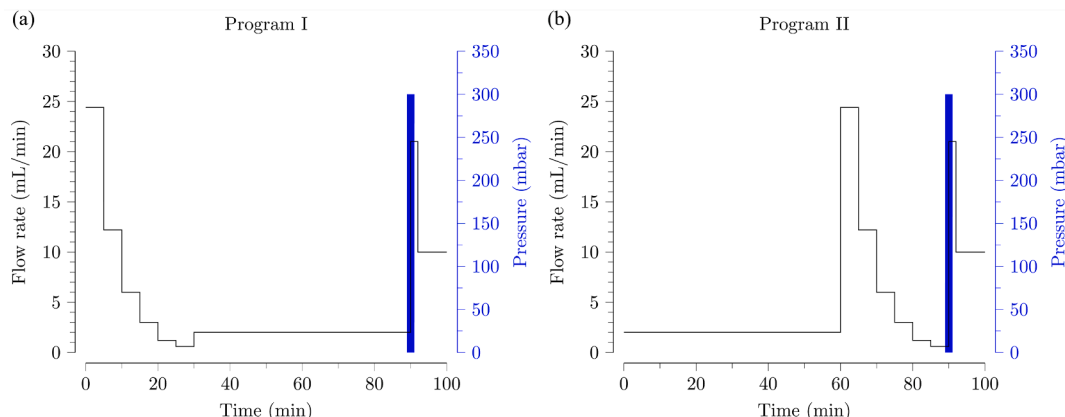


Fig. 1. Schematic representations of the test programs applied in the GastroDuo experiments. Blue bars represent the time and extent of simulated pressure events.

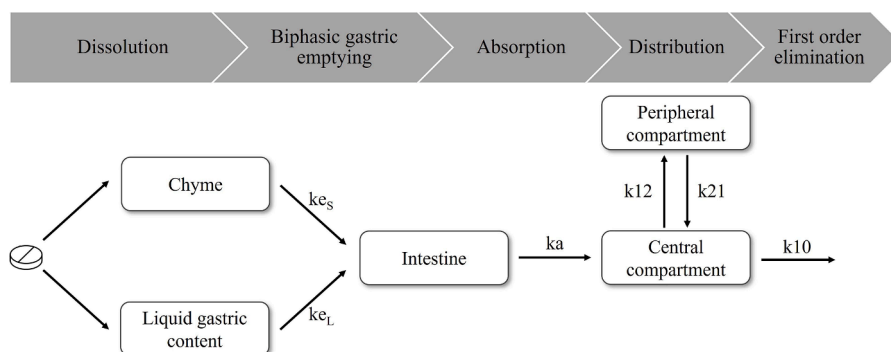


Fig. 2. Schematic presentation of the model structure build in PK-Sim/Mobi to simulate the pharmacokinetics of the different drugs. k_{e_s} = gastric emptying rate from the chyme as calculated by Eq. (1), k_{e_L} = gastric emptying rate from the liquid gastric contents, k_a = absorption rate, k_{12}/k_{21} = distribution rates, k_{10} = elimination rate constant.

Table 2

Model parameters used in the PBPK-simulations for each drug.

drug	V_d (L)	k_{10} (min^{-1})	k_{12} (min^{-1})	k_{21} (min^{-1})
caffeine	90	0.0020	–	–
theobromine	50	0.0007	–	–
sildenafil	135	0.0100	0.1000	0.1900
febuxostat	28	0.0060	0.0020	0.0018
acetylsalicylic acid	21	0.0350	0.0270	0.0500

V_d = Volume for distribution of the central compartment, k_{10} = elimination rate constant from the central compartment, k_{12}/k_{21} = distribution rate constant between the central and peripheral compartment, k_a = absorption rate constant from the intestine to the central compartment.

2.2.3. Impact of different meal types

To simulate the impact of different meals on the pharmacokinetics of theobromine, the amount of drug initially emptied from the stomach is remains the same. Transport of drug from the chyme to the duodenum is changed based on the simulated emptying profile for the new meal using input of meal volume, calories and percentage of calories derived from fat. The input parameters for the light-meal were 466 kcal in total, 11,8% of calories derived from fat and a total volume of 460 mL.

3. Results

3.1. Theobromine PK-Data

Salivary concentration profiles for the pharmacokinetic studies of theobromine are presented in Fig. 3. Graphs A-C show the individual profiles of all study arms whereas in graph D, a comparison of the mean curves is presented. A summary of the pharmacokinetic parameters is given in Table 3.

Fasted state salivary concentrations of theobromine exhibit expectable pharmacokinetics with the lowest t_{max} of 115.9 ± 62 min and a higher C_{max} of 766.7 ± 331.6 compared to the profile under postprandial conditions at the same dose. Comparing both postprandial conditions, theobromine salivary concentration increases up to the end of the observation period at 240 min after intake of a high-calorie high-fat meal whereas t_{max} is reached after 219.3 ± 76.4 min in the Light-Meal study. A decrease in $\text{AUC}_{0-\text{tlast}}$ between fasted and fed state with equal doses and mean concentration still increasing to $t = 240$ min suggest that absorption of theobromine in fed conditions isn't finished up to 240 min which is in line with the observation that the concentration is still increasing at time $t = 240$ min.

3.2. In vitro experiments with theobromine ice capsules in the GastroDuo

Results from the experiments performed in the GastroDuo using an ice capsule filled with 35 mg of theobromine are shown in Fig. 4. Results

with 75 mg of theobromine are presented in the supplemental material.

Emptying of theobromine into the acceptor vessel was incomplete in both test programs. After 100 min $89.5 \pm 3.9\%$ and $94.9 \pm 2.7\%$ of the dose were transported to the acceptor vessel in programs I and II respectively. The high initial flow rate in program I resulted in a rapid emptying rate of theobromine in the first 10 min of the experiment while the low but steady flow in program II lead to slower but prolonged initial emptying phase. After 60 min, $57.0 \pm 6.5\%$ of the dose were found in the acceptor vessel, while only $49.1 \pm 2.3\%$ were found in the acceptor vessel in program II at the same time. Overall, a phase with increased flow rate resulted in an increased emptying rate, whereas a lower flow rate lead to increased concentrations at the outlet of the gastric cell, as can be seen in program II. High pressure, high flow events after 90 min led to transport of all remaining drug from the gastric cell into the vessel within 10 min.

3.3. Impact of high and low calorie meals on theobromine pharmacokinetics

The results from the *in vitro* experiments in the GastroDuo were subsequently incorporated into the *in silico* model. Fasted salivary concentrations were used to estimate pharmacokinetic parameters of Theobromine. To simulate the salivary concentrations under postprandial conditions, only the gastric emptying rates were changed while all other parameters were kept unchanged. Under postprandial conditions $57.0 \pm 6.5\%$ and $49.1 \pm 2.3\%$ of the dose were emptied through the stomach road compartment. The emptying parameters of the chyme compartment were set as described above for the of the two meals. Simulated and observed salivary concentration time graphs for each prandial condition are shown in Fig. 5.

The simulated results correspond very well with the observed profiles. Pharmacokinetic results are shown in Table 4. Simulated times for maximum salivary concentration were within 6 min of the observed results, while AUC for the simulated time were within 89 to 113% for all programs. The two programs did not result in major differences. The overall longer emptying time after intake of a high-calorie high-fat meal led to a longer t_{max} and lower C_{max} despite the same percentage of drug being emptied via the stomach road.

3.4. Impact of solubility on the gastric emptying rate of caffeine and theobromine

The effect of solubility on the gastric emptying was investigated by comparing caffeine and theobromine in postprandial conditions using the same dosage form. Salivary concentrations of 35 mg each in form of an ice capsule after intake a high-calorie high-fat meal are shown in Fig. 6. The simulated time profiles based on the *in vitro* experiments in the GastroDuo differ significantly between the two drugs while they are

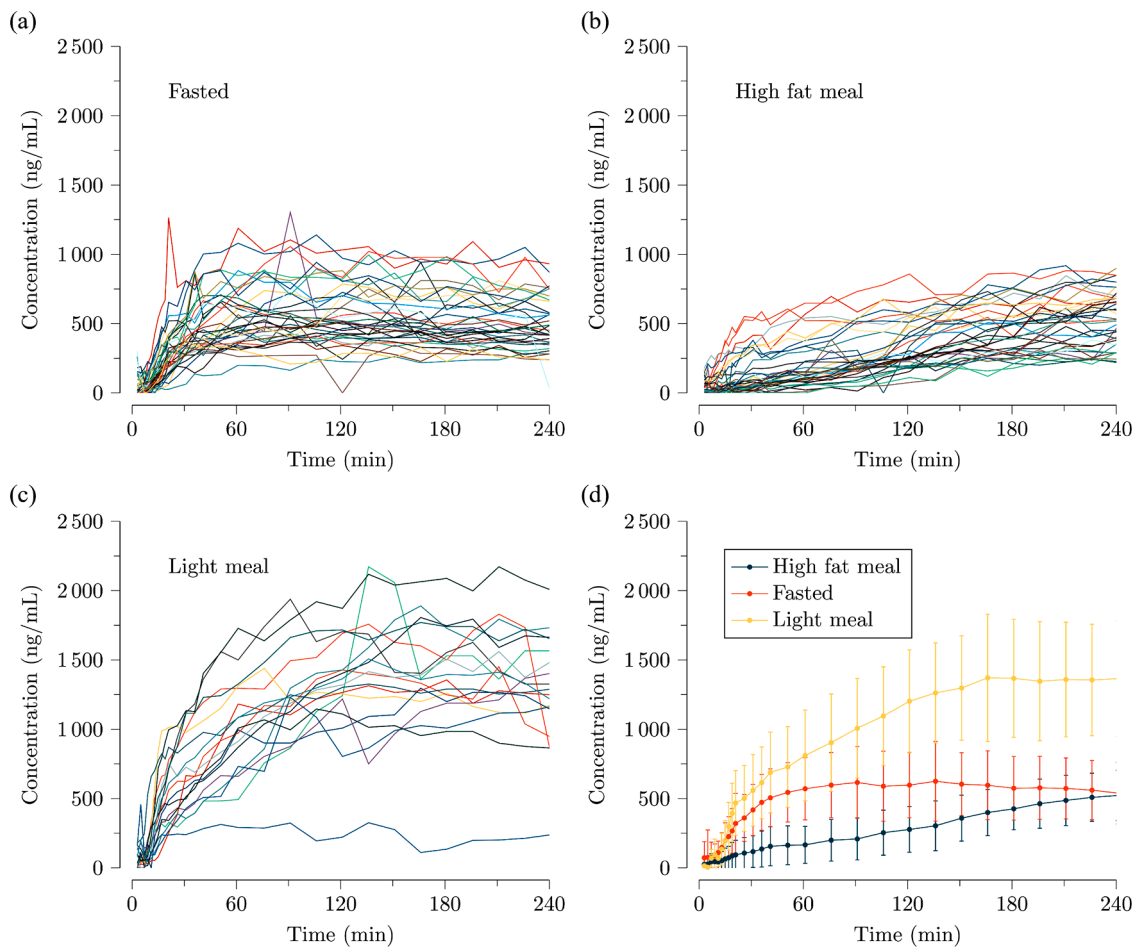


Fig. 3. Theobromine salivary concentration over time after intake of 35 mg caffeine in fasted condition (a), 70 mg caffeine 30 min after a light meal (b) and 35 mg caffeine 30 min after intake of a high fat meal (c). Mean values and standard deviation for each study (d, yellow = light-meal, blue = fasted, orange = high fat meal).

Table 3
Pharmacokinetic parameters of the performed *in vivo* studies with theobromine.

Condition (dose)	parameter	mean \pm SD	median	minimum	maximum
Fasted (35 mg, $n = 56$)	$AUC_{0-t_{last}}$ (ng*min/mL)	128,128.0 \pm 47,465.3	122,322.9	46,562.2	235,389.8
	C_{max} (ng/mL)	766.7 \pm 331.6	741.0	286.2	1890.4
	t_{max} (min)	115.9 \pm 62.0	106	5	241
	$AUC_{0-t_{last}}$ (ng*min/mL)	81,778.7 \pm 84,972.1	83,447.4	29,152.5	168,676.4
High fat meal (35 mg, $n = 52$)	C_{max} (ng/mL)	597.0 \pm 184.2	630.3	249.6	918.3
	t_{max} (min)	–	–	–	–
	$AUC_{0-t_{last}}$ (ng*min/mL)	347,300.6 \pm 92,664.2	360,985.9	76,955.9	529,251.4
Light meal (75 mg, $n = 16$)	C_{max} (ng/mL)	1654.7 \pm 481.4	1546.7	561.1	2838
	t_{max} (min)	219.3 \pm 76.4	211	91	331

$AUC_{0-t_{max}}$ = Area under the salivary concentration time curve from $t = 0$ min to last sampling time, C_{max} = maximum plasma concentration, t_{max} = time of maximum plasma concentration.

in good agreement with the respective *in vivo* observations. Due to its higher solubility, 98% of caffeine was found in the acceptor vessel even in conditions with lower flow rates (Schick et al., 2019). This resulted in a nearly all of the drug being emptied via the stomach road which in turn led to a low t_{max} of 58 and 67 min in the two programs. For theobromine on the other hand, only 57 and 49% of the drug were emptied via the stomach road as described above resulting in a $t_{max} > 240$ min. Due to the rapid emptying even in postprandial conditions for caffeine, C_{max} does not differ compared to fasted conditions (Sager et al., 2018).

The effect of delayed gastric emptying for theobromine in comparison to caffeine is visualized in Fig. 7. While both drugs are rapidly absorbed in the fasted state (a), only theobromine shows delayed gastric emptying leading to a lower C_{max} and higher t_{max} .

3.5. Impact of tablet dissolution on gastric emptying rate of acetylsalicylic acid

To compare the effect of the same drug in two different formulations, we compared two oral tablets of acetylsalicylic acid. The results obtained in *in vitro* experiments with the same setup as described above for theobromine have been published previously (Schick et al., 2020). In brief, the fast disintegrating and dissolving tablet (FDDT) acted as expected and demonstrated high emptying rates under high and low flow conditions resulting in 97.1 and 92.3% of the drug being emptied into the acceptor vessel within the first 45 min. In contrast, the regular tablet (RT) showed low disintegration rates under these conditions with a maximum of 28.4% being found in the acceptor vessel after 45 min. Simulated plasma concentration after integration of the *in vitro* results

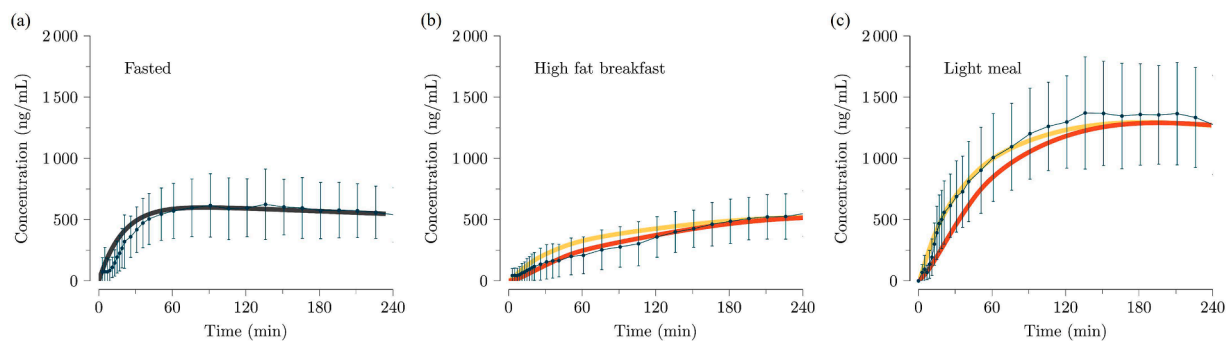


Fig. 4. Concentration and pH profiles at the outlet of the gastric cell as well as the amount of theobromine emptied into the acceptor vessel over time in test programs I (a) and II (b) with a dose of 35 mg.

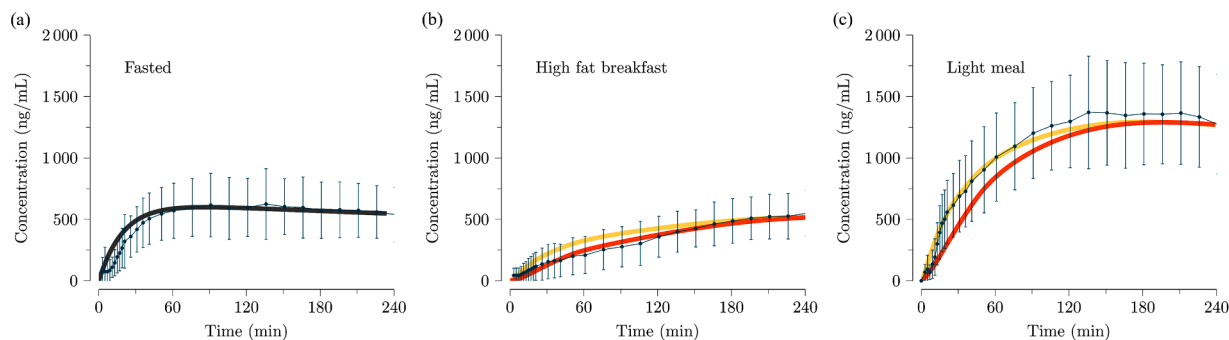


Fig. 5. Simulated and observed salivary concentration after intake of Theobromine under different prandial conditions. Observed data are shown as mean \pm standard deviation. (a) 35 mg Theobromine in fasted conditions. (b) 35 mg Theobromine after intake of a high-calorie high-fat meal. Program I = yellow, program II = red. (c) 75 mg Theobromine after intake of a light meal. Program I = yellow, program II = red.

Table 4

Comparison of simulated and observed pharmacokinetic parameters of theobromine in different prandial conditions.

Parameter	Fasted		High fat meal			Light meal		
	<i>In vivo</i>	simulated	<i>In vivo</i>	Program I	Program II	<i>In vivo</i>	Program I	Program II
t_{max} (min)	116	115	–	–	–	220	213	226
$AUC_{0-tlast}$ (ng*min/mL)	128,128	127,866	81,775	92,887	81,265	267,189	257,698	239,065

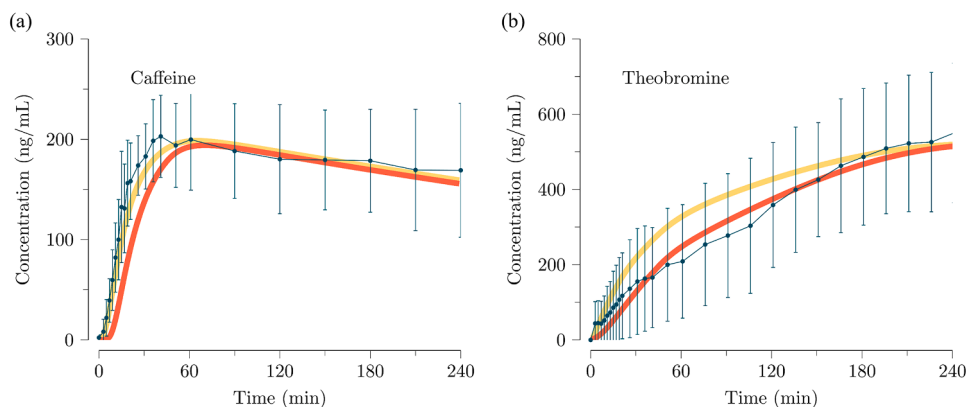


Fig. 6. Simulated and observed (blue) salivary concentration after intake of 35 mg caffeine (a) and theobromine (b) in postprandial conditions. Program I (yellow) and program II (red).

compared to the observed *in vivo* concentration-time profiles are shown in Fig. 8.

The difference in dissolution rate between the two formulations results in a very different pharmacokinetic profile after intake in postprandial conditions. Depending on the program, C_{max} for the regular

tablet is simulated to be between 2.35 and 1.85 $\mu\text{g/mL}$. The results for the regular tablet are in good agreement with the observed profiles showing that the slow initial dissolution rate results in an emptying process mainly via the chyme which in turn leads to a low C_{max} and higher t_{max} . Simulated concentrations for the FDDT formulation

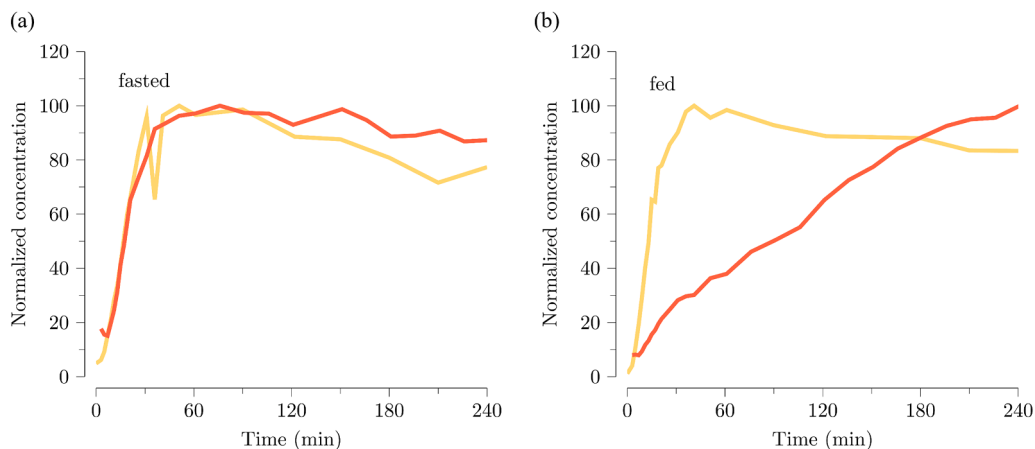


Fig. 7. Normalized mean salivary concentrations after intake of 35 mg caffeine (yellow) and theobromine (red) in fasted state (a) and after a high fat meal (b).

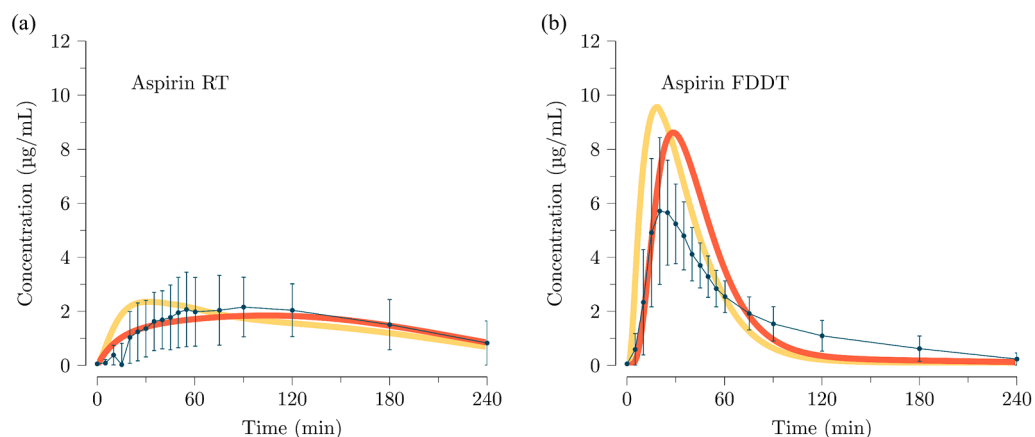


Fig. 8. Simulated and observed (blue) salivary concentration after intake of 500 mg acetylsalicylic acid as a regular tablet (a, $n = 29 \pm SD$) and in form of a fast disintegrating and dissolving tablet (b, $n = 30 \pm SD$) in postprandial conditions. Program I (yellow) and program II (red).

overestimate C_{max} underestimate the terminal phase. C_{max} was simulated to be between 9.55 and 8.61 $\mu\text{g/mL}$ while maximum concentration of the mean profile was only 5.71 $\mu\text{g/mL}$. Changing the amount of drug being emptied via the stomach road from 92 to 97%, as estimated by the *in vitro* experiments, to 70%, as estimated from optimizing simulation results with *in vivo* measurements, resulted in a much better fit (Fig. 10).

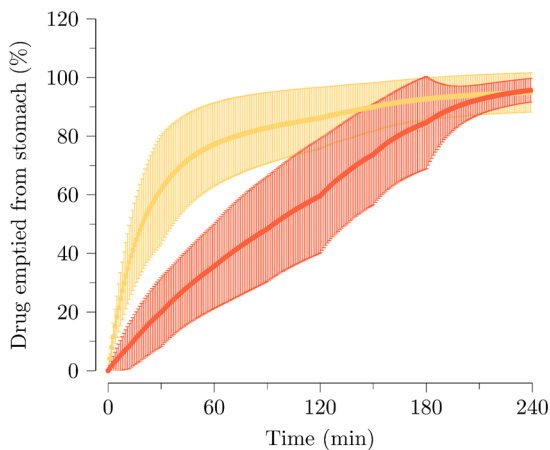


Fig. 9. Gastric emptying of acetylsalicylic acid obtained by deconvolution of individual plasma concentration profiles from Schick et al. Presented as mean \pm SD (regular tablet: $n = 29$ (red), FDDT: $n = 30$ (yellow)).

The effect of tablet dissolution on the emptying rate of acetylsalicylic acid from the stomach is also evident after deconvolution of the *in vivo* data (Fig. 9). While on average only 28% of the dose is emptied from the stomach within the first 45 min after intake of the regular tablet, the fast dissolution rate of the FDDT formulation leads to 71% of the dose being emptied at the same time. In addition, deconvolution of the FDDT profiles reveals a distinct biphasic process where gastric emptying rate decrease significantly after the initial water emptying, while drug released from the regular tablet is emptied mainly with the chyme and therefore shows a continuous slow pattern over several hours.

3.6. Febuxostat

Fig. 11 shows the simulated variability of febuxostat under food-effect bioavailability and fed bioequivalence conditions as proposed with the predetermined programs. The *in vitro* programs showed a markedly different response of the formulation to the simulated conditions (Schick et al., 2019). A first-order-like emptying of the co-administered fluid, mimicked by high flow rates in program I, resulted rapid onset of plasma levels after integration into the PBPK models. Low flow rates in program II lead to only 1% of the drug being emptied via the stomach road which consequently lead to a reduction of C_{max} from 2.30 to 1.29 $\mu\text{g/mL}$ and a prolongation of t_{max} from 46.2 to 177 min in comparison to program I.

Deconvolution of *in vivo* plasma levels showed a high inter-individual variability in gastric emptying which is reflected by the *in silico* simulated emptying profiles (Fig. 12). As the drug is mainly emptied via the

stomach road in program I, high emptying rates can be observed within the first 45 min. Emptying via the chyme compartment in the terminal phase results in lower transport rates > 45 min, demonstrating the biphasic characteristics of the gastric emptying process. With nearly no drug transported via the stomach road into the duodenum in program II, caused by low dissolution rates in the low flow setup, gastric emptying of febusostat follows a zero-order-like process together with the chyme.

Comparing the simulated plasma concentration levels with individual data from the *in vivo* study grouped into the two onset behaviors as proposed by Schick et al. shows that program I correlates well with the individuals in whom a rapid onset of plasma levels was observed (Fig. 13). Program II demonstrates that location of the dosage form away from the stomach road may lead to a prolonged gastric emptying process.

3.7. Sildenafil

After estimating the distribution and elimination parameters for sildenafil from intravenous and fasted oral *in vivo* concentrations, the effect of delayed gastric emptying was on the pharmacokinetics of sildenafil was simulated by integrating the *in vitro* dissolution results from two GastroDuo programs. The results from the *in vitro* experiments have been published previously (Schick et al., 2019). Simulated and observed plasma concentrations are shown in Fig. 14.

In vivo, a reduction in C_{max} from to 0.39 to 0.27 $\mu\text{g}/\text{mL}$ was observed. In comparison, simulated fed state C_{max} was between 0.26 $\mu\text{g}/\text{mL}$ for program I and 0.21 $\mu\text{g}/\text{mL}$ for program II. From the *in silico* models a prolongation of t_{max} from 24 min (fasted) to 100.2 min and 183.0 min in programs I and II respectively. Mean observed t_{max} was 120 ± 60 min in postprandial conditions.

4. Discussion

The process of gastric emptying is of major importance for drug pharmacokinetics. Particularly for highly permeable drugs, gastric emptying has been identified as the step that limits the rate of absorption (Koziolek et al., 2016). Rubbens et al. demonstrated that the duodenal appearance of diclofenac, a BCS class II drug, was noticeably influenced by delayed gastric emptying resulting from the concomitant intake of a high-fat meal (Rubbens et al., 2019). The same has been shown for Ibuprofen, where, despite higher solubility in the postprandial stomach, mixing of drug and chyme delayed gastric emptying (Koenigsknecht et al., 2017). Subsequent research has highlighted the utility of Physiologically Based Pharmacokinetic (PBPK) models as an ideal tool for exploring complex dynamic phenomena, including food effects. In a study by Andreas et al., delayed gastric emptying was assumed to be the primary cause of a negative food effect, utilizing a combination of bio-relevant dissolution and PBPK models (Andreas et al., 2017). This effect was particularly evident in the case of immediate release formulations. Therefore, the precise simulation of gastric emptying is crucial for accurately predicting food effects induced by delayed gastric emptying.

However, the rate of transport drug transport from the stomach into the duodenum can be highly variable. Not only is a distinction between fed and fasted conditions necessary, but also between different postprandial conditions since caloric content, volume, viscosity, macronutrient composition and motility can influence gastric emptying (Paixão et al., 2018; Vasavid et al., 2014; Moore et al., 1990; Marciani et al., 2001; Hellström et al., 2006). Additionally, water can empty the stomach in postprandial conditions as fast as under fasted conditions because of a process called “Magenstrasse” which allows noncaloric liquids to bypass solid particles through narrow paths along the fundus and corpus to the duodenum (Waldemeyer, 1908; Scheunert, 1912). This may result in some drugs showing no delayed gastric emptying in postprandial conditions as has been demonstrated for caffeine (Fig. 6) (Sager et al., 2018). In contrast, larger particles like pellets have been shown to mix with the chyme and consequently empty from the stomach over longer

time (Davis et al., 1987; Kelly et al., 2003). In addition, Senekowitsch et al. recently demonstrated that carbon dioxide release by effervescent granules prolonged gastric residence time of caffeine in postprandial conditions, demonstrating that formulation changes can lead to prolonged gastric emptying times, even for highly soluble drug that previously have not delayed gastric emptying (Senekowitsch et al., 2023).

Therefore, the process of postprandial gastric emptying should not be considered as a uniform and constant transport, but rather as a biphasic process, with drug being emptied into the duodenum in the initial rapid water transport via the stomach road or together with the chyme in the following hours. In contrast, many currently available *in silico* models simulate gastric emptying as a single first or zero-order process in postprandial conditions, neglecting key aspects of the physiological process of gastric emptying. For this reason, we have previously introduced a mathematical model to simulate gastric emptying in PBPK models, that not only can simulate gastric content volumes for various meals based on total calories, fat content and meal volume but can also be combined with a second gastric compartment to simulate non-caloric liquids emptying the stomach via the stomach road.

Koziolek et al. also proposed three types of onset of plasma levels determined by gastric emptying in postprandial conditions (Koziolek et al., 2016). With type I being comparable to fasting intake conditions, reflecting that the drug is rapidly transported to the duodenum due to the presence of stomach road. Type II can be identified as a rapid onset of the drug plasma level after a lag time of at least 1 h. Type III is characterized by a slow onset of drug plasma concentrations over several hours. In this case, the drug is mixed into the gastric content and continuously emptied into the small intestine along with the chyme (Fig. 15). Food or water intake several hours after start of the could lead to another increase in gastric emptying rate this later timepoint.

Building upon this, we wanted to investigate the factors governing whether a drug shows no (type I), some or extensive (type III) prolonged gastric emptying and if the amount of drug emptied either via the stomach road or the chyme could be predicted using the GastroDuo as an *in vitro* tool.

4.1. Influence of different meals and solubility

In a first example we investigated whether the amount of drug emptied during the initial rapid emptying phase via the stomach road changes between different meals. Theobromine was administered in the form of an ice capsule to mitigate the effect of tablet dissolution. Use of oral solutions was not possible due to contamination of the oral cavity prior to salivary sampling.

The GastroDuo experiments revealed that under biorelevant *in vitro* conditions, compared to caffeine, only 57% and 49% of the theobromine dose were found in the acceptor vessel in the respective program after 45 min. Solubility of caffeine in water is 21,7 mg/mL and of theobromine 0,33 mg/mL respectively at room temperature. Due to its higher solubility, caffeine dissolves immediately after melting of the ice capsule while theobromine forms a suspension which is emptied slower from the gastric cell (DrugBank (Caffeine), DrugBank (Theobromine)). After integration into the *in silico* model we were able to simulate theobromine pharmacokinetics when taken 30 min after a high-fat high-caloric or a light meal. The amount of drug emptied via the liquid and the chyme compartment remained constant with only the rate of transport from the chyme compartment to the duodenum changing as simulated by the model based on meal volume, caloric content and fat content. Estimation of the impact of different meals is based on the assumption that the occurrence of the stomach road is not dependent on meal type or composition. Grimm et al. have shown that the stomach road does occur under different conditions independent of viscosity, caloric density or meal volume (Grimm et al., 2017). Therefore, the amount of drug emptied during the initial rapid emptying phase is determined by dissolution of the dosage form and drug solubility in the gastric media. In comparison, under identical conditions, nearly all of the caffeine was

found in the acceptor vessel in the *in vitro* experiments after 45 min, hence all of the drug was emptied via the stomach road in the *in silico* simulations leading to no prolonged gastric emptying under fed conditions compared to fasted conditions (Fig. 7).^{15,17} Transfer of results between different meals under postprandial conditions could be of importance for many reasons. Firstly, as highlighted in the introduction, request from administrators regarding meals for bioequivalence investigations for certain drugs can differ. FDA requests patients to be tested in a fed-state study after light breakfast, recognizing that cancer patients may experience difficulties with the standard high-fat high-calorie meal. EMA on the other hand prefer fasted state condition or a fed study according to the Guideline on the investigation of bioequivalence. Secondly, while the meals used for clinical investigations are meant to simulate extreme conditions, they do not resemble the conditions in patient-oriented non-clinical setting where calories, volumes and macronutrients of meals are certainly much more variable.

Considering the proposed types of onset, subjects administered theobromine as an ice capsule in postprandial conditions nearly exclusively showed type III.

4.2. Influence of dosage form

Two different marketed formulations of acetylsalicylic acid were used to investigate the effect of different dosage forms on fed state gastric emptying. The difference in dissolution rate between the FDDT and the RT formulation observed *in vitro* resulted in markedly different plasma concentrations simulated by the *in silico* model. The reduction in C_{max} and prolonged t_{max} of the RT formulation was simulated well by the model. However, for the FDDT formulation, C_{max} was overpredicted (9.55 and 8.61 $\mu\text{g}/\text{mL}$ vs. 5.71 $\mu\text{g}/\text{mL}$). Even though the FDDT formulation showed rapid dissolution under all conditions, *in vivo* only 70% of the drug were emptied via the stomach road as determined by deconvolution (Fig. 9, 10). A possible explanation for increased mixing of drug and chyme specifically for this formulation could be carbon dioxide production of the effervescent tablet which has been shown to prolong gastric emptying in postprandial conditions by promoting the mixing of drugs into the chyme (Senekowitsch et al., 2023). Since there is no chyme in the gastric cell of the GastroDuo, the apparatus cannot capture this effect. Instead, small particles that could be emptied with liquid flowing around the chyme are separated by a mesh at the bottom of the gastric cell. This, in turn, does not hinder drug, once it is dissolved or disintegrated, from emptying the gastric cell the same way that mixing with the chyme would do. This mechanism is more likely than low

solubility of acetylsalicylic hindering drug dissolution because the higher gastric pH under postprandial conditions improves solubility due to its acidic nature. Additionally, the release of sodium carbonate increased the pH in *in vitro* experiments further increasing its solubility in the co-administered water.

On the other hand, results for the regular tablet are in line with other *in silico* models, where a mechanistic or semi-mechanistic approach to gastric emptying was applied. Andreas et al. showed that absorption of zolpidem from different formulation in the fed state was mainly determined by gastric chyme emptying (Andreas et al., 2017). They as well as Koziolok et al. also suggested that the tablet formulation could become embedded in the chyme with little access to water for dissolution resulting in prolonged delay in release (Andreas et al., 2017; Koziolok et al., 2016). This, at least for the FDDT seems unlikely since deconvolution showed that in subjects, less than 50% of the drug were emptied via the stomach road. Near complete emptying with the chyme was only observed with the regular tablet. Very recently, Kiyota et al. showed that only 0–25% of a drug were emptied via the stomach road when administered as a soft gelatine capsule while 75% of the drug in an oral solution could empty at the same time while using a similar approach to gastric emptying modeling (Kiyota et al., 2022). In contrast, an amorphous solid dispersion of the low solubility drug itraconazole showed emptying rates slower than that of water after administration directly to the antrum (Pentafragka et al., 2019). In a similar study, paracetamol suspension and solution did not differ in gastric emptying rates, highlighting that study conditions might influence the results due to different distributions of the drugs in stomach (Dietrich et al., 2024). These results suggest that rapid disintegration or dissolution promote the onset of plasma levels comparable to fasted conditions (type I) while slow release from the formulation leads to slow gastric emptying with chyme resulting in a lower C_{max} and a prolonged t_{max} (type III).

4.3. Influence of motility and gastric conditions

While the examples discussed above showed relatively low intra-subject variability in the sense that under specified conditions, nearly all subjects showed the same type of onset, febusostat and sildenafil were different. Febusostat release from Adenuric tablets was highly dependent on flow rates as observed in *in vitro* investigations (Schick et al., 2019). As a result, the *in silico* model simulated the highest variance between the two program. When comparing the simulated plasma levels with the mean concentration observed *in vivo*, one might conclude that the programs either over or underpredicted plasma concentrations

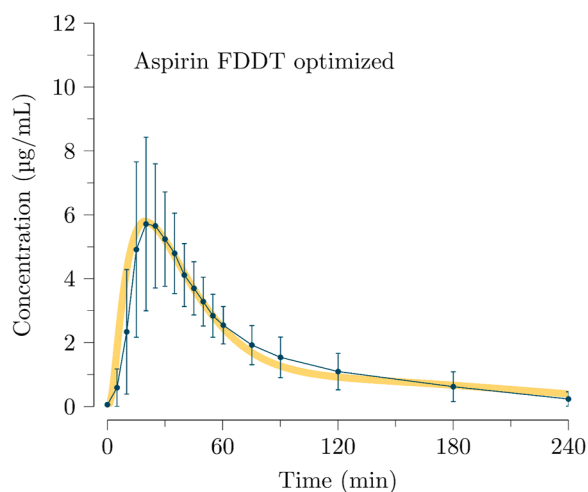


Fig. 10. Observed (blue, $n = 30 \pm \text{SD}$) and simulated plasma concentration with optimized gastric emptying profile (yellow) obtained from matching simulation results with *in vivo* measurements to best fit.

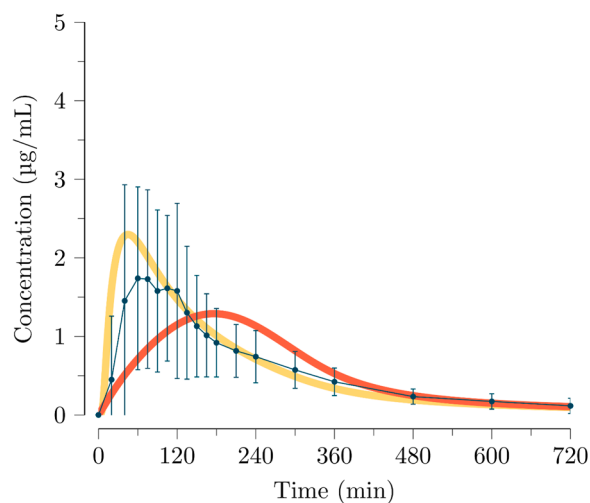


Fig. 11. Simulated and observed (blue) salivary concentration after intake of 80 mg febusostat ($n = 14 \pm \text{SD}$) in postprandial conditions. Program I (yellow) and program II (red).

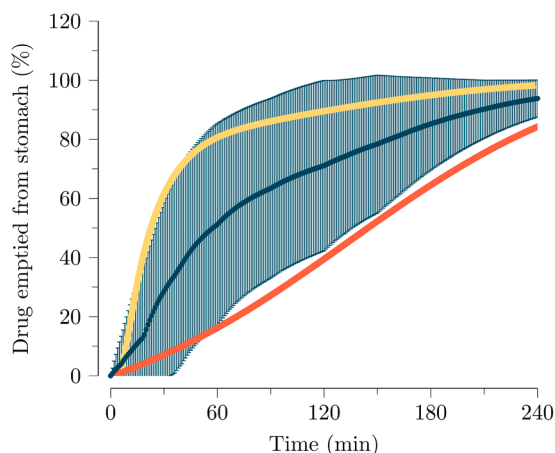


Fig. 12. Gastric emptying of febxostat obtained by deconvolution of individual plasma concentration profiles from Schick et al. Presented as mean \pm SD ($n = 14$) compared to simulated gastric emptying profiles from program I (yellow) and program II (red).

(Fig. 11). However, when looking at individual subject, two distinct groups were apparent. 9 of 14 subjects showed type I onset, corresponding to the simulations with program I, while 2 and 3 subject showed type II and III onset. Plasma concentration of the 3 subjects with type III onset were simulated well with program II, where low flow rates were used to simulate a location of the dosage form away from the stomach road or mixing with the chyme (Fig. 13). In comparison, after intake of Viagra in postprandial conditions, only 6 subjects showed type I as opposed to 20 subject who demonstrated kinetics similar to the proposed type III (Fig. 16). In contrast to the results from febxostat however, *in silico* simulations with program I as the input could not simulate the plasma levels of subjects that showed a type I onset. This suggests, that an additional factor, other than contact with the ingested liquid, must have led to a rapid disintegration of the dosage form. One explanation could be, that Viagra showed the highest susceptibility to the simulated pressure events. While there was nearly no release from the regular Aspirin tablet and the Adenuric tablet, following the simulated pressure events in the GastroDuo, release from the Viagra tablet increased significantly (Schick et al., 2019). Location of the tablet in areas with more motility could therefore be a reason for a rapid disintegration of the tablet leading fast gastric emptying and high initial plasma concentrations. It has also been described that small tablets can sometimes bypass the chyme and empty the stomach prior to

disintegration (Koziolok et al., 2016). Although it seems unlikely that this would have only happened in case of Viagra and not in any of the other included studies.

4.4. Further considerations and limitations

First of all, several factors influence the gastric emptying rate of food have not been incorporated in this model or are sufficiently investigated. For example, disease, osmolarity, gender, exercise, obesity, age and viscosity all impact the rate of gastric emptying (Moore et al., 1990; Cardoso-Júnior et al., 2007; Watson et al., 2019). Further, changes in meal viscosity and consistency can lead to water not being able to empty the stomach completely via the stomach road as shown by Grimm et al. using a homogeneous chocolate meal (Grimm et al., 2017). Gastric secretion also plays an important role in drug dissolution. Not only does it influence pH and therefore solubility of a drug in the gastric fillings, but it also impacts gastric content volumes and therefore gastric emptying rates. Koziolok et al. Stated that high secretion rates could lead compensate for the emptying of the gastric contents leading to an overall constant gastric content volume in the first minutes after intake (Koziolok et al., 2014). However, gastric secretion rates are difficult to estimate and can change depending on meal composition, age and concomitant medication (Marciani et al., 2001; Pentafragka et al., 2020; Steingoetter et al., 2015; Koziolok et al., 2015). Additionally, in food effect BA/BE studies, a next meal will already be served after 4–5 h according to the guidelines, resetting the postprandial cycle. The guidelines also recommend the intake of water 2 h post dose which is again emptied via the stomach road even at this time point, as Grimm et al. have demonstrated (Grimm et al., 2017). This could lead to another rapid emptying of drug from the stomach. However, estimating the amount emptied via the second occurrence of the stomach road was not possible for us, since in many studies, water intake is allowed ad libitum 2 h post dose and we therefore cannot retrace when water was ingested.

Body posture has recently been considered as a source of variability for gastric emptying in the fasted state in an *in silico* study (Lee et al., 2022). This could be true for the fed state as well. Especially when considering dosage forms with different densities like capsules and tablets, body posture could influence the location of the dosage or local drug concentration near the pylorus, even though *in vivo* relevance remains to be fully investigated.

Delayed or prolonged gastric emptying can not only influence the rate of absorption but also the extent of absorption, leading to negative or positive food effects. A multitude of explanations have been offered including effects of food on drug metabolism, elimination and

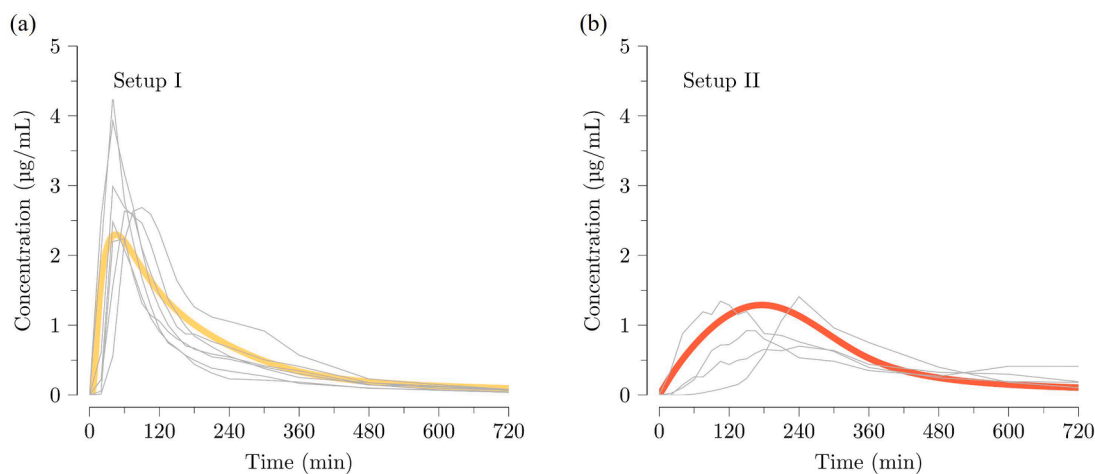


Fig. 13. Simulated (yellow = program I, red = program II) and observed plasma concentration levels after intake of 80 mg febxostat in postprandial conditions. Individual profiles divided into (a, $n = 9$) rapid onset of plasma levels and (b, $n = 4$) slow onset of plasma levels as proposed by Schick et al.

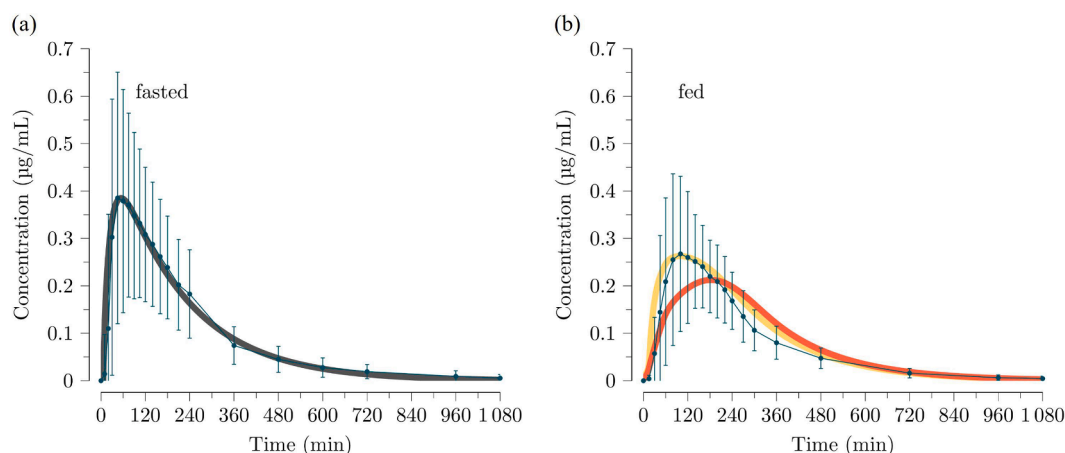


Fig. 14. Simulated and observed plasma concentration ($n = 34$) of sildenafil after intake of Viagra 100 mg in fasted state (a) and fed state (b). Fasted state was fitted to estimate pharmacokinetic parameters. Fed state pharmacokinetics were simulated based on *in vitro* results using program I (yellow) and program II (red).

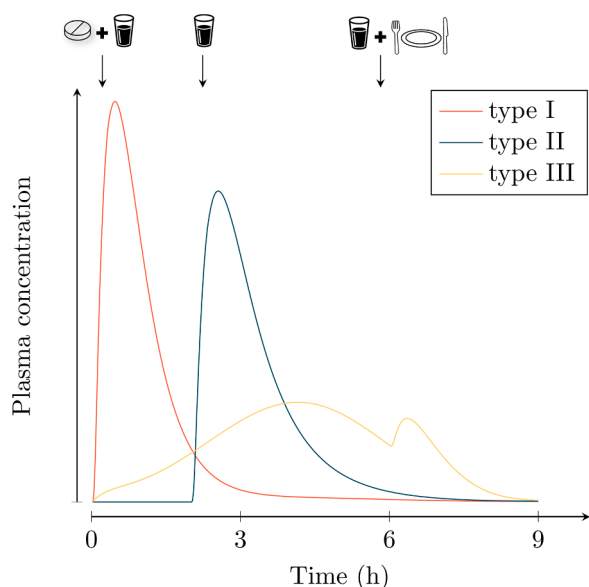


Fig. 15. Effects of the Magenstrasse on plasma concentration profiles obtained after ingestion of immediate release dosage forms. Type I: rapid onset of drug plasma concentrations, type II: rapid onset of drug plasma concentration after a lag time, type III: slow onset of drug plasma concentrations over several hours. Modified from [Koziolek et al. \(2016\)](#).

distribution, specific food and transporter interactions and influence on intestinal fluid, volumes, bile concentration, pH, osmolality and buffer capacity ([Koziolek et al., 2019](#)). However, in this study we specifically looked at drug where the extent of drug absorption was not influenced by food and absorption is rapid to mitigate confounding influences ([Schick et al., 2020](#); [Nichols et al., 2002](#); [Khosravan et al., 2008](#)). In addition, the drugs investigated in this study all high absorption drugs. While the investigated effect could apply to low permeability drugs, the presented model is probably not able to capture them due to its simplicity regarding the first order absorption process that is not limited by solubility. Furthermore, the disconnect between gastric emptying and plasma concentration for low permeability drugs would limit interpretability.

Lastly, neither *in vitro*, nor *in silico* investigations could predict the possibility of a certain type of onset to occur. While the small difference in dissolution rates for both acetylsalicylic acid formulations, caffeine and theobromine between the two tested *in vitro* programs suggested a

small inter-subject variability derived from a difference in dissolution rate, we could not predict the possibility of a specific type of onset when the difference between the two programs was more pronounced. Nonetheless, these types of experiments can help understand if a larger variability should be considered because of a dosage form being located away from the stomach road or mixing with the chyme (febuxostat) or the effect of pressure (sildenafil).

All this together demonstrates that gastric emptying and gastric drug dissolution are highly complex processes. Small changes in dissolution behavior can lead to major differences in pharmacokinetics. These effects are even more pronounced in the fed state than in the fasted state. Investigating these influences is therefore of major importance, especially with high absorption drugs where gastric emptying is of major influence on the rate of absorption. PBPK models have been proposed as a relevant tool to predict food effects ([Kesisoglou, 2020](#); [Cheng and Wong, 2020](#)). Tistaert et al. even suggested modeling and simulation could replace clinical studies for new formulations that would meet the BCS I dissolution criteria ([Tistaert et al., 2019](#)). However, to reliably predict these effects, a mechanistic understanding of the processes involved is needed and subsequent incorporation into the models is necessary. But still, many available software solutions used simple zero or first-order equations to simulate gastric emptying ([Winter et al., 2023](#)). While this could be a valid estimation, this does not reflect the critical physiological processes, limiting the ability of these models to help understand the key mechanisms involved not only to aid the development of new drugs and formulations but also to translate clinical data into patient-oriented scenarios.

5. Conclusion

The process of gastric emptying is of major importance for determining drug plasma levels of high absorption drugs in the fed state. If a drug is emptied mainly via the stomach road or together with the chyme over several hours can significantly change maximum plasma concentration and the time to reach it. In this work we investigated several factors that can lead to delayed gastric emptying in postprandial conditions, including drug solubility, dosage form, meal type and gastric motility. We showed that by combining biorelevant dissolution setups in the GastroDuo and a mechanistic *in silico* gastric emptying model that we could simulate the amount of drug emptied via the stomach road or together with the chyme. Additionally, simulation of pharmacokinetics of theobromine with different meals was possible. Overall, a mechanistic representation of gastric emptying in PBPK models can help understand the factors defining the pharmacokinetics of a drug in postprandial conditions and facilitate more informed decision-making in drug

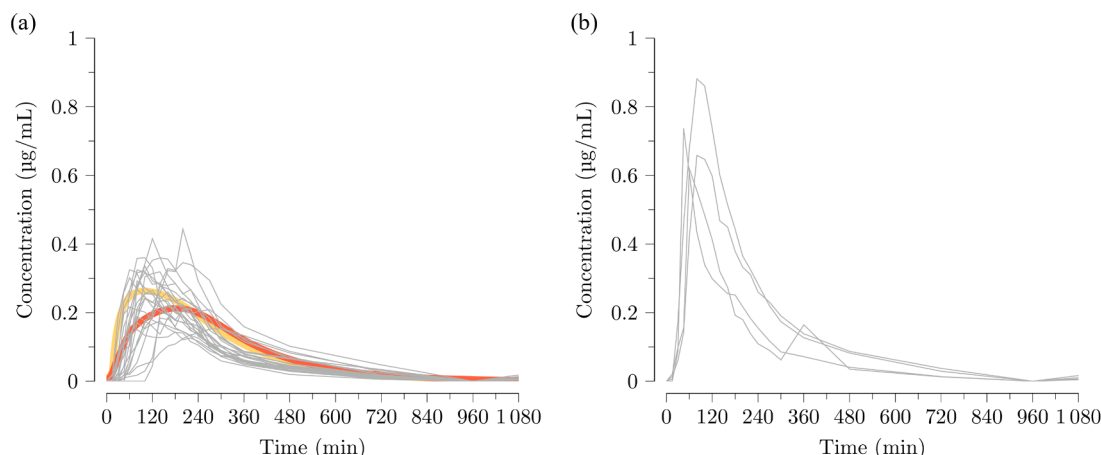


Fig. 16. Plasma concentration after intake of 100 mg silednafil under postprandial conditions grouped by subjects with type III onset (a, $n = 20$) and type I onset (b, $n = 6$). Simulated plasma concentration from program I (yellow) and program II (red).

development and optimize therapeutic outcomes for diverse patient populations.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

CRediT authorship contribution statement

Fabian Winter: Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation. **Constantin Foja:** Investigation, Formal analysis, Data curation. **Maximilian Feldmüller:** Methodology, Investigation, Formal analysis, Data curation. **Marie-Luise Kromrey:** Supervision. **Philipp Schick:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Mladen Tzvetkov:** Supervision. **Werner Weitschies:** Writing – review & editing, Supervision, Project administration, Conceptualization.

Declaration of competing interest

The authors declare no competing financial interest.

Data availability

Data will be made available on request.

Acknowledgements

We thank Mahmoud Hasan for his support with GC–MS analytics.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.ejps.2024.106788](https://doi.org/10.1016/j.ejps.2024.106788).

References

- Andreas, C.J., Pepin, X., Markopoulos, C., et al., 2017. Mechanistic investigation of the negative food effect of modified release zolpidem. *Eur. J. Pharm. Sci.* 102, 284–298. <https://doi.org/10.1016/j.ejps.2017.03.011>.
- Back, H., Song, B., Pradhan, S., et al., 2018. A mechanism-based pharmacokinetic model of fenofibrate for explaining increased drug absorption after food consumption. *BMC Pharmacol. Toxicol.* 19 (1), 4. <https://doi.org/10.1186/s40360-018-0194-5>.
- Cardoso-Júnior, A., Gonzaga Vaz Coelho, L., Savassi-Rocha, P.R., et al., 2007. Gastric emptying of solids and semi-solids in morbidly obese and non-obese subjects: an

- assessment using the 13C-octanoic acid and 13C-acetic acid breath tests. *Obes. Surg.* 17 (2), 236–241. <https://doi.org/10.1007/s11695-007-9031-4>.
- Cheng, L., Wong, H., 2020. Food effects on oral drug absorption: application of physiologically-based pharmacokinetic modeling as a predictive tool. *Pharmaceutics* 12 (7), 672. <https://doi.org/10.3390/pharmaceutics12070672>.
- Cooper, S.A., Voelker, M., 2012. Evaluation of onset of pain relief from micronized aspirin in a dental pain model. *Inflammopharmacology* 20 (4), 233–242. <https://doi.org/10.1007/s10787-012-0121-0>.
- Davis, S.S., Khosia, R., Wilson, C.G., et al., 1987. Gastrointestinal transit of a controlled-release pellet formulation of tiaprofenic acid and the effect of food. *Int. J. Pharm.* 35 (3), 253–258. [https://doi.org/10.1016/0378-5173\(87\)90137-2](https://doi.org/10.1016/0378-5173(87)90137-2).
- Devriese, L.A., Koch, K.M., Mergui-Roelvink, M., et al., 2014. Effects of low-fat and high-fat meals on steady-state pharmacokinetics of lapatinib in patients with advanced solid tumours. *Invest. New Drugs* 32 (3), 481–488. <https://doi.org/10.1007/s10637-013-0055-4>.
- Dietrich, S., Ceulemans, J., Hermans, E., et al., 2024. Understanding the conditions under which drugs are transferred from the stomach through the upper small intestine after a high-calorie, high-fat meal. *J. Pharm. Sci.* 000, 1–9. <https://doi.org/10.1016/j.xphs.2024.01.001>.
- DrugBank (Caffeine). <https://go.drugbank.com/drugs/DB00201> (Accessed 3 December 2024).
- DrugBank (Theobromine). <https://go.drugbank.com/drugs/DB01412> (Accessed 3 December 2024).
- Grimm, M., Scholz, E., Koziolok, M., et al., 2017. Gastric water emptying under fed state clinical trial conditions is as fast as under fasted conditions. *Mol. Pharm.* 14 (12), 4262–4271. <https://doi.org/10.1021/acs.molpharmaceut.7b00623>.
- Hellström, P.M., Grybäck, P., Jacobsson, H., 2006. The physiology of gastric emptying. *Best Pract. Res. Clin. Anaesthesiol.* 20 (3), 397–407. <https://doi.org/10.1016/j.bpa.2006.02.002>.
- Kelly, K., O'Mahony, B., Lindsay, B., et al., 2003. Comparison of the rates of disintegration, gastric emptying, and drug absorption following administration of a new and a conventional paracetamol formulation, using gamma scintigraphy. *Pharm. Res.* 20 (10), 1668–1673. <https://doi.org/10.1023/a:1026155822121>.
- Kesisoglou, F., 2020. Can PBPK modeling streamline food effect assessments? *J. Clin. Pharmacol.* 60 (S1), S98–S104. <https://doi.org/10.1002/jcph.1678>.
- Khosravan, R., Grabowski, B., Wu, J., et al., 2008. Effect of food or antacid on pharmacokinetics and pharmacodynamics of febusostat in healthy subjects. *Br. J. Clin. Pharmacol.* 65 (3), 355–363. <https://doi.org/10.1111/j.1365-2125.2007.03016.x>.
- Kiyota, T., Kambayashi, A., Takagi, T., et al., 2022. Importance of gastric secretion and the rapid gastric emptying of ingested water along the lesser curvature (“Magenstraße”) in predicting the in vivo performance of liquid oral dosage forms in the fed state using a modeling and simulation. *Mol. Pharm.* 19 (2), 642–653. <https://doi.org/10.1021/acs.molpharmaceut.1c00778>.
- Koenigsnecht, M.J., Baker, J.R., Wen, B., et al., 2017. In vivo dissolution and systemic absorption of immediate release ibuprofen in human gastrointestinal tract under fed and fasted conditions. *Mol. Pharm.* 14 (12), 4295–4304. <https://doi.org/10.1021/acs.molpharmaceut.7b00425>.
- Koziolok, M., Alcaro, S., Augustijns, P., et al., 2019. The Mechanisms of pharmacokinetic food-drug interactions – a perspective from the UNGAP group. *Eur. J. Pharm. Sci.* 134 (January), 31–59. <https://doi.org/10.1016/j.ejps.2019.04.003>.
- Koziolok, M., Grimm, M., Garbacz, G., et al., 2014. Intragastric volume changes after intake of a high-caloric, high-fat standard breakfast in healthy human subjects investigated by MRI. *Mol. Pharm.* 11 (5), 1632–1639. <https://doi.org/10.1021/mp500022u>.
- Koziolok, M., Grimm, M., Schneider, F., et al., 2016. Navigating the human gastrointestinal tract for oral drug delivery: uncharted waters and new frontiers. *Adv. Drug Deliv. Rev.* 101, 75–88. <https://doi.org/10.1016/j.addr.2016.03.009>.

- Koziolek, M., Schneider, F., Grimm, M., et al., 2015. Intra-gastric PH and pressure profiles after intake of the high-caloric, high-fat meal as used for food effect studies. *J. Control. Release* 220, 71–78. <https://doi.org/10.1016/j.jconrel.2015.10.022>.
- Lee, J.H., Kuhar, S., Seo, J.-H., et al., 2022. Computational modeling of drug dissolution in the human stomach: effects of posture and gastroparesis on drug bioavailability. *Phys. Fluids* 34 (8), 1–17. <https://doi.org/10.1063/5.0096877>.
- Li, M., Zhao, P., Pan, Y., et al., 2018. Predictive performance of physiologically based pharmacokinetic models for the effect of food on oral drug absorption: current status. *CPT Pharmacometr. Syst. Pharmacol.* 7 (2), 82–89. <https://doi.org/10.1002/psp4.12260>.
- Lin, L., Wong, H., 2017. Predicting oral drug absorption: mini review on physiologically-based pharmacokinetic models. *Pharmaceutics* 9 (4), 41. <https://doi.org/10.3390/pharmaceutics9040041>.
- M, V., BP, S., SA, C., et al., 2016. Efficacy of disintegrating aspirin in two different models for acute mild-to-moderate pain: sore throat pain and dental pain. *Inflammopharmacology* 24 (1), 43–51. <https://doi.org/10.1007/s10787-015-0253-0>.
- Marciani, L., Gowland, P.A., Spiller, R.C., et al., 2001. Effect of meal viscosity and nutrients on satiety, intra-gastric dilution, and emptying assessed by MRI. *Am. J. Physiol. Liver Physiol.* 280 (6), G1227–G1233. <https://doi.org/10.1152/ajpgi.2001.280.6.G1227>.
- Moore, J.G., Datz, F.L., Christian, P.E., 1990. Exercise increases solid meal gastric emptying rates in men. *Dig. Dis. Sci.* 35 (4), 428–432. <https://doi.org/10.1007/BF01536914>.
- Nichols, D.J., Muirhead, G.J., Harness, J.A., 2002. Pharmacokinetics of sildenafil after single oral doses in healthy male subjects: absolute bioavailability, food effects and dose proportionality. *Br. J. Clin. Pharmacol.* 53 (s1), 84–92. <https://doi.org/10.1046/j.0306-5251.2001.00027.x>.
- O'Shea, J.P., Holm, R., O'Driscoll, C.M., et al., 2019. Food for thought: formulating away the food effect – a PEARRL review. *J. Pharm. Pharmacol.* 71 (4), 510–535. <https://doi.org/10.1111/jphp.12957>.
- Paixão, P., Bermejo, M., Hens, B., et al., 2018. Gastric emptying and intestinal appearance of nonabsorbable drugs phenol red and paromomycin in human subjects: a multi-compartment stomach approach. *Eur. J. Pharm. Biopharm.* 129, 162–174. <https://doi.org/10.1016/j.ejpb.2018.05.033>.
- Pentafragka, C., Symillides, M., McAllister, M., et al., 2019. The impact of food intake on the luminal environment and performance of oral drug products with a view to in vitro and in silico simulations: a PEARRL review. *J. Pharm. Pharmacol.* 71 (4), 557–580. <https://doi.org/10.1111/jphp.12999>.
- Pentafragka, C., Vertzoni, M., Symillides, M., et al., 2020. Disposition of two highly permeable drugs in the upper gastrointestinal lumen of healthy adults after a standard high-calorie, high-fat meal. *Eur. J. Pharm. Sci.* 149 (January), 105351. <https://doi.org/10.1016/j.ejps.2020.105351>.
- Pepin, X.J.H., Huckle, J.E., Alluri, R.V., et al., 2021. Understanding mechanisms of food effect and developing reliable pbpk models using a middle-out approach. *AAPS. J.* 23 (1), 12. <https://doi.org/10.1208/s12248-020-00548-8>.
- Rubbens, J., Brouwers, J., Tack, J., et al., 2019. Gastric and duodenal diclofenac concentrations in healthy volunteers after intake of the FDA standard meal: in vivo observations and in vitro explorations. *Mol. Pharm.* 16 (2), 573–582. <https://doi.org/10.1021/acs.molpharmaceut.8b00865>.
- Sager, M., Jedamzik, P., Merdivan, S., et al., 2018. Low dose caffeine as a salivary tracer for the determination of gastric water emptying in fed and fasted state: a MRI validation study. *Eur. J. Pharm. Biopharm.* 127, 443–452. <https://doi.org/10.1016/j.ejpb.2018.0a3.011>.
- Sager, M., Schick, P., Mischek, M., et al., 2019. Comparison of in vitro and in vivo results using the GastroDuo and the salivary tracer technique: immediate release dosage forms under fasting conditions. *Pharmaceutics* (12), 11. <https://doi.org/10.3390/pharmaceutics11120659>.
- Scheunert, A., 1912. Über den magenmechanismus des hundes bei der getränkeaufnahme. *Pflügers Arch. für die Gesamte Physiol. des Menschen und der Tiere* 144 (11–12), 569–576.
- Schick, P., Sager, M., Voelker, M., et al., 2020. Application of the GastroDuo to Study the interplay of drug release and gastric emptying in case of immediate release aspirin formulations. *Eur. J. Pharm. Biopharm.* 151 (April), 9–17. <https://doi.org/10.1016/j.ejpb.2020.03.013>.
- Schick, P., Sager, M., Wegner, F., et al., 2019. Application of the GastroDuo as an in vitro dissolution tool to simulate the gastric emptying of the postprandial stomach. *Mol. Pharm.* 16 (11), 4651–4660. <https://doi.org/10.1021/acs.molpharmaceut.9b00799>.
- Senekowitsch, S., Foja, C., Wildgrube, T., et al., 2023. Intra-gastric carbon dioxide release prolongs the gastric residence time of postprandially administered caffeine. *Pharmaceutics* 15 (3), 1012. <https://doi.org/10.3390/pharmaceutics15031012>.
- Shono, Y., Jantravid, E., Janssen, N., et al., 2009. Prediction of food effects on the absorption of celecoxib based on biorelevant dissolution testing coupled with physiologically based pharmacokinetic modeling. *Eur. J. Pharm. Biopharm.* 73 (1), 107–114. <https://doi.org/10.1016/j.ejpb.2009.05.009>.
- Steingoetter, A., Sauter, M., Curcic, J., et al., 2015. Volume, distribution and acidity of gastric secretion on and off proton pump inhibitor treatment: a randomized double-blind controlled study in patients with Gastro-Esophageal Reflux Disease (GERD) and healthy subjects. *BMC Gastroenterol.* 15 (1), 111. <https://doi.org/10.1186/s12876-015-0343-x>.
- Tistaert, C., Heimbach, T., Xia, B., et al., 2019. Food effect projections via physiologically based pharmacokinetic modeling: predictive case studies. *J. Pharm. Sci.* 108 (1), 592–602. <https://doi.org/10.1016/j.xphs.2018.05.024>.
- Vasavid, P., Chaiwatanarat, T., Pusuwan, P., et al., 2014. Normal solid gastric emptying values measured by scintigraphy using Asian-style meal: a multicenter study in healthy volunteers. *J. Neurogastroenterol. Motil.* 20 (3), 371–378. <https://doi.org/10.5056/jnm13114>.
- Waldemeyer, M. Die Magenstraße, 1908. *Sitzungsberichte der königlichen preuss. Akad. der Wissenschaften Berlin* 595–606.
- Watson, L.E., Xie, C., Wang, X., et al., 2019. Gastric emptying in patients with well-controlled type 2 diabetes compared with young and older control subjects without diabetes. *J. Clin. Endocrinol. Metab.* 104 (8), 3311–3319. <https://doi.org/10.1210/je.2018-02736>.
- Winter, F., Schick, P., Weitschies, W., 2023. Bridging the gap between food effects under clinical trial conditions and real life: modeling delayed gastric emptying of drug substances and gastric content volume based on meal characteristics. *Mol. Pharm.* 20 (2), 1039–1049. <https://doi.org/10.1021/acs.molpharmaceut.2c00782>.