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Research paper

Age-dependent oral drug absorption in children: Assessment of a bottom-up modelling approach

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ABSTRACT

Paediatric drug development poses significant challenges due to the unique physiological and ethical considerations in children. Physiologically Based Pharmacokinetic (PBPK) modelling has emerged as a valuable tool for predicting paediatric drug absorption and optimising dosing strategies. This study aimed to refine PBPK modelling for paediatric applications by developing a customised PK-Sim-based paediatric PBPK (pPBPK) model for four drugs that are part of the Model List of Essential Medicines for Children by the World Health Organisation: paracetamol, ibuprofen, darunavir, and itraconazole. The model incorporated age-specific gastrointestinal parameters for four paediatric age groups, minimising the need for parameter interpolation or scaling. The effect of food on drug absorption was investigated by extending the absorption model to account for bile and excipient solubilisation. A literature review identified gaps in the understanding of paediatric intestinal parameters necessary for pPBPK modelling. Biorelevant *in vitro* dissolution and solubility data were integrated to enhance prediction accuracy. Validation with clinical pharmacokinetic data demonstrated the model's reliability across different paediatric age groups. Sensitivity analyses highlighted the influence of gastric emptying time, small intestinal transit, and bile salt concentration on drug pharmacokinetics. This research underscores the potential of pPBPK modelling to inform paediatric dosing strategies while addressing current gaps and challenges.

1. Introduction

The lack of suitable paediatric medicines has long been a significant challenge. Despite regulatory efforts in the United States and the European Union since the early 2000s, including obligations, rewards and incentives to promote paediatric drug development, many therapeutic areas still lack appropriately tested and formulated medicines for children. This is due to several factors, most notably the unique challenges associated with paediatric drug therapy. Age-related differences in drug absorption, distribution, metabolism, and excretion introduce significant variability in pharmacokinetics across the paediatric population. At the same time, children represent a highly vulnerable patient group, requiring stringent ethical and regulatory safeguards to minimise the risks involved in clinical pharmacokinetic studies. To address these challenges and support the development of safe and effective medicines for children, various extrapolation approaches are being explored. These include the use of pharmacokinetic modelling to minimize the need for extensive clinical studies in paediatric populations [1]. Traditional pharmacokinetic modelling is often based on extrapolation from adult data, which may not accurately capture the dynamic physiological changes that occur during childhood [2]. Accordingly, the validity of the corresponding models for the paediatric population is rather questionable. As a result, there is a critical need for paediatric-specific modelling approaches to guide safe and effective drug dosing in this vulnerable population. A recent article summarising the experience gained by the European Medicines Agency (EMA) on this topic even discusses that for very rare diseases with high medical need, a waiver of paediatric clinical trials based on population pharmacokinetics (PopPK) and/or physiology-based pharmacokinetic modelling (PBPK) may be possible [3]. This has led to a sharp increase in the use of paediatric PBPK (pPBPK) modelling in academia, the pharmaceutical industry and regulatory authorities. Overall, a 33-fold increase was reported between 2005 and 2020 [4]. The FDA reported that pPBPK modelling applications were used in 15 % and 9 % of the total applications received between 2008–2017 and 2018–2019, respectively [5,6].

Although pPBPK and PBPK have generally gained importance, they

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are mainly used for the prediction of PK covariates and population parameters that may affect dose selection, while formulation- and absorption modelling are only considered in very few studies [4,7]. The latter would be particularly important for children, where clinical or pharmacokinetic studies raise ethical concerns for several reasons, but where not only the administered drug dose and the dosage form, but also the mode of administration of a dosage form can differ significantly from drug administration to adults. In clinical studies in adults, an oral dosage form is usually administered with a glass of water on an empty stomach or after a standardised meal, which is very often a high-calorie, high-fat standard breakfast [8,9]. For children, there is no such standard protocol for clinical studies, which would also be difficult to implement given the wide age range covered by the term 'children'. It is clear that the standard meal used in clinical studies with adults would be absolutely unsuitable for young children and that the amount of water to be administered with the dosage form would also have to be adapted to the age of the children. To improve the acceptance of oral medicines by children, the medications are often administered during a meal. Since, compared to fasted dosing, this mode of administration may affect the *in vivo* performance of a dosage form, it is equally important to consider both the quantity and characteristics of the meal administered and how this relates to the anatomy and physiology of the child in question when assessing the *in vivo* performance of a medicine.

According to the FDA's Draft Guidance on "General Clinical Pharmacology Considerations for Pediatric Studies of Drugs, Including Biological Products", if a medication formulation approved for use in adults is also intended for paediatric use, an additional food-effect study may not be required [10]. Likewise, if a paediatric formulation closely resembles the adult version and is approved based on *in vitro* dissolution tests, a separate food-effect study might not be necessary. However, it is important to bear in mind the physiological and nutritional differences between adults and children, including differences in the anatomy and function of the gastrointestinal tract. It is precisely because of these differences that extrapolation of food-drug interactions from adults to children, especially very young children, is not always appropriate.

PBPK modelling offers a promising approach in this case by capturing the complex interplay between drug properties, formulation characteristics, physiological factors, and dosing regimens in paediatric patients. Unlike traditional empirical approaches, PBPK models incorporate detailed anatomical, physiological, and biochemical parameters to simulate drug disposition across different age groups and developmental stages, providing valuable insights into paediatric pharmacokinetics [11]. However, detailed and reliable data on age-specific physiology, especially needed for modelling oral absorption, are currently sparse. Despite that fact, the fixed compartmental structure of many commercially available software solutions requires the input of a large number of physiological parameters, even when age-dependent data are lacking. In many cases these parameters are therefore estimated, assumed or scaled according to age, bodyweight or height, regardless of whether a relationship to any of these factors is known or not [12]. In addition to physiological changes, non-scalable factors such as specific diets and paediatric formulations pose challenges and limit the possibility of directly comparing and translating adult pharmacokinetic data to children.

According to a recent review of pPBPK model usage in clinical and drug development contexts, PK-Sim has emerged as the second-most widely used platform, following proprietary commercial software for pPBPK modelling [4]. This platform estimates absorption rates based on solubility and membrane affinity estimated from logP and molecular weight [13,14]. Additionally, it accounts for the diffusion of the drug molecules through the unstirred water layer. However, particularly in the case of poorly soluble drugs, absorption is not only determined by these factors, but rather by a complex interplay of solubilisation, diffusion, distribution and permeation. Accordingly, an improvement in solubility does not necessarily result in increased absorption [15,16]. In its current form, the PK-Sim model does not account for the interplay between increased drug solubility mediated by food components, formulation excipients and bile salts, nor for the resulting effects on diffusion and permeation. This limitation is significant, as these interactions are considered fundamental to mechanistic absorption modelling and are essential for accurately estimating the impact of complex gastrointestinal contents, such as those present in different regions of the GI tract under fed or fasted conditions, on oral drug absorption [17–19].

This study aimed to address key gaps in paediatric pharmacokinetic modelling by developing a pPBPK model using PK-Sim for four drugs on the Model List of Essential Medicines for Children (EMLc) published by the World Health Organisation (WHO): paracetamol, ibuprofen, darunavir, and itraconazole. The initial step involved a comprehensive review of the current literature to assess the availability of reliable data on intestinal physiological parameters and their applicability in establishing a pPBPK model. Particular emphasis was placed on identifying knowledge gaps in order to reduce the reliance on parameter scaling and instead utilise robust *in vivo data* wherever possible. The identified data were then incorporated into the compartment structure of the PK-Sim-based pPBPK model. Both the model structure and absorption mechanism were modified from the standard PK-Sim model to allow investigation into the effects of excipients and food components on drug absorption. Following validation through comparison with available *in vivo* data, the model was further refined by integrating *in vitro* solubility- and dissolution data from a previously published study in biorelevant media designed to simulate postprandial intestinal conditions in preschool children [20,21]. Finally, the potential of incorporating such biorelevant paediatric *in vitro* data into in the *in silico* model was evaluated with the aim of estimating the effects of co-administered child-specific meals on the absorption of the studied drugs in children of defined age groups.

2. Methods

2.1. Model drugs and formulations

Four model drugs, i.e., paracetamol, ibuprofen, darunavir and itraconazole, which are all part of the WHO's EMLc were selected for this study [22]. These model drugs cover a wide range of properties that may have different effects on *in vivo* solubility and −absorption. Additionally, they support the stepwise integration of model functions such as pH-dependent solubility (ibuprofen), bile micelle-mediated solubilisation (darunavir), and formulation-specific effects (itraconazole). The corresponding drug products investigated were three commercial liquid formulations suitable for paediatric use: Perdolan® Syrup 32 mg/mL (paracetamol), Prezista® Oral Suspension 100 mg/mL (darunavir), Sporanox® Oral Solution 10 mg/mL (itraconazole) and an oral immediate-release tablet formulation: IbuHEXAL® akut tablets 200 mg (ibuprofen). The specific formulations were selected based on two previously published in-house studies, in which they were extensively investigated using biorelevant *in vitro* dissolution testing. The resulting data, obtained under both simulated fasted and various postprandial paediatric dosing conditions, provided a comprehensive and publicly available *in vitro* dataset that served as a solid foundation for the present study [20,21]. Table 1 shows the physicochemical characteristics of the model drugs and the dosing recommendations of the corresponding drug products to be considered in the *in silico* model to be established.

2.2. Biorelevant in vitro solubility- and dissolution data

Biorelevant solubility and dissolution of the model drugs paracetamol, ibuprofen, darunavir and itraconazole were investigated in two previous studies by Freerks *et al.* [20,21]. The cited study aimed to mimic gastric and small intestinal conditions in children of different age groups following the consumption of an age-appropriate volume of water or various types of paediatric breakfast meals. The authors

Table 1
Physicochemical properties of the investigated model drugs and recommended dosing in paediatric patients.

	Paracetamol	Ibuprofen	Darunavir	Itraconazole
pKs	9.38 [23]	4.45 [24]	2.39 [25]	3.7 [26]
Molar mass (g/mol)	151.16 [27]	206.28 [24]	547.7 [28]	705.64 [26]
logP	0.46 [23]	3.97 [23,29]	1.88 [30]	5.66 [26]
Recommended dose	12.5 mg/kg	10 mg/kg	Toddler: not applicable Pre-School child: 600 mg[a] School child: 600 mg[a] Adolescent: 600 mg[a]	5 mg/kg up to 200 mg

[a] Dosing for darunavir based on dosing recommendations for treatment-naïve paediatric patients or antiretroviral treatment-experienced paediatric patients with no darunavir resistance-associated mutations according to the Prezista® Oral Suspension label. [b]Prezista® is not recommended for patients aged 3 years or younger.

reported a comprehensive dataset detailing the solubility of all model drugs in simulated resting gastric- and intestinal fluids, as well as in various simulated paediatric breakfast meals (SPBMs). Additionally, they provided dissolution profiles of the studied drugs, generated using a biorelevant paediatric *in vitro* dissolution model. This model accounts for the oral administration of the model drugs in the form of the above-mentioned marketed products, taken with a glass of water or a paediatric breakfast meal. The cited *in vitro* simulations replicated conditions in the stomach and small intestine of a pre-school child for different ingestion scenarios, incorporating average physiological gastric residence times and the transfer of gastric contents into the small intestine, followed by a one-hour intestinal residence period. To assess whether administering an age-appropriate amount of a simulated standardised breakfast, as used in clinical studies in adults, would provide comparable results, the *in vitro* study was expanded to include such a simulation. As will be explained in detail in the following sections, the data reported by Freerks *et al.* were incorporated at multiple stages of the modelling process to inform the *in silico* model.

2.3. *In silico model*

The customised *in silico* model was created in MoBi Version 11.1 – Build 133 from Open Systems Pharmacology (*www.open-systems-pharmacology.org*). After model development, it was transferred to PK-Sim® Version 11.1 – Build 133 from the same platform to perform the subsequent simulations. PK-Sim was selected for this step due to its capability to conduct population-based simulations through parameter variation. The focus was on the simulation of gastrointestinal parameters and absorption. Instead of attempting to adjust or estimate physiological values for all intestinal parameters required to populate a pre-built model in PK-Sim or other software solutions such as GastroPlus® and Simcyp®, extrapolations and estimates were avoided in favour of building the structure of the *in silico* model around the available and reliable *in vivo* data. Consequently, the number and distribution of the gastrointestinal compartments as well as some other parameters implemented differ from the more commonly used models. The customised *in silico* model consists of a stomach compartment, four small intestinal compartments and one compartment representing the large intestine. Absorption, distribution and elimination is handled using a two-compartment model. The *in silico* model was developed based on four reference individuals, each representing a specific age group. The respective age groups were defined in the EMA Note for Guidance on Clinical Investigation of Medicinal Products in the Paediatric Population and further subdivided as recommended in the EMA Reflection Paper on Formulations of Choice for the Paediatric population. The age groups included were toddlers (12–23 months), pre-school children (2–5 years), school children (5–12 years) and adolescents (12–18 years) [31,32]. Further details about the general structure of the model and the parameters included are described below.

2.3.1. *Gastrointestinal compartments*

2.3.1.1. Stomach. The stomach serves as the first relevant compartment in the gastrointestinal model. Upon ingestion, the orally administered dosage form enters the stomach along with co-administered water, which mixes with the resting gastric fluid. When administered during a meal, the meal contents – specific to the type of meal consumed by the child – also mix with these fluids. Notably, the volume of resting gastric fluid increases with age. However, when normalised to bodyweight, there is no significant difference in gastric fluid volume between infants and adults [33,34]. In the present model, the resting gastric fluid volume was set at 0.28 mL/kg and multiplied by the median bodyweight for each age group. The volumes of simulated co-ingested water and food, if applicable, were then added to the resting gastric fluid volume and the resulting combined volume served as the basis for calculating drug solubility and transport.

Gastric secretion rates were not included in the present model, as the volume of resting gastric fluid volume was maintained constant due to the balance between gastric secretion and gastric emptying. However, for a more mechanistic model or in cases where gastric solubility is not evaluated through *in vitro* testing, incorporating gastric secretion rates may be valuable. According to the literature basal gastric secretion rates in newborns and toddlers range from 1.2 to 2.67 mL/kg/h and can increase to as high as 2.9 mL/kg/h under stimulated conditions in adults [33].

Gastric emptying and the transport of the dissolved or undissolved drug from the stomach into the proximal small bowel, representing the first compartment of the small intestine in the model is highly variable and influenced by many factors, including the solubility of the drug and the dosage form administered, water intake, portion size, composition and caloric content of the co-administered meal, the viscosity and osmolality of the gastric contents, as well as the age and the disease state of the patient. Depending on the type of meal consumed, gastric emptying can be described as a first-order or zero-order process. It is therefore not possible to specify a fixed value for the gastric emptying time. Instead, in the present study, the effect of gastric emptying time was investigated by a sensitivity analysis over a range from 20 to 160 min.

Gastric pH was not directly included in the calculations but was instead accounted for through biorelevant *in vitro* solubility- and dissolution testing. The pH values investigated ranged from pH 2.7 to 6.8, depending on the simulated prandial state and the composition of the SPBMs used in biorelevant *in vitro* experiments. Drug-specific solubility data obtained under these gastric conditions were subsequently incorporated into the simulations.

2.3.1.2. Small intestine. When emptied from the stomach, the drug enters the small intestine. In the present model, the small intestine is subdivided into 4 compartments, namely the duodenum, proximal, middle and distal small intestine. Compared to other models that often use up to seven small intestinal segments, the number of segments was reduced in this approach. This decision was based on the fact that when assessing regional differences such as small intestinal fluid volumes, pH, and bile salt concentration in *in vivo* studies, or reporting data in the literature, the small intestine is typically subdivided into these four segments, if at all.

The length of the small intestine increases with the height of the child and increases linearly with body size from around one year of age until adulthood [35]. The total length of the small intestine for each age group is shown in Table 3. The length of each of the 4 individual small intestinal segments implemented in the model was calculated from the total length of the small intestine.

The diameter of the small intestine also increases during growth. It is reported as 1.2–2.6 cm in 1 to 8 day old newborns and increases to 3–6 cm in the proximal part and 1.5–2.5 cm in the distal part by the time of reaching adulthood [36]. Since no corresponding data are currently available for other age groups, a fixed small intestine diameter of 2 cm was used in the model for these groups instead of age-specific *in vivo* values.

The pH in the small intestine is higher than in the stomach. Moreover, *in vivo*, a mean pH gradient with ascending pH values in the direction of the distal ileum can be observed. Accordingly, each of the four small intestine segments established in the model was assigned to an individual pH value. The division was made into duodenum, a proximal-, middle- and distal section of the small intestine and not into the usual three sections, i.e., duodenum, jejunum and ileum. Average pH values in the small intestine of healthy children between 8 and 14 years of age (median 12 years) are pH 6.4 in the duodenum, pH 6.6 in the proximal section, pH 6.9 in the middle and pH 7.4 in the distal section of the small intestine [37]. Unfortunately, there are no studies to date that have investigated the influence of age on intraluminal small-intestinal pH. However, the pH values measured children are approximately the same as those reported for adults, suggesting that there is little or no difference between the age groups with regard to this parameter [38].

In order to describe the transport of an orally administered drug through the small intestine, data on *in vivo* transit times of dosage forms through the paediatric gastrointestinal tract were required. First, data from published capsule-endoscopy studies with various non-disintegrating telemetric capsules were considered. Results form these studies indicate that transit through the small intestine is highly variable, resulting in large fluctuations between and within studies. The average total small intestinal transit time measured in children in the studies considered ranged from 294 to 450 min, which corresponds to around 5 to 7.5 h [37,39–43]. However, particularly after administering an immediate-release formulation, the drug is not transported through the small intestine as a non-disintegrating capsule, but is rather present as a dissolved substance or, if not yet completely dissolved or if the solubility is exceeded, as a suspension. Therefore, the literature was searched for transit times that better describe the gastrointestinal transit of dissolved or suspended drugs. One possible transit time in this context would be the oro-caecal transit time (OCTT), i.e. the time that elapses from the oral intake of a liquid until it reaches the caecum. The OCTT can be determined using the lactulose breath test. This utilises the fact that lactulose cannot be digested in the small intestine and is only partially digested by bacteria in the cecum and large intestine after passing the ileocecal valve. The resulting hydrogen is absorbed and exhaled. The increase in the hydrogen content in the exhaled air can be used to indicate when the lactulose has reached the caecum and thus its OCTT. A limitation of the OCTT is that the gastric and small intestinal residence times cannot be considered separately. Hence, it does not provide an accurate measure of the small intestinal transit time. Instead, it should always be combined with reliable gastric residence time data to estimate small intestinal transit time. Table 2 shows OCTTs measured in children of different age groups. For the dispersed drug included in the present model, small intestinal transit time was set to 80 min representing the difference between OCTT and gastric emptying time. Additionally, a sensitivity analysis was performed across a range of 50 to 120 min. The fact that the small intestine is divided into four sections in this model made it necessary to set a residence time for each of the four sections. Due to the lack of corresponding data for fluids or dispersed drug, the relative transit time of a telemetric capsule was used for this purpose. Fallingborg *et al.* reported that this capsule spent 8 % of the small intestinal transit time in the duodenum, 5 % in the proximal, 12 % in the middle and 75 % in the distal section of the small bowel [37]. The transport of the drug through the individual sections of the small intestine and its emptying from these was considered as a first-order process and calculated similarly to the emptying of the drug from the stomach (Eq. (1)):

Table 2
Overview of oro-caecal transit times (OCTTs) reported for different age groups.

Study	Age (years)	OCTT (min) (mean ± standard deviation (min − max))
Khin *et al.* [44]	1–2	92.2 ± 30.6
	2–3	85.8 ± 11.0
	3–4	91.8 ± 19.9
	4–5	93.7 ± 19.3
	1–5	90.2 ± 20.2
Madrid *et al.* [45]	4–6	68.0 ± 4.6
	7–9	89.5 ± 17.6
	10–12	69.5 ± 9.3
	13–15	73.3 ± 8.8
Vreugdenhil *et al.* [46]	0–1 months (mean: 2.3 months)	96.7 ± 25.2 (70–120)
	1–14 (mean: 7.3)	82.3 ± 25.6 (50–120)
	22–27 (mean: 24)	74.4 ± 24.8 (30–140)

$$\frac{dn}{dt} = n^* \frac{\ln(2)}{SITT^*fraction\ of\ each\ segment} \tag{1}$$

While dispersed drug is transported continuously through the small intestine and a single dose can spread over various small intestinal sections, as described above, non-disintegrating solids, such as monolithic oral dosage forms, can only occupy one compartment at a time. These are moved discretely from one compartment to the next at defined time points following ingestion.

The fluid volumes within the small intestine across various paediatric age groups were recently quantified by Van der Veken *et al.* using magnetic resonance imaging [12]. Although an age-dependent increase in intestinal fluid volume was observed, the correlation with commonly accessible anthropometric parameters such as body mass index (BMI), bodyweight, height, and small intestinal length was limited. In the present study, the reported data were stratified according to the relevant age groups. However, due to differences in the anatomical segmentation of the small intestine between the study by Van der Veken *et al.* and the current investigation, direct comparison was limited to the duodenal segment. Consequently, the reported duodenal volumes were adopted directly, while the fluid volumes for the proximal, middle, and distal segments of the small intestine were estimated by subtracting the duodenal volume from the total small intestinal volume and dividing the remainder equally among the three segments.

Another critical parameter influencing the *in vivo* solubility and dissolution of drugs in the gastrointestinal tract is the concentration of bile salts in the intestinal fluid. Bile salt concentrations in paediatric populations range from 1.36 to 13.55 mmol/L in the fasting state and from 0.50 to 14.5 mmol/L in the fed state across all age groups [33]. However, due to the limited availability of age-specific data in the literature, a mean bile salt concentration of 7.77 mmol/L was adopted as a standard value for all paediatric age groups in the present study. This value originates from the only study that investigated small intestinal bile concentration in in the small intestine of children aged 4 to 14 years, a range that that closely corresponds to the school-age paediatric subgroup, and includes sufficient information regarding the clinical background of the participants [47]. To evaluate the impact of bile salt concentration on drug solubility, a sensitivity analysis was performed using the minimum and maximum values reported for school-aged children to investigate the importance of this parameter and evaluate the necessity of more studies measuring bile salt concentration in paediatrics.

2.3.1.3. Large intestine. As shown by Strujis *et al.*, the length of the small intestine correlates well with bodyweight, although their study only included children with a bodyweight of no more than 20 kg [48]. By contrast, Wozniak *et al.* also measured the length of the large bowel in children with a bodyweight higher than 20 kg [49] The available data indicate that the colon grows until a bodyweight of about 20 kg is reached and then no longer grows significantly. The mean value reported for subjects over 20 kg in bodyweight was 129.29 cm. No data was found for the diameter of the large intestine in children. Based on the comparison of small and large intestinal diameters in adults, it was assumed that the large intestinal diameter would be greater than that of the small intestine. Accordingly, a diameter of 3 cm was set for the paediatric model.

In the large intestine, the pH value is slightly lower than in the small intestine and also varies between the segments. According to pH values measured in children between the ages of 8 and 14 years, the mean pH is 5.9 in the cecum, 5.5 in the ascending section, 5.3 in the transverse section, 5.8 in the descending section and 6.5 in the sigmoid colon [37]. Due to very limited available data, no additional age dependency or tendency can be determined in this age range. Overall, the available data show a low variability. In the established model, the colon was divided into cecum, ascending, transverse, descending and sigmoid colon. Since the reported large intestinal pH values are within a quite narrow pH range and the absorption efficiency in the large intestine is very limited compared to the small intestine, the large intestinal pH was set as a constant and not investigated as a source of variability in the paediatric population in order to avoid further complicating the model.

The colonic transit time (CTT) varies greatly. In the literature, values of 26.4 to 39.6 h have been described for children, whereby the variations within the studies were very high [37,39,43,50]. Wagner *et al.* reported colon transit times of 7.2 to 86.4 h from a study in children whose average age was 10 years (range: 4–15 years). The transit time used in the present model was 39.6 h. Similar to the small intestine, the transport of dispersed and dissolved drug through the large intestine follows a first-order kinetic process, as described by Eq. (1). Undisintegrated dosage forms were assumed to enter the large intestine after an average transit time of 6.2 h in the small intestine (Table 3) [38–42].

The volume of free fluid available for drug dissolution in the colon is generally very low. Van der Veken *et al.* and Goelen *et al.* investigated this parameter using MRI imaging of the gastrointestinal tract in children. Goelen *et al.* studied children aged 0 to 16 years and reported a mean free fluid volume of 22.45 mL with a large standard deviation (±41.30 mL) [12,51]. This mean appears unusually high, especially when compared to other studies, including those involving adult participants. However, the reported median volume of 0.80 mL aligns closely with findings from Van der Veken *et al.*, who stratified their data by age groups and found similar values in school-aged children. In the present model, the data set reported by Van der Veken *et al.* was considered.

Table 3
Values of intestinal physiological parameters used in the *in silico* simulations for each paediatric population addressed in the study. Values in bracket denote the range between minimum and maximum values investigated in the sensitivity analysis.

Parameter	Toddlers	Pre-school children	School children	Adolescents
Age	12–23 months	2 – 5 years	6–11 years	12–18 years
Bodyweight (kg)	11 (10–12.5)	15.5 (12.5–19)	28 (19–42)	56 (42–60)
Height (cm)	78 (76–80)	96 (83–109)	130 (109–150)	167 (150–170)
Resting gastric fluid volume (mL)		4.79–9.17	11.2–27.1	28.8–33.0
Gastric emptying time (min)	94–256	128 (80–175)	20–147	84–157
Small intestine length (cm)	431 (387–475)	453 (302–603)	528 (403–652)	545 (412–677)
Small intestinal transit time of non-disintegrating solids (min)	372 (294–450)			
Small intestinal transit time of solutes and suspensions (min)	80 (50–120)			
Duodenal fluid volume (mL)	2.5 (0.2–12.3)	4.2 (0.3–19.0)	5.9 (1.5–15.5)	7.6 (3.3–21.9)
Small intestinal fluid volume (mL)	31 (4–105)	37 (3–147)	45 (5–105)	62 (22–225)
Duodenal bile salts (mmol/L)	7.77 (3.35–14.68)			
Small intestinal pH	Duodenum: 6.4 (6.2–6.6), proximal: 6.6 (6.4–6.8), middle: 6.9 (6.7–7.1), distal: 7.4 (7.2–7.6)			
Large intestine length (cm)	82.2	105.6	129.29	129.29
Large intestinal fluid volume (mL)	1.1 (0.1–8.7)	0.5 (0.1–35)	0.5 (0.1–12)	0.3 (0.1–21)
Large intestinal pH	Caecum: 5.9, ascending colon: 5.5, transverse colon 5.3, descending colon: 5.8, sigmoid colon: 6.5			

2.3.2. *Integration of biorelevant solubility and dissolution data*

The solubility of the investigated drug substances in aqueous media of different pH values, SPBMs and Ensure® Plus, as well as the *in vitro* dissolution (and precipitation) of the corresponding commercial drug products under conditions simulating gastrointestinal conditions after their administration with a glass of water or an age-appropriate breakfast meal, were investigated in *in vitro* studies by Freerks *et al.* [20,21]. They had established a toolbox of complex media that allow the fundamental physiological elements of the intraluminal fluids in the different segments of the gastrointestinal tract of children to be mimicked and also a two-stage dissolution model allowing to mimic gastric and small intestinal conditions in an age-specific scale.

In the present model, the solubility data of the drugs under investigation in Fasted and Fed State Simulated Paediatric Small Intestinal Fluids for pre-school children (FaSPSIFpsc and FeSPSIFpsc) were incorporated as "small intestinal solubility" and consequently used for calculating the absorption rate for all simulations addressing the administration of the respective drugs in the fasted state.

The dissolution and precipitation behaviour of the tested formulations was obtained from the two-stage dissolution experiments described by Freerks *et al.* [20,21]. The corresponding *in vitro* test design considered physiological gastric and small intestinal resting fluid volumes, composition, and pH, as well as age-appropriate co-administered water volumes (90 mL). For postprandial conditions, age-appropriate food portions were simulated using different SPBMs: 260 mL for the cassava porridge, 213 mL for the toast breakfast, 290 mL for the American breakfast. To represent a corresponding food portion of an adult standard breakfast, 250 mL Ensure® Plus was included in the study [21]. Gastric residence time and small intestinal transit time were set to 30 and 60 min, respectively. A physiological pH gradient (pH 6.5 to 7.2) was applied to simulate transit through the different regions of the small intestine.

2.3.3. *Absorption*

Calculation of the absorption rate from the lumen of the small intestine was entirely changed from the default PK-Sim model. The new absorption model is based on the work of Sugano *et al.* and incorporates the effect of bile micelles on the solubility and ability of drugs to diffuse through the unstirred water layer (UWL). In its default version, PK-Sim does not account for the influence of bile salts on drug solubility or the UWL as a diffusion barrier as many other software programs do. This is particularly important, however, as the effect of age on bile salt concentration was to be investigated. Age-dependent variations in bile salt levels can significantly impact drug solubilisation, thereby altering the effective concentration of poorly soluble drugs available for absorption.

In the new model effective intestinal membrane permeability (P_{eff}) is calculated according to Eq. (2), where $f_{dissolv}$, f_{mono} and f_{bm} are the fraction of dissolved, free (free monomer molecule) and micelle-bound drug, respectively.

$$P_{eff} = \frac{1}{\frac{1}{f_{dissolv}\left(\frac{D_{mono}*f_{mono}+A'*D_{bm}*f_{bm}}{h_{iUWL}}+P_{WC}\right)} + \frac{1}{f_{dissolv}*f_{mono}*P_{ep}*Acc*VE}}*PE \quad (2)$$

P_{eff} = effective membrane permeability, $f_{dissolv}$ = fraction of drug dissolved, D_{mono} = diffusivity of the free drug, f_{mono} = fraction of freely soluble drug, A' = interaction between the mucus layer and bile micelles, D_{bm} = diffusivity of the micelle bound drug, f_{bm} = fraction of micelle bound drug, h_{iUWL} = thickness of the UWL, PWC = permeability by water convection, P_{ep} = epithelial membrane permeability, VE = villi expansion, PE = plicate expansion, Acc = accessibility to the villi surface.

$f_{dissolv}$ is calculated using Eq. (3) and is set to 1 unless the drug concentration in the small intestine exceeds the maximum solubility in the simulated small intestinal media measured *in vitro* ($S_{dissolv}$).

$$f_{dissolv} = c > S_{dissolv}?\left(\frac{S_{dissolv}}{c}\right) : 1 \quad (3)$$

$$f_{mono} = \frac{S_0}{S_{dissolv}} \quad (4)$$

$$1 = f_{mono} + f_{bm} \quad (5)$$

f_{mono} is calculated using Eq. (4), where S_0 represents the solubility of each drug in the FaSPSIFpsc or FeSPSIFpsc underlying Blank, i.e., the corresponding buffer without added bile salt but otherwise with the same composition and pH.

f_{bm} is calculated by subtraction of the free fraction from $f_{dissolv}$, which has been set to 1 (Eq. (5)). Diffusivity of the free drug (D_{mono}) can be estimated from its molecular weight (Eq. (6)), while the diffusivity of the micelle bound drug (D_{bm}) is calculated based on the radius of the micelles (d_{bm}) (Eq. (7) [52].

$$D_{mono} = 10^{-4.113-0.4609*\log(MW)}*1.41 \quad (6)$$

$$D_{bm} = \frac{6.63}{d_{bm}}*10^{-6} \quad (7)$$

Eq. (2) comprises two key fractions that describe distinct aspects of the intestinal absorption process. The first fraction represents the diffusion of the dissolved drug ($f_{dissolv}$) through the unstirred water layer (UWL). This diffusion is influenced by the thickness of the UWL (h_{iUWL}) and the permeability associated with water convection (P_{WC}) [53–55]. The second fraction describes the drug's permeation through the epithelial membrane, which is governed by the membrane permeability (P_{ep}). In addition, physiological characteristics of the small intestinal mucosa, such as accessibility to the villi surface (Acc), villi expansion (VE), and plicate expansion (PE) also contribute to this process [56–58]. As in other *in silico* models, P_{ep} is estimated from the drug's logP value, as defined in Eq. (8) [59].

$$P_{ep} = \left(2.36*10^{-6}*10^{logP^{1.10}}\right)\frac{cm}{s} \quad (8)$$

For ionisable drugs, the uncharged fraction (f_0) reduces the epithelial permeability. f_0 is calculated according to the Henderson-Hasselbalch equation Eq. (9).

$$f_0 = \frac{1}{1+10^{pH-pK_a}} \quad (9)$$

Finally, the rate at which the drug is absorbed from the small intestinal lumen is calculated by Eq. (10), where D_{GI} and V_{GI} are the radius and the volume of the small intestine respectively.

$$\frac{dn}{dt} = DF*\frac{2}{\frac{D_{GI}}{2}}*P_{eff}*V_{GI}*c_{perm} \quad (10)$$

The impact of drug complexation and solubilisation by cyclodextrins on P_{eff} is addressed by expanding Eq. (2) to include the modifying term shown as Eq. (11), similar as done for the fraction of drug solubilised by bile micelles, resulting in Eq. (12), where D_{cyc} denotes the diffusivity of the cyclodextrin complexes, calculated based on Eq. (7), assuming D_{bm} is substituted with D_{cyc} and f_{cyc} is the fraction of drug solubilised by cyclodextrin.

$$D_{cyc}*f_{cyc} \quad (11)$$

$$P_{eff} = \frac{1}{\frac{1}{f_{dissolv}\left(\frac{D_{mono}*f_{mono}+A'*D_{bm}*f_{bm}+D_{cyc}*f_{cyc}}{h_{iUWL}}+P_{WC}\right)} + \frac{1}{f_{dissolv}*f_{mono}*P_{ep}*Acc*VE}}*PE \quad (12)$$

2.3.4. Distribution, metabolism and elimination

2.3.4.1. Distribution model. The volume of distribution (V_D) and the distribution parameters k_{12}, k_{21} and k_{10} for all investigated drugs were estimated from clinical data after intravenous administration. All included studies are listed in the Supplemental material, comprising 14 studies for paracetamol, 8 for ibuprofen, 1 for darunavir, and 8 for itraconazole. The parameters were optimised using the Levenberg-Marquardt algorithm included in PK-Sim. For all drugs, volume of distribution is dependent on bodyweight and is calculated using Eq. (13) [60–63]. The exact values for all parameters are given in Table 4. A schematic representation of the full compartmental model is shown in Fig. 1. Moreover, the Mobi file containing the exact model structure used for the simulations is included part in the Supplemental material.

$$V_D = BW*V_D^{70kg}\frac{L}{70kg} \quad (13)$$

2.3.4.2. First-pass effect. The first-pass metabolism was incorporated as a transfer compartment between the intestinal lumen and the central compartment. Paracetamol absorption from the gastrointestinal tract is almost complete. The unchanged drug and its metabolites excreted in the urine account for almost 100 % of the administered oral dose. In a pharmacokinetic study in adults, Rawlins *et al.* observed an increase in the oral bioavailability of paracetamol with increasing dose. The bioavailability was 63 % after a 500 mg dose, increasing to 89 % after a 1000 mg dose and 87 % after a 2000 mg dose, respectively [64]. Depré *et al.* and Fulton *et al.* calculated an oral bioavailability of 82.2 % and 88.3 % after administering a 500 mg dose to healthy adults based on the reported AUC [65,66]. Data on oral bioavailability of paracetamol in children is scarce. Kleiber *et al.* conducted a study on paediatric intensive care patients, 0–6 years old, with a median age of 6.1 months. Paracetamol was administered orally and intravenously. The oral bioavailability was 72 % (range 11–91 %) [67]. For Ibuprofen, absolute bioavailability was set to 100 % according to literature data [68,69]. The bioavailability of darunavir varies greatly and can be strongly

Table 4
Distribution and elimination constants for each drug under investigation estimated from *in vivo* observations after intravenous and oral administration in different age groups from toddlers to adults. All included studies are listed in the supplemental material.

Parameter	Paracetamol	Ibuprofen	Darunavir	Itraconazole
V_D (L/kg)	0.3580	0.057	0.5000	0.8900
k_{12} (min^{-1})	0.0200	0.900	0.1400	0.0091
k_{21} (min^{-1})	0.0200	0.00042	0.0024	0.0016
k_{10} (min^{-1})	0.0090	1.100	0.0400	0.0081

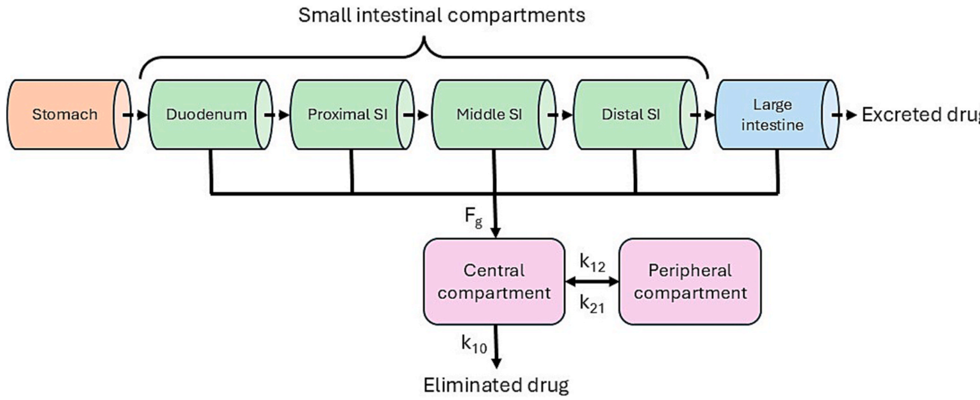

Fig. 1. Schematic representation of the compartmental structure of the *in silico* model.

influenced by the co-administration of low-dose ritonavir. By inhibiting CYP enzymes, ritonavir increases the bioavailability of darunavir. Studies in adults have shown that co-administration of appropriate doses of ritonavir almost completely eliminates the first-pass effect and can increase the bioavailability of darunavir from 37 % to 82 % [70,71]. For the parameter estimation and validation process, the present study only included data from studies in which darunavir was co-administered with ritonavir.

In the case of itraconazole, non-linear pharmacokinetics have been reported [72,73]. The first-pass metabolism of itraconazole in the present model is based on the population pharmacokinetic analysis by Abuhelwa *et al.* who evaluated single-dose studies from 50 mg to 300 mg [74]. They estimated the fraction of itraconazole escaping first-pass metabolism to be approximately 0.45, with this fraction decreasing at higher doses. In multiple-dose studies with doses up to 400 mg, the fraction escaping first-pass metabolism further decreased to around 0.1, reflecting saturation effects and nonlinear absorption.

2.3.4.3. Enterohepatic circulation. Darunavir belongs to the class of protease inhibitors. For several protease inhibitors multiple peaks in plasma concentrations have been observed. For lopinavir, this is particularly evident [75,76]. The secondary peaks can have various underlying causes, with one possible explanation being enterohepatic circulation, where the drug is distributed into the gallbladder and later released into the intestine. Gallbladder emptying is often triggered by food intake. Since in clinical studies, food intake is typically scheduled according to the study protocol, this phenomenon can be observed at similar times. However, this may differ in paediatric studies, where adherence to a strict feeding regimen is less common. In the present study, for darunavir, gallbladder emptying was set to occur 4 h post-dose, aligning with the recommended timing of food intake in clinical studies.

2.3.5. Validation

After estimating the volume of distribution V_D and distribution parameters from intravenous data, the model was validated using plasma concentration data after oral administration of the model drugs across different age groups. An overview of all included studies, along with the observed versus predicted results is provided in the Supplemental material. For each study, the median characteristics of the study population, such as age and bodyweight, were used to calculate V_D and adjust the intestinal parameters accordingly.

2.3.6. Simulations

Following export of the MoBi model, Simulations were run in PK-Sim due to population-variation of parameters being only available in PK-Sim. For each age group, a simulation with all physiological parameters set to the mean value of each parameter listed in Table 3 was conducted. In addition, a sensitivity analysis was performed for each parameter by simulating the effects of the minimum and maximum values of each parameter on t_{max}, C_{max} and AUC for each age group.

To investigate the impact of co-administration of the studied drug products with various paediatric breakfast meals, solubility and dissolution data from the corresponding *in vitro* experiments were incorporated in the model and the bile salt concentration and total solubility of the drugs in the small intestine were adjusted accordingly. As stated before the investigated paediatric breakfast meals included a cassava porridge, a toast breakfast, an American breakfast, and, for comparison, an age adapted portion of the FDA standard breakfast that is commonly used in adult food effect studies and here represented by Ensure® Plus [77].

3. Results

3.1. Parameter estimation and validation

Clinical data from 25 (paracetamol), 17 (ibuprofen), 10 (darunavir) and 9 (itraconazole) studies were used for parameter estimation and validation. V_D and intestinal parameters were adjusted based on the reported patient characteristics for each individual study included in the validation process. An overview of all included studies, together with the reported population characteristics, dosages, dosage forms and routes of administration, is included in the Supplemental material. The estimated distribution and elimination parameters for all drugs are listed in Table 4. Fig. 2 shows the individual plots for the prediction accuracy of the established model with respect to the measured plasma concentration for each of the four drugs showing that the model performed very well in all age- and dose ranges.

In the case of paracetamol, some outliers resulted from studies that included patients with a wide age range or did not report bodyweight, which is required for V_D calculation. For example, Kelly *et al.* reported mean age (5.8 ± 2.8), but no bodyweight [78]. The mean bodyweight therefore had to be assumed based on the reported age. The outliers in the ibuprofen plot could all be attributed to a single study by Pavliv *et al.* [79].

Fig. 3 shows the simulated plasma concentration for a representative (mean) individual from each age group. For reference, observed plasma concentrations from *in vivo* paediatric studies with similar dose-to-bodyweight ratios are also shown. Since *in vivo* data matching the exact characteristics of the reference individuals is lacking, the V_D was not adjusted to patient characteristics in these simulations. Adjusted simulations and detailed predicted-versus-observed comparisons, based on study-specific patient characteristics, are provided in Fig. 2 and the Supplemental material.

Simulations for paracetamol and ibuprofen showed minimal variation across age groups, as both dose and V_D scale proportionally with

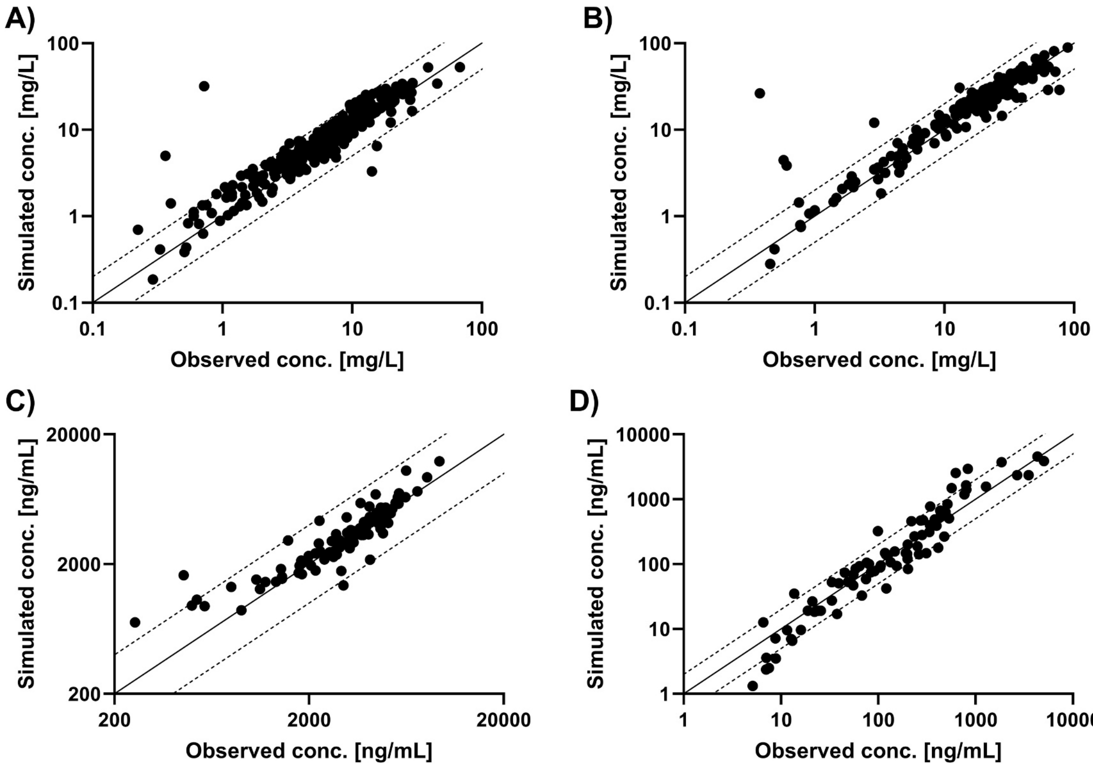

Fig. 2. Validation of the performance of the pPBPK model by comparing predicted and observed plasma concentration for paracetamol (A), ibuprofen (B), darunavir (C) and itraconazole (D). The dashed lines represent a two-fold deviation range (0.5–2.0) between observed and simulated values.

bodyweight, and small intestinal transit time and fasted state gastric emptying time, assumed consistent across all age groups. In contrast, for darunavir, differences in AUC were primarily attributed to variations in dose-to-bodyweight ratios based on paediatric dosing recommendations. Additionally, age-dependent intestinal parameters significantly influenced absorption rates and the fraction absorbed for both darunavir and itraconazole, resulting in substantial variability between age groups (Fig. 2). In the case of itraconazole, $AUC_{(0\text{-}24\ h)}$ was increased by 55 % in toddlers compared to adolescents. Moreover, even after adjusting the dose to account for the recommended non-linear increase in the dose-to-bodyweight ratio, the $AUC_{(0–24\ h)}$ in toddlers would still be approximately 40 % higher than in adolescents when reaching adulthood.

3.2. *Impact of age-dependent intestinal physiology on drug absorption*

Fig. 4 illustrates the impact of various intestinal parameters across the four paediatric age groups on $AUC_{(0\text{-}24\ h)}$, C_{max} and t_{max}. For paracetamol, only gastric emptying time had a significant influence on pharmacokinetics. A prolonged gastric emptying time resulted in a longer time to reach maximum plasma concentration and to a lower C_{max}. Gastric and small intestinal pH, the volume of small intestinal fluid and bile concentration had next to no effect on the predicted plasma concentration in each age group. A faster transit reduced the fraction absorbed by approximately 2.6 %. The simulations for ibuprofen revealed similar trends. As with paracetamol, gastric emptying time was the only parameter that significantly influenced ibuprofen pharmacokinetics. In addition, pH had a minor effect on ibuprofen absorption, distinguishing it from paracetamol. However, despite the pH-dependent solubility of ibuprofen, variations in pH resulted in only a slight shift in t_{max}. The volume of small intestinal fluid had the strongest influence on the $AUC_{(0\text{-}24\ h)}$, albeit minimal compared to results obtained for darunavir and itraconazole. Several parameters had a strong impact on the pharmacokinetics of these two BCS class II drugs. For both darunavir and itraconazole, the volume of small intestinal fluid significantly influenced the $AUC_{(0\text{-}24\ h)}$. In toddlers, the fraction absorbed increased by up to 116 % and 126 % for darunavir and itraconazole, respectively. The effect of gastric emptying on darunavir C_{max} and t_{max} was similar to that observed for paracetamol and ibuprofen. By contrast, for itraconazole delayed gastric emptying resulted in a smaller decrease in C_{max}, which was due to the higher fraction absorbed due to the prolonged gastric emptying time. The pH had a pronounced effect on itraconazole pharmacokinetics. Due to the basic nature of the drug, an increase in intestinal pH led to a lower overall solubility and thus a lower fraction absorbed and a lower C_{max}. Overall, the most pronounced difference between age groups was observed in the effect of gastric emptying on t_{max} and C_{max}, with toddlers showing significant deviations from other groups due to the highest reported *in vivo* variability.

3.3. *Food effect prediction for darunavir and itraconazole*

The impact of food on intestinal conditions and the resulting effects on drug absorption and pharmacokinetics was assessed using simulations for four distinct breakfast meal compositions. The simulated plasma concentration–time profiles for darunavir and itraconazole are shown in Fig. 5 with the corresponding pharmacokinetic parameters summarised in Table 5. The integration of *in vitro* dissolution data obtained with SPBM and Ensure® Plus led to marked differences in the predicted pharmacokinetics of both darunavir and itraconazole. Although a significant food effect was observed for both compounds, the direction of the effect was reversed. While simulation of the coadministration of the two drugs with the different breakfast meals led to an increased fraction absorbed, $AUC_{(0\text{-}24\ h)}$ and C_{max} in the case of darunavir, it provided a decrease of the same parameters for itraconazole, indictaing a negative food effect. Among the tested meals, Ensure® Plus was the only one that produced a distinguishable effect on darunavir pharmacokinetics; the other meals did not show meaningful differences in their impact. By contrast, the type of simulated breakfast meal did markedly affect the plasma concentration of itraconazole. Simulations

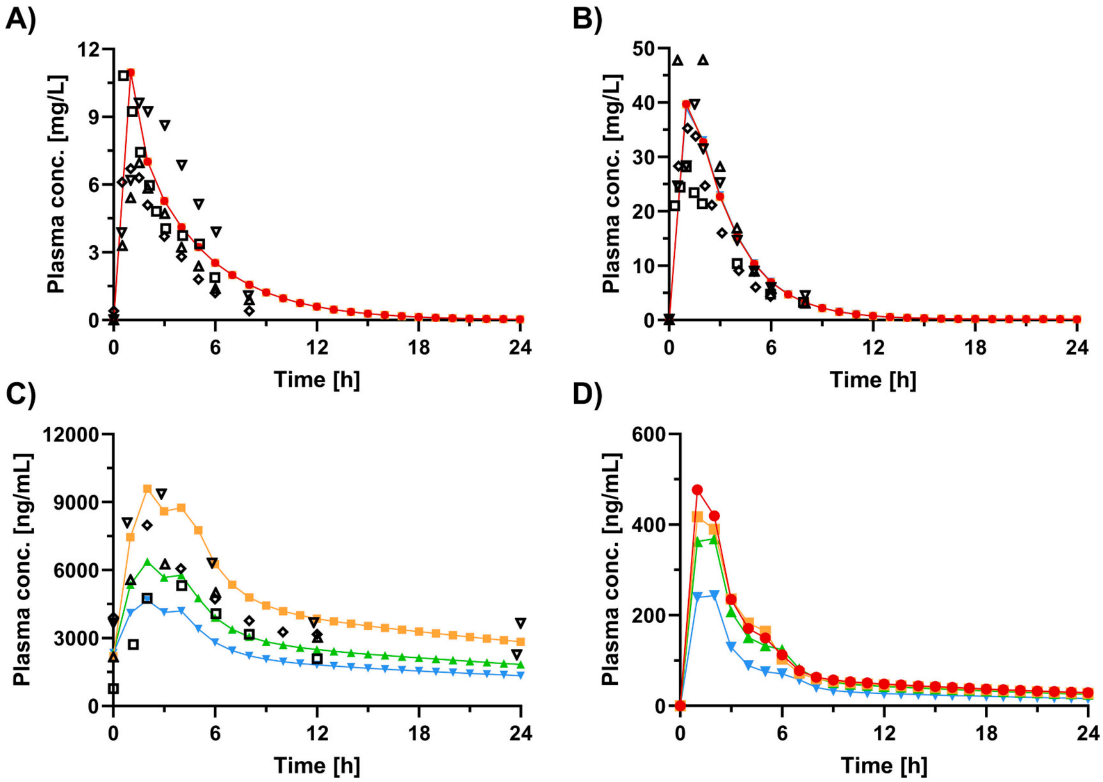

Fig. 3. Simulated plasma concentration profiles of paracetamol (A), ibuprofen (B), darunavir (C), and itraconazole (D) in fasted conditions for reference individuals representing each age group from toddlers to adolescents. For reference (black symbols), observed plasma concentrations from various *in vivo* paediatric studies (ages 0–18 years) with similar dose-to-bodyweight ratios are included (paracetamol [80–83], ibuprofen [78,80,83,84], darunavir [85,86], study population characteristics and dosing are available in the Supplementary material), although *in vivo* data directly matching the exact characteristics of the reference individuals are not available. For paracetamol, reference data include four studies with patients ranging from 3 months to 12 years. The reference data for ibuprofen comprise four studies with mean ages between 5.8 and 8.9 years. Since darunavir is indicated for patients aged ≥ 3 years, toddlers were excluded from the simulation; reference data for darunavir includes patients between 3 and 18 years. No oral pharmacokinetic data for itraconazole in paediatric patients were available. With the exception of Fig. 3C (darunavir), where no simulation was performed for toddlers for the reasons stated above, all panels show simulated plasma concentration profiles color-coded by age group: toddlers = red, pre-school children = orange, school children = green, adolescents = blue. In Fig. 3A and B (paracetamol and ibuprofen), overlapping curves are observed due to both VD and dose scaling linearly with body weight, resulting in similar exposure across age groups. In contrast, darunavir dosing is based on discrete weight bands (e.g., identical doses for all children weighing 20–30 kg), leading to more pronounced differences in simulated plasma concentrations. For itraconazole, although the dose is also scaled linearly with body weight, the age-dependent physiological differences result in more clearly distinguishable plasma profiles between age groups. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

with the Ensure® Plus medium resulted in the highest $AUC_{(0\text{-}24\ h)}$ and C_{max} for both drugs. Overall, the $AUC_{(0\text{-}24\ h)}$ of darunavir increased by 29.9 %, 36.0 %, 39.1 % and 58.9 % for darunavir when simulating co-administration with the cassava breakfast porridge, the toast breakfast, an American breakfast and the FDA standard breakfast (adult breakfast – represented by Ensure® Plus), respectively, while the $AUC_{(0\text{-}24\ h)}$ of itraconazole decreased by 7.6 %, 42.9 % and 17.2 % when simulating co-administration with the cassava breakfast, the toast breakfast, an American breakfast. Due to the significantly higher *in vitro* release of itraconazole when simulating co-administration with an age-appropriate portion of the FDA standard breakfast reported by Freerks *et al.*, the $AUC_{(0\text{-}24\ h)}$ actually increased by 35.4 % in simulations considering this dosing scenario.

4. Discussion

4.1. General considerations

The model drugs were selected based on their formulation and physicochemical properties, each introducing an additional mechanistic layer and enabling a stepwise evaluation of the absorption model. While paracetamol, a BCS class I drug, is highly soluble and permeable and does not show pH dependent solubility changes, ibuprofen is a weak acid and therefore pH changes must be considered (Eq. (9)). Darunavir solubility and subsequent absorption is additionally influenced by bile micelle-mediated solubilisation which impacts the free fraction available for absorption and the diffusion through the unstirred water layer (Eq. (4)). Lastly itraconazole, formulated as a solution containing 40 % (m/V) hydroxypropyl-β-cyclodextrin, presents further complexity due to potential interactions between the formulation excipients and intestinal contents like bile salts or food components [15,87]. These multifactorial interactions necessitate a more mechanistic approach to absorption modelling than the one currently implemented in PK-Sim (Eq. (2)) [18,55,59]. Alternative platforms, such as SimCyp's MechPeff model, already provide these advanced capabilities [88,89].

4.2. Availability of physiological data

Children younger than 12 months were not considered in this study since in addition to gastrointestinal changes they undergo rapid changes in metabolism and clearance rates which was outside the focus of this work [90–92]. By limiting the paediatric population to four discrete age groups, the need to scale each parameter based on body size or other physiological characteristics was avoided. This approach enabled the incorporation of realistic, age-specific variability for individual parameters, rather than applying a uniform coefficient of variation across all

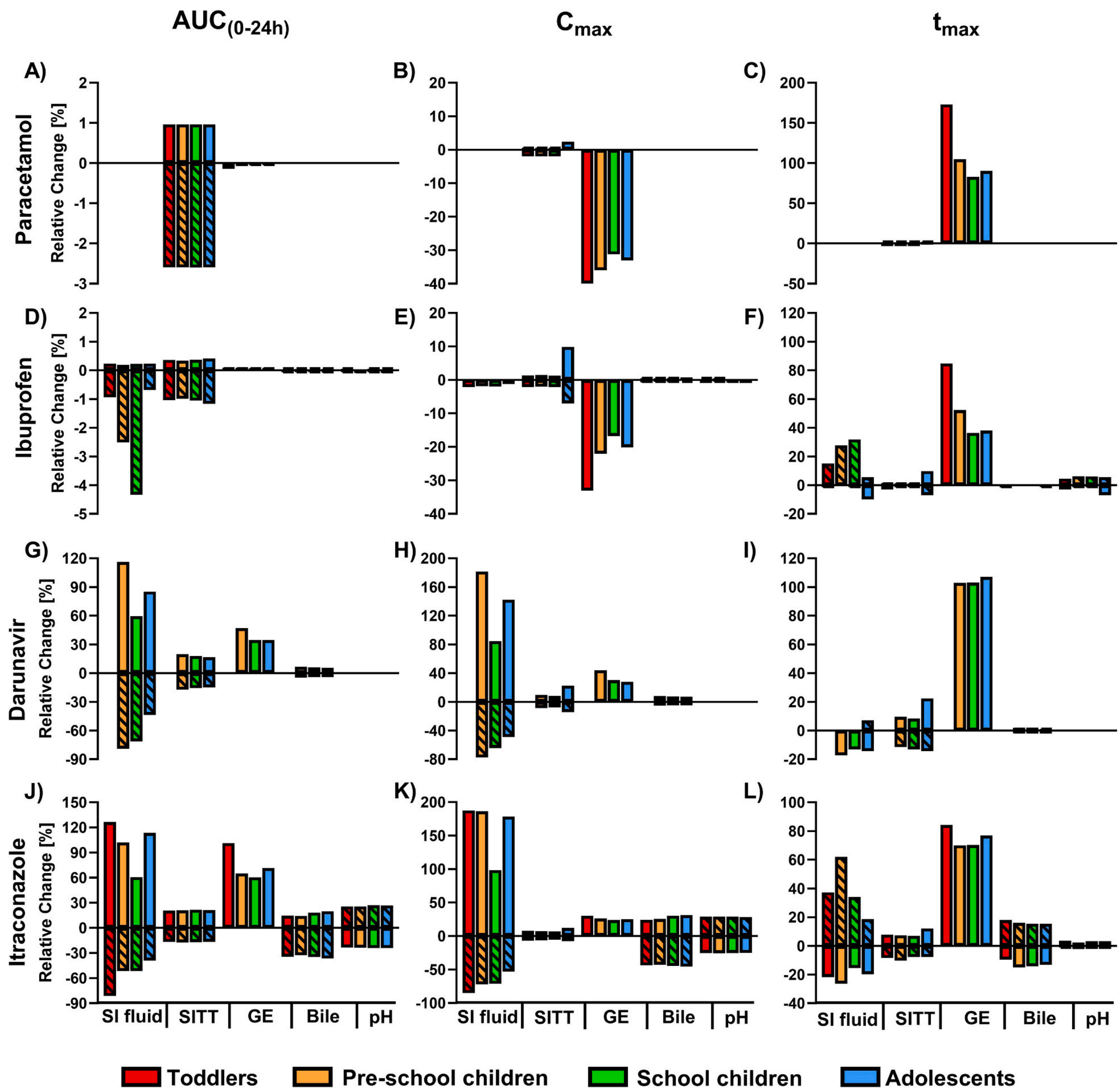

Fig. 4. Relative changes in $AUC_{(0\text{-}24\ h)}$, C_{max} and t_{max} due to variation in intestinal parameters, i.e., small intestinal fluid volume (SI fluid), small intestinal transit time (SITT), gastric emptying (GE), small intestinal bile concentration (Bile), and small intestinal pH (pH), as evaluated in the sensitivity analysis. Dashed columns represent relative changes calculated based on the minimum reported values, and solid columns represent those based on the maximum values for each individual parameter. The mean values, along with the lower and upper bounds of the corresponding *in vivo* data used in the sensitivity analysis, are provided in Table 3.

age groups. Moreover, it should be noted that for many physiological parameters, age dependency or correlation with anthropometric measures has not been well established or systematically investigated. Consequently, scaling such parameters would often rely on assumptions or interpolations rather than empirically verified data.

Values for the gastrointestinal parameters included in this model were mainly taken from a recent review by Wollmer *et al.* on paediatric gastrointestinal physiology relevant to the absorption of orally administered medicines [33]. This comprehensive overview consolidates data from over 750 studies, providing detailed insights into gastrointestinal physiology in children. The results for each parameter are categorised by age groups, which align with those defined earlier in this study. In addition to data from the review article and the corresponding original publications, data from various other studies were incorporated, specifically those examining parameters essential for pPBPK modeling that were not addressed by Wollmer *et al.* [12,42–45,48–51,93]. However, it is important to note that despite the extensive body of research aimed at better understanding paediatric gastrointestinal physiology, significant gaps in knowledge still exist. This is further complicated by the fact that not all the information available to date is suitable for use in pPBPK models. For example, Fallingborg *et al.* investigated small intestinal pH values in children [37]. While they reported regional differences, which are required for a compartmental pPBPK model, they only reported the median age of the study population and did not investigate the effect of age on this parameter. Similarly, while data on bile salt concentrations in the small intestine are available for certain age groups, regional differences within the small intestine remain largely unknown. Ethical constraints limit investigations into various factors, such as age-related morphological changes of the intestinal barrier. For example, paediatric biopsies are rarely feasible, which restricts the availability of data on structural parameters like villus height, crypt depth, or surface area. To our knowledge, only one study has reported villus height and surface

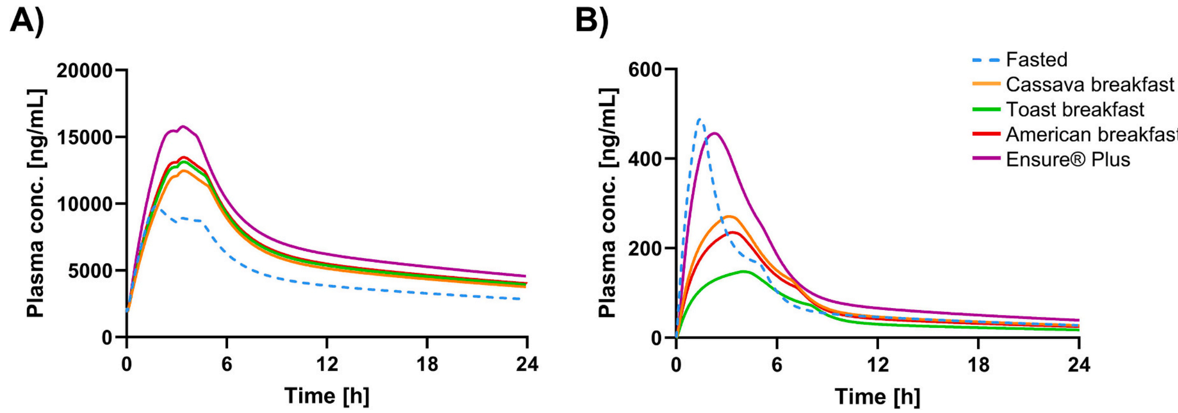

Fig. 5. Simulated plasma concentration of the pre-school reference individual following administration of darunavir (A) and itraconazole (B) under various prandial conditions based on *in vitro* dissolution data reported by Freerks *et al.* [21].

Table 5
Pharmacokinetic parameters for the simulated prandial conditions in the pre-school reference individual. For the postprandial conditions, the values in brackets indicate the percentage change relative to fasted dose administration.

Simulated co-administration with	Parameter	Darunavir	Itraconazole
Water (fasted state)	$AUC_{(0\text{-}24\ h)}$ (ng*h/mL)	114475.52	2288.71
	C_{max} (ng/mL)	9807.92	488.05
	t_{max} (h)	1.70	1.50
Cassava breakfast	$AUC_{(0\text{-}24\ h)}$ (ng*h/mL)	148783.85 (129.9 %)	2115.36 (92.4 %)
	C_{max} (ng/mL)	12459.25 (127.0 %)	270.83 (55.5 %)
	t_{max} (h)	3.40 (198 %)	3.10 (217 %)
Toast breakfast	$AUC_{(0\text{-}24\ h)}$ (ng*h/mL)	155703.90 (136.0 %)	1307.55 (57.1 %)
	C_{max} (ng/mL)	13127.39 (133.8 %)	147.56 (30.2 %)
	t_{max} (h)	3.40 (198 %)	3.90 (274 %)
American breakfast	$AUC_{(0\text{-}24\ h)}$	159205.58 (139.1 %)	1895.10 (82.8 %)
	C_{max} (ng/mL)	13470.01 (137.3 %)	235.03 (48.2 %)
	t_{max} (h)	3.40 (198 %)	3.40 (231 %)
FDA standard breakfast	$AUC_{(0\text{-}24\ h)}$ (ng*h/mL)	181995.84 (158.9 %)	3098.46 (135.4 %)
	C_{max} (ng/mL)	15768.06 (160.8 %)	456.30 (93.5 %)
	t_{max} (h)	1.70 (194 %)	2.3 (158 %)

area in healthy children [94]; although values were comparable to adults, age-dependency was not assessed, limiting the applicability of expansion factors such as VE in children [95]. Finally, several studies lack comprehensive background on diseases, disorders or prandial state which significantly influence intestinal measurements [33].

For gastric emptying, data are available concerning the emptying of capsules and liquids in the fasted state, obtained from children aged 4 years or older who had fasted overnight [93]. However, in children medicines are often co-administered with food, especially in younger children who often are fed multiple times a day, or more generally, to mask an unpleasant taste if necessary. In the postprandial state, gastric emptying is highly variable and the assumption that complete gastric emptying occurs within 30 to 60 min may not be realistic. Rather, depending on the portion size, composition and viscosity of the food, and viscosity, gastric emptying may take several hours.

Small intestinal transit times reported in the literature may be affected by the study design and the measurement methods employed [96]. Similarly, the type of dosage form and the physical state of the drug can substantially impact transit time. For example, shorter small intestinal passage times are often observed for liquids containing dissolved or finely suspended drugs compared to solid monolithic dosage forms [97]. To simulate small intestinal transport of dissolved or dispersed drug in the established model the difference between OCTT measured lactulose hydrogen breath test and gastric emptying time was used, while measurements from telemetric capsules were used to describe the transport of monolithic tablets. Overall, no age-related effects on this parameter have been described, despite sufficient studies being available for both methods in paediatric patients [96]. Although all formulations addressed in the present study were liquid-based, the transport of monolithic tablets was also incorporated to allow for future extension of the model to other age groups and dosage forms.

Due to a lack of data, it was not possible to investigate the effects of age on the pharmacokinetics of drugs related to potential changes in bile concentration in the duodenum and small intestine. Currently, only very limited data are available on this topic, and only data from a single study are available for some of the examined age groups, specifically toddlers and pre-school children [47]. To address this data gap in the development of a previously published pPBPK model, Johnson *et al.* fitted published data from children under one year of age and adults into an equation to describe age-dependent bile salt concentrations in the duodenum of children in the fasted state [98]. Their assumption here was a significant decrease in duodenal bile salt concentration within the age range of 1 to 18 years, although only very limited information exists for this age range. Such an approach was not considered suitable in the present study, as the established model aimed to be based on real and reliable data, even if this meant that not all influences could be examined in detail. Al-Amiry Santos *et al.* recently highlighted regional differences in bile concentrations along the small intestine focusing on the application in PBPK models for the adult population [99]. They found that bile salt concentrations vary not only between prandial states but also between proximal and distal regions of the small intestine. Due to the lack of available data in children, only duodenal bile salt concentrations could be incorporated into the current model. However, the range explored in the parameter sensitivity accounts for the regional variability reported in adults.

Especially for drugs with low solubility, the available free fluid volume is crucial for determining the rate of drug absorption (Fig. 4). Since publication of the review by Wollmer *et al.* in 2022, Van der Veken *et al.* investigated the small intestinal fluid volumes in children [12]. To date, the study by Van der Veken *et al.* is the only study to account for age and regional differences, so it cannot be compared with alternative data. Nevertheless, the results of this study provide extremely valuable information for pPBPK modelling, as they indicate that small intestinal fluid volume cannot be reliably predicted from body characteristics, although this is the method of choice for many models, including PK-Sim.

In summary, great progress has been made in understanding age-related changes in paediatric gut physiology. However, some gaps still exist, including gastrointestinal pH and bile salt concentration in both stomach and small intestine. Furthermore, many physiological mechanisms observed in adults have not been studied in children or incorporated into pPBPK models. Likewise, gastrointestinal motility, which has been shown to affect absorption rates, is rarely considered in PBPK models, especially not in pPBPK models [100].

4.3. Influence of age-dependent intestinal physiology on oral drug absorption

For all four drugs and their corresponding drug products investigated, especially the poorly soluble compounds darunavir and itraconazole, all parameters implemented in the model had a significant impact on pharmacokinetics. For these two drugs, a change in small intestinal fluid volume to the maximum value observed *in vivo* could lead to a twofold change in drug exposure. However, it is important to note that water is typically absorbed rapidly from the small intestine, and fluid volumes generally return to baseline shortly after ingestion. In addition to the volume of fluid ingested, the osmolality and composition of the fluid also strongly influence both the extent and duration of increased small intestinal fluid volume [101,102]. Although the exact extent and duration of the increase in fluid volume in the lumen of the small bowel cannot be predicted exactly, it is important to address the extreme conditions in the model in order to assess potential risks. This approach is particularly supported by findings from Tanaka *et al.*, which clearly showed that the intraluminal fluid volume in the small intestine has a significant impact on intestinal absorption rates [103].

To evaluate the individual impact of each parameter, only one variable was altered at a time, while all others were kept constant. Although this approach aids in interpreting simulation results, it does not always reflect *in vivo* conditions. For example, an increase in small-intestinal fluid volume dilutes the concentrations of bile salts and cyclodextrins, which may reduce their effectiveness in solubilising poorly soluble drugs. As all three parameters positively influence $AUC_{(0\text{-}24\ h)}$ (Fig. 4) the decrease in intestinal cyclodextrin or bile salt concentration would counteract the positive effect of an increased small intestinal fluid volume. This finding aligns with data reported by Berben *et al.*, who administered a cyclodextrin-containing itraconazole solution and investigated the relationship between intraluminal dilution and absorption *in vivo* [87]. They found that concomitant water intake had no significant impact on systemic exposure to itraconazole, suggesting that reduced water volumes, though leading to higher intraluminal drug concentrations, did not enhance absorption, likely due to drug entrapment in cyclodextrin complexes. Similar observations were made for other low solubility drugs and formulation excipients, highlighting the importance of considering the solubility-permeability interplay in absorption modeling [16,17,104,105].

A non-linearity of intestinal physiology across the different paediatric age groups was only observed for the gastric emptying time and the small intestinal fluid volume. Not only do these two parameters have the greatest influence on the pharmacokinetics of drugs, but overall, they are also the most variable parameters, being strongly influenced by external factors such as diet, study conditions and daily routines. In particular, in children, clinical trial conditions are often less controlled, leading to higher variability. However, it has been suggested that the non-linearity in the reported mean values may be attributable to outliers caused by resulting from these less controlled conditions, potentially skewing the results. In contrast, median values appear more consistent with those observed in adults [12].

4.4. Food effects

To date, only a limited number of studies have investigated the impact of food on the bioavailability of orally administered drugs in children. While regulatory authorities such as the EMA and FDA allow for the extrapolation of adult data, potential food effects in paediatric populations should not be entirely disregarded, even when no clinically significant effects are observed in adults [31,106]. In a previous *in vitro* study, simulated co-administration of various SPBMs showed no relevant impact on the dissolution of paracetamol, suggesting that a clinically significant food effect is unlikely *in vivo* [21]. These findings are in line with those from a similar approach by Villiger *et al.* who implemented dissolution of paracetamol in formula milk into a pPBPK model using GastroPlus® [107]. Due to their low solubility and based on results from studies in adults, of the four drugs investigated only darunavir and itraconazole were expected to show a significant change in bioavailability after co-administration with food [71,108]. This expectation was confirmed in the present study, where simulations indicated a pronounced food effect for both compounds. The positive food effect of darunavir predicted by the model aligns with clinical data [71]. Based on a study performed in adult healthy volunteers, Sekar *et al.* concluded that concomitant food intake resulted in an approximately 30 % increase in darunavir AUC, irrespective of the type of the co-administered meal. The negative impact of food on the bioavailability of the itraconazole hydroxypropyl-β-cyclodextrin solution predicted by the model is also consitent with *in vivo* observations [108]. Under fasted conditions, cyclodextrin enhances solubility and absorption; however, this benefit is reduced when the formulation is diluted by food and gastrointestinal secretions. The resulting decrease in the free drug fraction (f_{mono}, Eq. (2)) leads to lower overall absorption. This loss of cyclodextrin effectiveness upon dilution is primarily attributed to interactions with bile salts. Such interactions, observed with itraconazole and other poorly soluble drugs, are critical considerations when predicting food effects for formulations containing solubility-enhancing excipients [17,87,104,105].

Overall, the simulations clearly demonstrated food effects, aligning with the *in vitro* dissolution study by Freerks *et al.* and highlighting the need for age-appropriate meals and portion sizes in the study design. For itraconazole, using a child-sized portion of an adult standard breakfast (e.g., the FDA standard breakfast) could overestimate *in vivo* exposure in the studied age groups. This emphasizes that directly extrapolating data from adult studies under typical clinical trial conditions is not appropriate, as the composition and quantity of co-administered food can significantly affect drug bioavailability, as shown in the darunavir study.

4.5. Limitations

In addition to changes in gastrointestinal physiology, children undergo significant changes in renal and hepatic systemic clearance pathways as well as active transport processes. Especially for very young patients, this can significantly change pharmacokinetics. While it is possible to implement such maturational factors and possible variability in pPBPK models, this was not the focus of the present study. Moreover, the mechanistic absorption model implemented in this study does not account for active transporters and paracellular absorption. While these processes usually play only a minor role compared to the passive absorption process, the ontogenesis of the active transport process could be relevant for paediatric patients. As soon as more information is available, the model could be expanded to include these aspects. Lastly, while the tested drugs cover a wide range of physicochemical properties, we did not include a BCS Class III drug, characterised by low permeability. The absorption of such drugs is more strongly influenced by small intestinal transit time, as limited permeability may not allow sufficient uptake before the drug passes into the colon. In contrast, the drugs evaluated in this study showed only a limited impact of this parameter on pharmacokinetics.

5. Conclusion

pPBPK modelling is a promising approach for predicting the bioavailability of orally administered drugs in children. However, current knowledge gaps and limitations in the capabilities of *in silico* models to realistically address the particular features of paediatric gastrointestinal physiology limit the accuracy and reliability of such predictions. In the present study, the availability and quality of physiological parameters specific to the paediatric gastrointestinal tract were critically evaluated, with a focus on their relevance and applicability to pPBPK modelling. Based on the information collected, a pPBPK model was established in MoBi/PK-Sim, which in the future can eliminate the need to scale parameters from adults to children without considering their age-related features. A mechanistic absorption model was integrated into PK-Sim, expanding the capabilities of this widely used platform to describe complex interactions between meal components, bile micelles and formulation excipients. The analysis of parameter variability within and among the four simulated age groups revealed significant differences in pharmacokinetics, particularly in the case of the poorly soluble drugs darunavir and itraconazole. By integrating results from biorelevant *in vitro* dissolution tests, in which the co-administration of the corresponding dosage forms with different paediatric breakfast meals was simulated, the effects of this mode of administration on the pharmacokinetics of darunavir and itraconazole could be demonstrated.

The developed model enables the estimation and/or verification of the impact of the age of a child, the constituents of the administered drug product, and the characteristics of a co-administered meal on drug pharmacokinetics. As such, this study provides a valuable contribution toward the development of age-appropriate and formulation-specific dosing recommendations for paediatric patients. By supporting the optimisation of therapeutic outcomes and minimising the risk of adverse effects, the model addresses a critical need in the safe and effective pharmacological treatment of this vulnerable population.

CRediT authorship contribution statement

Fabian Winter: Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis. **Jonas Lange:** Methodology, Investigation, Formal analysis. **Sandra Klein:** Writing – review & editing, Supervision, Resources, Project administration, Formal analysis, Conceptualization.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejpb.2025.114815.

Data availability

Data will be made available on request.

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