



The top-down Physiologically Based Finite Time Pharmacokinetic (PBFTP) models open a new avenue for early drug development

Athina Kalantzi^a, Antony Simitopoulos^a, Athanasios A. Tsekouras^b, Panos Macheras^{a,c,*} 

^a Faculty of Pharmacy, Laboratory of Biopharmaceutics Pharmacokinetics, National and Kapodistrian University of Athens, Athens, Greece

^b Department of Chemistry, Laboratory of Physical Chemistry, National and Kapodistrian University of Athens, Athens, Greece

^c Finite Absorption Time (F.A.T.) Laboratories, National and Kapodistrian University of Athens, Athens, Greece

ARTICLE INFO

Keywords:

Finite absorption time
F.A.T.
Oral absorption
Pharmacokinetics
Physiologically based finite time
pharmacokinetic models PBFTP

ABSTRACT

We explored the use of top-down Physiologically Based Finite Time Pharmacokinetic (PBFTP) models in early drug development. The Absorption number, An of drugs was re-defined as the ratio of residence time of drug in the gastrointestinal tract and the half duration of its absorption, τ . Using estimates for τ of several drugs derived from the fittings of PBFTP models to literature experimental data and the mean intestinal transit time, 199 min, we calculated the corresponding An values and discussed them in terms of their BCS classification. Analysis of amoxicillin data using PBFTP models with passive absorption or carrier mediated transport was also carried out. Low τ values result in high An estimates. The mean duration of absorption for Class I, II and III drugs was found to be equal to 1.96 ± 1.91 , 3.63 ± 8.71 , 1.81 ± 1.02 h, respectively. The shorter duration of absorption for Class I and III drugs was attributed to their high solubility. The analysis of PBFTP model fittings revealed that amoxicillin absorption follows carrier mediated transport since both the peak blood concentration and AUC values are increasing as a function of dose nonlinearly following the same pattern. The definition of An in terms of the duration of absorption is physiologically sound since the high blood flow rate in the portal vein imposes sink conditions, namely zero order kinetics in oral drug absorption. The use of the PBFTP models in early drug development provides meaningful estimates for the number of absorption stages and their duration as well as the corresponding input rates.

1. Introduction

In the mid-1980s, the first pioneering work for the prediction of the fraction of dose absorbed based on drug's physicochemical properties was published by Professor Gordon Amidon's research group (Dressman et al., 1985). In this work, Eq. (1) expressing the absorption potential, (AP), concept was developed and its utility as a predictor of fraction of dose absorbed, F_a was demonstrated,

$$AP = \log \left(P \cdot F_{non} \cdot \frac{S_0 \cdot V_L}{X_0} \right) \quad (1)$$

where P is the n-octanol-water partition coefficient, F_{non} is the fraction in nonionized form at pH 6.5, S_0 is the intrinsic solubility (aqueous solubility of the nonionized species at 37 °C), X_0 is the dose administered, V_L is the volume of the luminal contents (250 mL) while the logarithmic function produces a convenient scale of values. Eq. (1) relies on passive absorption, which is the most common mechanism of drug absorption in

accord with the pH-partition hypothesis principles. The drug data reported in (Dressman et al., 1985) were further analyzed (Macheras, Symillides, 1989) using a pseudo steady-state model assuming first-order absorption since the absorption rate constant, k_a is related proportionally to the three terms (drug properties) of Eq. (1). In this study a quantitative relationship between F_a and AP was developed, while the first classification of drugs in terms of the physicochemical properties P , F_{non} , $\frac{S_0 V_L}{X_0}$ was attempted (see Table 1 in (Macheras, Symillides, 1989)). These two studies were followed by elegant macroscopic and microscopic analyses (Sinko et al., 1991; Oh et al., 1993) by Gordon Amidon's research teams using the tube model for the intestinal absorption of drug, which eventually led to the BCS publication in 1995 (Amidon et al., 1995). In 2000 FDA issued the relevant BCS guideline (Food and Drug Administration, 2017) whereas solubility and permeability are used to classify drugs in four classes, I, II, III and IV.

These advances (Sinko et al., 1991; Oh et al., 1993; Food and Drug Administration, 2017) led to the development in late 1990s and

* Corresponding author.

E-mail address: macheras@pharm.uoa.gr (P. Macheras).

<https://doi.org/10.1016/j.ejps.2026.107485>

Received 12 January 2026; Received in revised form 13 February 2026; Accepted 22 February 2026

Available online 23 February 2026

0928-0987/© 2026 Published by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Table 1

Absorption number, An estimates of different drugs along with the τ estimates derived from the fitting of PBFTPK models to experimental data.

Drug	BCS class	An	$\tau \pm SD$ (h)	Source, subject, formulation or Figure in supplementary material
Paracetamol	I	12.94	0.51 \pm 0.03	(Chryssafidis et al., 2022)
Paracetamol	I	7.86	0.82 \pm 0.05*	(Kalantzi et al., 2006), (S1)
Ibuprofen	II	2.87	2.30 \pm 0.2*	(Chryssafidis et al., 2022)
Almotriptan Malate	III	2.28	2.89 \pm 0.39*	(Chryssafidis et al., 2022)
Mavoglurant	II	3.19	2.07 \pm 0.03	(Macheras, Tsekouras, 2023)
		2.83	0.03	IR S16
		1.29	2.33 \pm 0.15	(Macheras, Tsekouras, 2023)
		1.06	5.13 \pm 0.22*	(Macheras, Tsekouras, 2023)
			6.21 \pm 0.32*	(Macheras, Tsekouras, 2023)
Etoricoxib	II	10.82	0.61 \pm 0.03	(Wu et al., 2023)
Gaboxadol	I	13.30	0.50 \pm 0.03*	(Wu et al., 2023)
Dipyridamole	II	10.65	0.62 \pm 0.14	(Wu et al., 2023)
Pioglitazone	II	4.31	1.53 \pm 0.12*	(Wu et al., 2023)
Losartan	III	3.93	1.68 \pm 0.1	(Wu et al., 2023)
Levonorgestrel	II	6.06	1.09 \pm 0.08	(Toulitsis et al., 2024)
		6.88	0.96 \pm 0.06	reference (Toulitsis et al., 2024) test
Theophylline	I	2.65	2.49 \pm 0.21*	(Toulitsis et al., 2024)
Theophylline	I	9.17	0.72 \pm 0.05	(Chryssafidis et al., 2021)
		8.80	0.75 \pm 0.03	product A (Chryssafidis et al., 2021)
		8.68	0.76 \pm 0.05	product B (Chryssafidis et al., 2021)
			0.76 \pm 0.05	product C (Chryssafidis et al., 2021)
Amlodipine	I	0.90	7.3 \pm 2.55*	(Toulitsis et al., 2024)
Ketoprofen	II	11.00	0.6 \pm 0.1	(Toulitsis et al., 2024)
Niraparib	I	1.93	3.42 \pm 0.42*	(Chryssafidis et al., 2022)
Cyclosporine	II	4.20	1.57 \pm 3.82	(Macheras et al., 2025) test
		2.31	1.73 \pm 0.13	(Macheras et al., 2025) test fed
		1.42	0.13	(Macheras et al., 2025) reference fasted
			2.86 \pm 0.10	(Macheras et al., 2025) reference fed
			4.66 \pm 0.22*	
Cyclosporine	II	3.55	1.86 \pm 0.18*	(Alimpertis et al., 2024)
Temsavir	II	8.35	0.79 \pm 0.02	(Chryssafidis et al., 2021)
Flubiprofen	II	9.43	0.7	(Macheras, Chryssafidis, 2020)
Ibuprofen	II	3.30	2.0	(Macheras, Chryssafidis, 2020)
Cephadrine	II	6.60	1.0	(Macheras, Chryssafidis, 2020)
Itraconazole	II	2.20	3.0	(Macheras, Chryssafidis, 2020)
Carbamazepine	II	0.35	17.1 \pm 0.41	(Alimpertis et al., 2024) B11
			2.02*	(Alimpertis et al., 2024) B12
			0.20	(Alimpertis et al., 2024) B21
			0.20	(Alimpertis et al., 2024) B23
			32.8 \pm 5.29*	
			31.3 \pm 2.14*	
Carbamazepine	II	0.20	32.52 \pm 2.07*	(Alimpertis et al., 2024) 400mg

Table 1 (continued)

Drug	BCS class	An	$\tau \pm SD$ (h)	Source, subject, formulation or Figure in supplementary material
Alendrolate	III	7.64	0.864 \pm 0.017	(Macheras et al., 2025)
Doxycycline	I	11.00	0.60 \pm 0.05	(Macheras et al., 2025)
Amoxicillin	I	2.12	2.12 \pm 0.06	(Thambavita et al., 2021), (S1)
Acetylsalicylic acid	I	4.29	1.54 \pm 0.08	(Ito et al., 1991), (S1)
Bisoprolol	I	6.23	1.06 \pm 0.03	(Leopold et al., 1986), (S1)
Fluconazole	I	3.14	2.1 \pm 0.81*	(DeMuria et al., 1993), (S1)
Levetiracetam	I	9.57	0.69 \pm 0.02	(Radtko, 2001), (S1)
Moxifloxacin	I	8.15	0.81 \pm 0.07	(Pathania, Sharma, 2010), (S1)
Ondansetron	II	7.95	0.83 \pm 0.07	(Roila, Del Favero, 1995), (S1)

* More than one input stage was found.

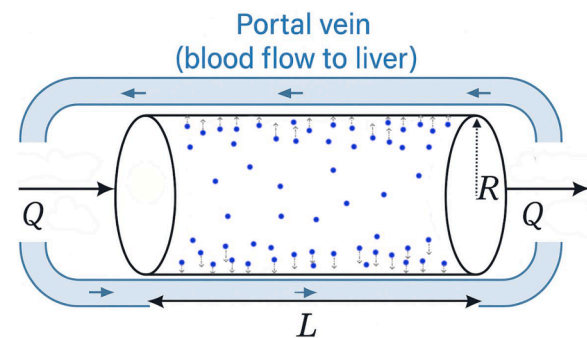


Fig. 1. The small intestine is modeled as a homogeneous cylindrical tube of length L and radius R (Sinko et al., 1991). Q is the volumetric flow rate. The tube is surrounded by the portal vein indicating the high blood flow rate (Iranpour et al., 2016) towards the liver maintaining sink conditions for the drug molecules in solution (denoted as circles) transfer.

widespread use later of physiologically based pharmacokinetic (PBPK) modeling in oral drug absorption (Boobis et al., 2002; Balhara et al., 2022; Lin et al., 2022). The availability of various user friendly commercial softwares such as GastroPlus, Simcyp and PK-Sim has made this predictive science accessible even to those without extensive modelling and/or programming experience. However, recently, multiple systematic evaluation studies independently suggested that the predictive power of current oral absorption PBPK models needs significant improvement (Sugano, 2021). According to Sugano, there is some disagreement between the industry and regulators about the credibility of PBPK modelling in oral drug absorption. For example, it has become common practice to back-calculate one or more parameters from the clinical concentration-time data on a drug-by-drug basis (Pepin et al., 2021). This strategy is known as the “(local) middle-out approach”; the effective permeability (P_e) is often selected as a target parameter in these cases. Besides, drug uptake in PBPK models typically employs a semi-empirical absorption rate constant, k_a . This parameter corresponds to the ratio of effective permeability P_e over the radius, R of the GI lumen as $k_a=2P_e/R$.

In this vein, we first examine the assumptions associated with the use of the fundamental relationship between absorption rate constant and effective permeability in PBPK, in the light of the recent advances based on the finite absorption time (F.A.T.) concept (Macheras, Chryssafidis, 2020). Second, we re-define the absorption number, An utilizing estimates for the duration of drug absorption derived from the fittings of the

top-down PBFTPK models to experimental data (Chryssafidis et al., 2022). Third, we re-analyze amoxicillin data reported originally in (Sinko et al., 1991) utilizing PBFTPK models with passive absorption or carrier mediated transport to explore the absorption mechanism.

2. Theory

The macroscopic mass balance approach that incorporates membrane permeability and solubility considerations relies on the tube model, Fig. 1, and utilizes mass transfer theory for the estimation of fraction of dose absorbed (Sinko et al., 1991). In this work, the dimensionless absorption number, An was defined assuming sink conditions for the drug transport, as follows

$$An = \frac{L}{R} \frac{P_e}{\langle v_z \rangle} \quad (2)$$

where R is the intestinal radius of the lumen, L is the intestinal length of the lumen, $\langle v_z \rangle$ is the axial fluid velocity of the drug solution in the tube and P_e is the effective permeability. Eq. (2) shows that An is proportional to P_e , which is the radial mass transfer velocity. Accordingly, Eq. (2) can be re-written expressing $\langle v_z \rangle$ in terms of the volumetric flow rate, Q , i.e. $Q = \pi R^2 \langle v_z \rangle$

$$An = P_e \left(\frac{Q}{\pi R L} \right)^{-1} \quad (3)$$

which reveals that An is the ratio over the radial absorption rate to the axial convection rate (Sinko et al., 1991). In other words, the kinetics of drug absorption of drug is determined by the magnitude of this anatomical-physiological ratio and P_e is the parameter controlling the rate of input. The microscopic mass balance approach (Oh et al., 1993) was used for the prediction of the fraction absorbed of suspensions of poorly soluble drugs. In this work, An was re-defined as shown in Eq. (3) since sink conditions were assumed for the absorption of drug in the fundamental differential equation (Eq. (8) in (Oh et al., 1993)) expressing the change of drug concentration in the lumen, C_L as a function of the differential element of distance z .

Surprisingly, the same quantity An is defined differently in (Amidon et al., 1995), (which relies exclusively on the findings of (Oh et al., 1993)), using the reciprocal of the mean absorption time, t^{-1} , and the mean intestinal residence time, t_{res}

$$An = \frac{2P_e}{R} t_{res} = t^{-1} t_{res} \quad (4)$$

Obviously, first-order absorption is considered since, t^{-1} is equal to the first-order absorption rate constant, k_a (Oh et al., 1993; Yamaoka et al., 1978)

$$k_a = t^{-1} = \frac{S}{V} P_{eff} = \frac{2\pi R L}{\pi R^2 L} P_{eff} = \frac{2P_{eff}}{R} \quad (5)$$

where S is the total surface area of the intestinal tube and V is the volume of the intestinal tube.

Furthermore, Gordon Amidon's research team carried out the analysis of experimental human small intestine transit time data collected from 400 studies and revealed a mean small intestinal transit time $\langle T_{si} \rangle = 199$ min (Yu et al., 1996; Yu, Amidon, 1998). This very valuable estimate was derived from the small intestinal transit time distribution based on the frequency and has been utilized extensively since then, e.g., (Kalampokis et al., 1999; Rinaki et al., 2004). Additionally, however, a model with mixing tanks in series with linear transfer kinetics from one to the next with the same transit rate constant was considered (Yu et al., 1996; Yu, Amidon, 1998). To estimate the optimal number of mixing tanks, the model equation was fitted to the cumulative curve derived from the distribution frequency of the entire set of small intestinal transit time data using under the first-order assumption, $k_t = m / \langle$

$T_{si} \rangle$ where m is the number of compartments constituting the small intestine and k_t is the first-order rate constant governing the transfer of drug amount from one tank to the next. The fraction of dose reaching the colon F_a for the model with seven compartments was found to be (Yu et al.; 1996; Yu, Amidon, 1998; Macheras, Iliadis 2016):

$$F_a = 1 - \left(1 + \frac{2P_e \langle T_{si} \rangle}{7R} \right)^{-7} \quad (6)$$

This model with the seven compartments in series has been and is being used in all software PBPK packages. We are questioning the best fit results of seven compartments for intestinal transit since Eq. (5) was applied in the calculations for the derivation of Eq. (6). Also, the mixing tanks in series models with linear transfer kinetics from one to the next with the same transit rate constant are not physiologically sound assumptions for the characteristics of flow in the human-small intestine (Yu et al., 1996; Yu Amidon, 1998). Besides, the best fit result of the seven compartments cannot be rigorously justified on statistical grounds given the similarity of the fits of the models with five, seven or nine compartments and the (not shown) variability encountered in the data points (see Fig. 5 in Yu, et al., 1996). The uncertainty about the "optimum" number of compartments was also expressed in a subsequent paper of the same authors (Yu, Amidon, 1998).

Eq. (5) is the crux of the matter in this section of the present work since k_a represents the classical absorption rate constant when the drug is absorbed passively under non-sink conditions. Overall, our main concern is the first-order hypothesis for the absorption process (Eq. (5)), which cannot be applied to oral drug absorption since the passive drug absorption operates under sink conditions because of the high blood flow rate (20–40 cm/s) in the portal vein (Iranpour et al., 2016), Fig. 1. Based on this observation, the Finite Absorption Time (F.A.T.) concept was developed, namely, the high blood flow in the portal vein ensures the rapid movement of drug molecules towards the liver and maintains sink conditions in the absorption process, which results in zero-order kinetics throughout drug's time course in the gastrointestinal lumen (Macheras, Chryssafidis 2020; Chryssafidis et al. 2022; Macheras et al. 2025; Macheras, Tsekouras, 2023).

3. Methods

In the last five years or so, we have provided conclusive evidence that drug absorption follows zero-order kinetics (single or multiple) because of the high blood flow rate in the portal vein, Fig. 1. This means that under sink conditions of absorption, the drug follows zero-order kinetics, and its mean absorption time is equal to $\tau/2$ (Yamaoka et al., 1978) whereas τ denotes the duration of absorption; thus, the absorption number An can be re-defined correcting Eq. (4) as follows.

$$An = \frac{2}{\tau} t_{res} = \frac{2}{\tau} \frac{\pi R^2 L}{Q} \quad (7)$$

where t_{res} is the mean residence time, which is equal to $\pi R^2 L / Q$; thus, An denotes how many times the half of the duration of drug absorption is faster than the mean residence time. For example, assigning an average value for the intestinal transit, $t_{res} = 3$ h (Amidon et al., 1995), a drug with duration of absorption, τ of two hours has $An = 3$.

We calculated the An values based on Eq. (7) for several drugs using the τ estimates derived from the fittings of PBFTPK models (Chryssafidis et al., 2022) to experimental data and discussed them in terms of their BCS classification. Moreover, we analyzed amoxicillin studies reported in (Sinko et al., 1991) using passive and carrier mediated transport PBFTPK models; the development of the carrier mediated transport PBFTPK model is quoted below.

The rate of decrease of the drug amount in the GI, A_{GI} following carrier mediated transport is

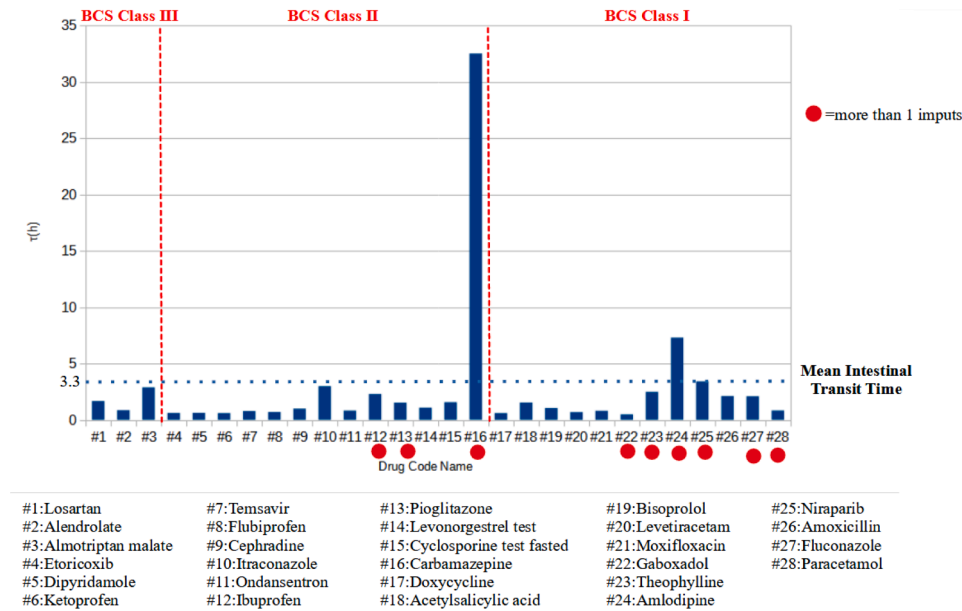


Fig. 2. Mean estimates for τ vis-a-vis the mean intestinal transit time.

$$\frac{dA_{GI}}{dt} = \frac{-T_{max}A_{GI}}{K_M + A_{GI}} \quad (8)$$

where T_{max} is the maximum transport capacity of the carrier and K_M is the Michaelis constant which upon integration from $t = 0$, $A_{GI} = FD$ to $t = t$, $A_{GI} = A_{GI}$ one obtains:

$$A_{GI} + K_M \ln A_{GI} = FD + K_M \ln FD - T_{max}t \quad (9)$$

Dividing by the volume of distribution V_d we transform Eq. (9) in terms of concentration

$$\frac{C_{GI}}{\lambda} + \frac{K_M}{V_d} \ln \frac{C_{GI}}{\frac{FD}{V_d}} = \frac{FD}{V_d} - \frac{T_{max}}{V_d}t \quad (10)$$

where $\lambda = \frac{V_d}{V_{GI}}$ and V_{GI} is the volume of fluids in the GI tract,

$$\text{or } C_{GI} = \lambda \left[\frac{FD}{V_d} - \frac{T_{max}}{V_d}t - \frac{K_M}{V_d} \ln \frac{C_{GI}}{\frac{FD}{V_d}} \right] \quad (10a)$$

Eq. (11) describes the rate of change of drug concentration in blood, C:

$$\frac{dC}{dt} = \frac{T_{max}C_{GI}}{K_M + C_{GI}} - k_{el}C \text{ for } t \leq \tau \quad (11)$$

If K_M is very small,

$$\frac{dC}{dt} = T_{max} - k_{el}C \text{ i.e., zero order absorption kinetics} \quad (11a)$$

If $K_M \gg C_{gi}$,

$$\frac{dC}{dt} = \frac{T_{max}}{K_M}C_{GI} - k_{el}C \text{ i.e., first order absorption kinetics} \quad (11b)$$

For $t > \tau$ Eq. 12 applies

$$C = C(\tau)e^{-k_{el}(t-\tau)} \quad (12)$$

The fitting of Eqs. (10), 11 and 12 to experimental data should provide estimates for the 5 model parameters T_{max} , K_M , FD/V_d , τ , k_{el} .

Fittings were performed using custom written functions using the programming environment of Igor software.

4. Results and discussion

4.1. Estimates for An utilizing the τ values derived from the fitting of PBFTP models to experimental data

Table 1 shows the estimates for An based on Eq. (7). In all cases, the τ values used were derived from the PBFTP model fittings to experimental literature data, while t_{res} was set equal to the mean small intestinal transit time, 199 min. When more than one absorption stage is operating, e.g., three with durations of absorption τ_1 , τ_2 , τ_3 respectively, Eq. (13) is used instead of Eq. (7),

$$An = \frac{2t_{res}}{\tau_1 + \tau_2 + \tau_3} = \frac{2}{\tau} \frac{\pi R^2 L}{Q} \quad (13)$$

where τ is the total duration of absorption. Caution should be exercised though with the use of Eqs. (5) and 13 for drugs exhibiting absorption beyond the small intestine with τ values higher than t_{res} Table 1. Although the mean time for the entire passage of drug from the gastrointestinal tract, 30 h (Macheras et al., 2020; Abuhelwa et al., 2016) could be used for drugs absorbed in the colon, we applied, for comparative purposes, in all cases the estimate of 199 min for the mean intestinal transit time (Yu et al., 1996; Yu Amidon, 1998); by doing so, small values of An denote prolonged absorption e.g. carbamazepine, Table 1. Overall, low τ values result in high An estimates.

The results listed in Table 1 verify the well-known fact that drugs are mainly absorbed in the small intestine. However, for most of the drugs analyzed, the duration of absorption is shorter than the mean intestinal transit time, which implies absorption from the upper part of the small intestine, Fig. 2. This observation applies to all drugs regardless their BCS classification. The mean duration of absorption for Class I, II and III drugs was found to be equal to 1.96 ± 1.91 , 3.63 ± 8.71 , 1.81 ± 1.02 h, respectively. The shorter duration of absorption for Class I and III drugs should be attributed to their high solubility. An exemption to this rule is amlodipine, which is also absorbed beyond the small intestines, $\tau = 7.3 \pm 2.55$ h, Table 1. The higher mean duration of absorption for Class II drugs is a reasonable result since their absorption can be extended to the colon e.g. carbamazepine, Table 1. Fig. 2, Alimpertis et al., 2024. This is reflected on the huge coefficient of variation $8.71.100/3.63=240\%$ and reveals the heterogeneous character in terms of the duration of absorption of Class II drugs. For example, cyclosporin has a short duration of absorption since it has a significant first-pass effect (Kolars et al.,

Table 2Formulations of theophylline, mesalazine and efodipine hydrochloride and their τ estimates.

Drug Formulation	τ (h)	Source
Theophylline IR	2.49*	(Toulitis et al., 2024)
Theophylline TheoDur	7*	(Toulitis et al., 2024)
Theophylline Theotrim	11.6*	(Toulitis et al., 2024)
Mesalazine TF3	26.3*	(Macheras et al., 2025)
Mesalazine RF3	23.6*	(Macheras et al., 2025)
Mesalazine TF6	16.1*	(Macheras et al., 2025)
Mesalazine TF12	23	(Macheras et al., 2025)
Mesalazine RF12	16.1*	(Macheras et al., 2025)
Efodipine Hydrochloride	6.8	(Macheras et al., 2025)
Efodipine Hydrochloride 1:1	3.3	(Macheras et al., 2025)
Efodipine Hydrochloride 1:3:1	0.7	(Macheras et al., 2025)

* More than one input stages were found.

1991) and its absorption terminates at t_{\max} , which coincides with τ (Macheras, Tsekouras, 2022); on the contrary, carbamazepine does not exhibit first-pass effect, its absorption is prolonged (Tsekouras, Macheras, 2024) and therefore is absorbed from the colon, too, Fig. 2.

The analytical power of PBFTP models in the analysis of data from sustained release formulations is presented in Table 2. The results for various formulations of theophylline, mesalazine and efodipine revealed that i) theophylline immediate release formulations has a much shorter duration of absorption than the sustained release formulations of TheoDur and Theotrim, ii) all mesalazine formulations exhibit long durations of absorption, which are in accord with their design in targeting the colon, and iii) the three formulations of efodipine hydrochloride have remarkably different estimates for τ , while Efodipine Hydrochloride 1:3:1 formulation behaves like an immediate release formulation ($\tau = 0.7$ h).

4.2. Analysis of amoxicillin data reported in (Sinko et al., 1991)

When An was originally defined (Sinko et al., 1991), the authors analyzed amoxicillin data using either the classical first-order

absorption model or carrier mediated transport. In this section we analyze these data using PBFTP models (Macheras, Chryssafidis, 2020; Chryssafidis et al. 2022). These models provide the number of drug input stages, their duration and input rates as well as an estimate for the concentration FD/V_d , which is indicative of the extent of drug's absorption. We present here our analysis based on the fittings of PBFTP model with one input stage and one compartment model disposition, Fig. 3. It can be seen that very nice fitting results were obtained and found to be superior to the fitting results of first-order absorption model quoted in the supplementary material. Reliable estimates were found for the three parameters (peak blood concentration, FD/V_d corresponding to the absorbed quantity, FD , the duration of absorption, τ and the elimination rate constant, k_{el}) of the best fitting model while the value of the correlation coefficient, R^2 was in all cases higher than 0.99. Most importantly, the plot of the concentration estimate FD/V_d as a function of dose exhibits an identical pattern with the corresponding plot of AUC versus dose plot, Fig. 4. This is a remarkable result since it is clear proof of evidence that the parameter FD/V_d is a metric for the extent of absorption since it is proportional to the bioavailable fraction. By logical extension, it can be concluded that C_{\max} used in bioequivalence studies does not represent a rate metric. Both parameters FD/V_d and AUC increase nonlinearly with dose, which indicates that nonlinear kinetics

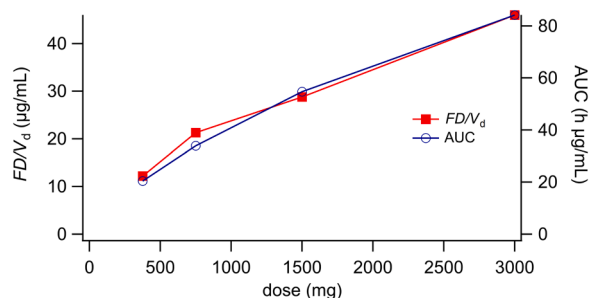
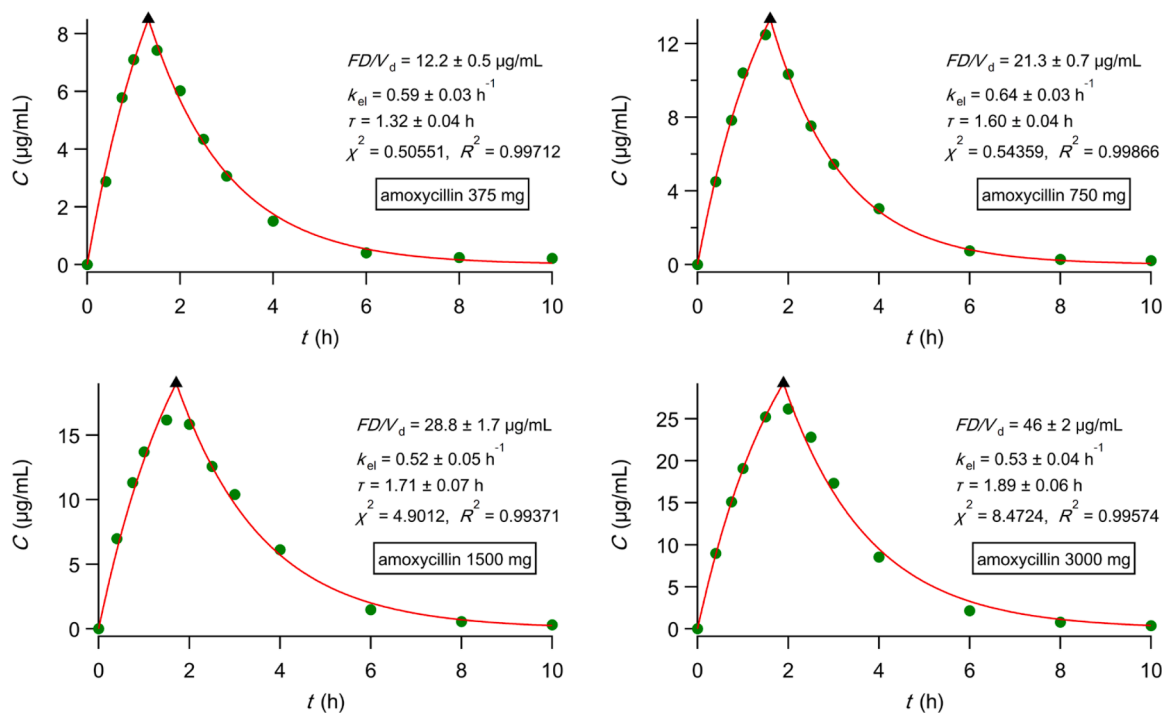
Fig. 4. Plot of FD/V_d and AUC versus dose for the amoxicillin data of Fig. 3.

Fig. 3. Data for different per os doses of amoxicillin [Thambavita et al., 2021] and corresponding fits with one zero-order absorption stage and one-compartment disposition model. Optimized parameters in the inset. The triangle denotes the end of the absorption processes.

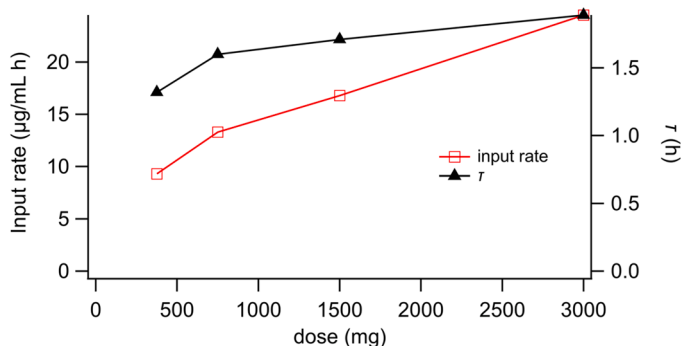


Fig. 5. Plot of the input rate and τ versus dose for the amoxicillin data of Fig. 3.

Table 3

Parameter estimates derived from the fitting of Eqs. (10–12) to amoxicillin data.

D (mg)	375	750	1500	3000
FD/V_d ($\mu\text{g mL}^{-1}$)	$695 \pm 3 \times 10^5$	$4718 \pm 7 \times 10^5$	65 ± 6	119 ± 27
T_{\max} ($\mu\text{g mL}^{-1} \text{h}^{-1}$)	9 ± 46	13 ± 54	26 ± 2	32 ± 4
K_M ($\mu\text{g mL}^{-1}$)	0	0	0	0
τ (h)	1.32	1.45	1.7	2
k_{el} (h^{-1})	0.58 ± 0.03	0.54 ± 0.02	0.46 ± 0.03	0.53 ± 0.04

(carrier mediated transport) describes the overall absorption kinetics of amoxicillin absorption. Also, a nonlinear increase as a function of dose is observed for the amoxicillin input rate, which is also indicative of the carrier mediated transport, Fig. 5. On the contrary, a slight nonlinear increase of τ as a function of dose is observed, Fig. 5.

Fits were also attempted using the carrier mediated model (Eqs. (10–12) for the four doses of amoxicillin per os administrations. Due to the limited number of data points and the large number of estimated parameters, we found that τ could not be determined algorithmically while K_M tended to go negative and FD/V_d and T_{\max} were very strongly correlated. Consequently, τ was set by inspection close to the value determined in corresponding PBFTP models and K_M was set to 0. The fitting results are listed in Table 3.

Based on the unsuccessful fittings derived from the PBFTP model with carrier mediated transport, we conclude that the Michaelis Menten constant K_M is much smaller than the concentrations encountered in the absorption of amoxicillin and transport follows zero-order kinetics governed only by the maximum transport velocity T_{\max} . This is particularly so for the fitting results using the highest doses (1500, 3000 mg) whereas reliable estimates for FD/V_d and T_{\max} were obtained, Table 3. This also explains the marvelous fittings of the PBFTP models, which rely on zero-order kinetics, Fig. 3. According to Eq. (11a) (limiting case for low K_M), the absorption rate is equal to the parameter T_{\max} . The approximation is confirmed by the comparison of the optimized parameters derived from two different methodologies for the highest dose administered (3000 mg), which favors zero-order absorption kinetics: $FD/V_d\tau = 24.5 \pm 0.8 \mu\text{g mL}^{-1} \text{h}^{-1}$ (depicted in Fig. 5) and $T_{\max} = 32 \pm 4 \mu\text{g mL}^{-1} \text{h}^{-1}$ listed in Table 3.

5. Conclusions

The initial definition of An in (Sinko et al., 1991; Oh et al., 1993) was based on Eqs. (2, 3) and associated with the governing role of P_e in the absorption processes assuming sink conditions. Since P_e is expressed in velocity units (cm/s), drug absorption was considered to follow zero-order kinetics. The inception-development of the physiologically sound F.A.T. concept based on the high blood flow rate (20–40 cm/s) in the portal vein, justifies the use of Eq. (7) in the present work and is in

full agreement with the zero-order absorption kinetics. Further justification of the zero-order absorption kinetics relies on the fact that this high value of the blood flow rate (20–40 cm/s) in the portal vein is six orders of magnitude higher than the effective permeability values of drugs, which are usually close to 10^{-4} cm/s.

Our results demonstrate that the use of the top down PBFTP models in a single bioavailability study provides a clear picture of drug's absorption profile in terms of the number of absorption stages and their duration as well as the input rate (s). The example of the analysis of amoxicillin data shows that the PBFTP models can be also used when carrier mediated transport is encountered. Overall, this work shows that the top down PBFTP models can guide reliably oral drug absorption in the early phases of drug development.

CRedit authorship contribution statement

Athina Kalantzi: Writing – review & editing, Formal analysis. **Antony Simitopoulos:** Writing – review & editing, Formal analysis. **Athanasios A. Tsekouras:** Writing – review & editing, Software, Methodology, Formal analysis. **Panos Macheras:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Conceptualization.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejps.2026.107485.

Data availability

Data will be made available on request.

References

- Abuhelwa, A., Foster, D., Upton, R., 2016. A quantitative review and meta-models of the variability and factors affecting oral drug absorption-part II: gastrointestinal transit time. *AAPS J.* 18 (5), 1322–1333. <https://doi.org/10.1208/s12248-016-9953-7>.
- Alimpertis, N., Simitopoulos, A., Tsekouras, A.A., Macheras, P., 2024. *IVIVC* revised. *Pharm. Res.* 41, 235–246. <https://doi.org/10.1007/s11095-024-03653-x>.
- Amidon, G.L., Lennernäs, H., Shah, V.P., Crison, J.R., 1995. A theoretical basis for a biopharmaceutical drug classification: the correlation of in vitro drug product dissolution and in vivo bioavailability. *Pharm. Res.* 12, 413–420. <https://doi.org/10.1023/a:1016212804288>.
- Balhora, A., Kale, S., Singh, S., 2022. Physiologically based pharmacokinetic (PBPK) modelling. In: Saharan, V.A. (Ed.), *Computer Aided Pharmaceutics and Drug Delivery*. Springer, Singapore. https://doi.org/10.1007/978-981-16-5180-9_9.
- Boobis, A., Gundert-Remy, U., Kremers, P., Macheras, P., Pelkonen, O., 2002. In silico prediction of ADME and pharmacokinetics. Report of an expert meeting organised by COST B15. *Eur. J. Pharm. Sci.* 17, 183–193. [https://doi.org/10.1016/s0928-0987\(02\)00185-9](https://doi.org/10.1016/s0928-0987(02)00185-9).
- Chryssafidis, P., Tsekouras, A.A., Macheras, P., 2021. Revising pharmacokinetics of oral drug absorption: II bioavailability-bioequivalence considerations. *Pharm. Res.* 38, 1345–1356. <https://doi.org/10.1007/s11095-021-03078-w>.
- Chryssafidis, P., Tsekouras, A.A., Macheras, P., 2022. Re-writing oral pharmacokinetics using physiologically based finite time pharmacokinetic (PBFTP) models. *Pharm. Res.* 39, 691–701. <https://doi.org/10.1007/s11095-022-03230-0>.
- DeMuria, D., Forrest, A., Rich, J., Scavone, J.M., Cohen, L.G., Kazanjian, P.H., 1993. Pharmacokinetics and bioavailability of fluconazole in patients with AIDS. *Antimicrob. Agents Chemother.* 37, 2187–2192. <https://doi.org/10.1128/AAC.37.10.2187>.
- Dressman, J.B., Amidon, G.L., Fleisher, D., 1985. Absorption potential: estimating the fraction absorbed for orally administered compounds. *J. Pharm. Sci.* 74, 588–589. <https://doi.org/10.1002/jps.2600740523>.
- Food and Drug Administration, 2017. Waiver of In vivo immediate-release solid oral bioequivalence studies for bioavailability and biopharmaceutics classification dosage forms based on biopharmaceutics classification dosage forms based on a biopharmaceutics classification system guidance for industry. <https://www.fda.gov/media/70963/download>.
- Iranpour, P., Lall, C., Houshyar, R., Helmy, M., Yang, A., Choi, J.I., Ward, G., Goodwin, S.C., 2016. Altered Doppler flow patterns in cirrhosis patients: an overview. *Ultrasonography.* 35, 3–12. <https://doi.org/10.14366/usg.15020>.
- Ito, S., Oka, R., Tsuchida, A., Yoshioka, H., 1991. Disposition of single-dose intravenous and oral aspirin in children. *Dev. Pharmacol. Ther.* 17, 180–186. <https://doi.org/10.1159/000457520>.

- Kalampokis, A., Argyrakis, P., Macheras, P., 1999. Heterogeneous tube model for the study of small intestinal transit flow. *Pharm. Res.* 16, 87–91. <https://doi.org/10.1023/a:1018874913372>.
- Kalantzi, L., Reppas, C., Dressman, J.B., Amidon, G.L., Junginger, H.E., Midha, K.K., Shah, V.P., Stavchansky, S.A., Barends, D.M., 2006. Biowaiver monographs for immediate release solid oral dosage forms: acetaminophen (Paracetamol). *J. Pharm. Sci.* 95, 4–14. <https://doi.org/10.1002/jps.20477>.
- Kolars, J.C., Awni, W.M., Merion, R.M., Watkins, P.B., 1991. First-pass metabolism of cyclosporin by the gut. *Lancet* 338, 1488–1490. [https://doi.org/10.1016/0140-6736\(91\)92302-i](https://doi.org/10.1016/0140-6736(91)92302-i).
- Leopold, G., Pabst, J., Ungethüm, W., Bühring, K.U., 1986. Basic pharmacokinetics of bisoprolol, a new highly Beta1-selective adrenoceptor antagonist. *J. Clin. Pharmacol.* 26, 616–621. <https://doi.org/10.1002/j.1552-4604.1986.tb02959.x>.
- Lin, W., Chen, Y., Unadkat, J.D., Zhang, X., Wu, D., Heimbach, T., 2022. Applications, challenges, and outlook for PBPK modeling and simulation: a regulatory, industrial and academic perspective. *Pharm. Res.* 39, 1701–1731. <https://doi.org/10.1007/s11095-022-03274-2>.
- Macheras, P., Symillides, M., 1989. Toward a quantitative approach for the prediction of the fraction of dose absorbed using the absorption potential concept. *Biopharm. Drug. Disp* 10, 43–53. <https://doi.org/10.1002/bdd.2510100106>.
- Macheras, P., Chryssafidis, P., 2020. Revising pharmacokinetics of oral drug absorption: i models based on biopharmaceutical/physiological and finite absorption time concepts. *Pharm. Res.* 37, 187. <https://doi.org/10.1007/s11095-020-02894-w>. Erratum in: *Pharm Res.* 2020;37:206.
- Macheras, P., Iliadis, A., 2016. *Modeling in Biopharmaceutics, Pharmacokinetics and Pharmacodynamics. Homogeneous and Heterogeneous Approaches* Springer, pp. 118–120.
- Macheras, P., Tsekouras, A.A., 2022. Columbus' egg: oral drugs are absorbed in finite time. *Eur. J. Pharm. Sci.* 176, 106265. <https://doi.org/10.1016/j.ejps.2022.106265>.
- Macheras, P., Tsekouras, A.A., 2023. The Finite Absorption time (FAT) concept en route to PBPK modeling and pharmacometrics. *J. Pharmacokinet. Pharmacodyn.* 50, 5–10. <https://doi.org/10.1007/s10928-022-09832-w>.
- Macheras, P., Tsekouras, A.A., Sánchez-Herrero, S., Kosmidis, K., 2025. The finite absorption time concept guiding model informed drug & generics development in clinical pharmacology. *Pharm. Res.* 42, 891–906. <https://doi.org/10.1007/s11095-025-03878-4>.
- Oh, D.M., Curl, R.L., Amidon, G.L., 1993. Estimating the fraction dose absorbed from suspensions of poorly soluble compounds in humans: a mathematical model. *Pharm. Res.* 10, 264–270. <https://doi.org/10.1023/A:1018947113238>.
- Pathania, R., Sharma, S.K., 2010. Pharmacokinetics and bioavailability of moxifloxacin in Buffalo calves. *Res. Vet. Sci.* 89, 108–112. <https://doi.org/10.1016/j.rvsc.2010.01.015>.
- Pepin, X.J., Huckle, J.E., Alluri, R.V., Basu, S., Dodd, S., Parrott, N., et al., 2021. Understanding mechanisms of food effect and developing reliable pbpk models using a middle-out approach. *AAPS. J.* 23, 12. <https://doi.org/10.1208/s12248-020-00548-8>.
- Radtke, R.A., 2001. Pharmacokinetics of Levetiracetam. *Epilepsia.* 42, 24–27. <https://doi.org/10.1046/j.1528-1157.2001.0420s4024.x>.
- Rinaki, E., Dokoumetzidis, A., Valsami, G., Macheras, P., 2004. Identification of biowaivers among class II drugs: theoretical justification and practical examples. *Pharm. Res.* 21, 1567. <https://doi.org/10.1023/b:pham.0000041450.25106.c8>.
- Roila, F., Del Favero, A., 1995. Ondansetron Clinical Pharmacokinetics. *Clin Pharmacokin* 29, 95–109. <https://doi.org/10.2165/00003088-199529020-00004>.
- Sinko, P.J., Leesman, G.D., Amidon, G.L., 1991. Predicting fraction dose absorbed in humans using a macroscopic mass balance approach. *Pharm. Res.* 8, 979–988. <https://doi.org/10.1023/A:1015892621261>.
- Sugano, K., 2021. Lost in modelling and simulation? ADMET. *DMPK.* 9, 75–109. <https://doi.org/10.5599/admet.923>.
- Thambavita, D.D., Galappathay, P., Jayakody, R.L., 2021. Pharmacokinetics and bioequivalence of two Amoxicillin 500 mg products: effect of food on absorption and supporting scientific justification for Biowaiver. *J. Pharm. Sci.* 110, 3735–3741. <https://doi.org/10.1016/j.xphs.2021.06.011>.
- Toullitsis, E., Tsekouras, A.A., Macheras, P., 2024. FDA and EMA oversight of disruptive science on application of finite absorption time (F.A.T.) concept in oral drug absorption: time for scientific and regulatory changes. *Pharmaceutics.* 16, 1435. <https://doi.org/10.3390/pharmaceutics16111435>.
- Tsekouras, A.A., Macheras, P., 2024. Application of the finite absorption time (F.A.T.) concept in the assessment of bioequivalence. *Pharm Res.* 41, 1413–1425. <https://doi.org/10.1007/s11095-024-03727-w>.
- Wu, D., Tsekouras, A.A., Macheras, P., Kesisoglou, F., 2023. Physiologically based pharmacokinetic models under the prism of the finite absorption time concept. *Pharm. Res.* 40, 419–429. <https://doi.org/10.1007/s11095-022-03357-0>.
- Yamaoka, K., Nakagawa, T., Uno, T., 1978. Statistical moments in pharmacokinetics. *J. Pharmacokinet. Biopharm.* 6, 547–558. <https://doi.org/10.1007/BF01062109>.
- Yu, L.X., Crison, J.R., Amidon, G.L., 1996. Compartmental transit and dispersion model analysis of small intestinal transit flow in humans. *Int. J. Pharm.* 140, 111–118. [https://doi.org/10.1016/0378-5173\(96\)04592-9](https://doi.org/10.1016/0378-5173(96)04592-9).
- Yu, L.X., Amidon, G.L., 1998. Characterization of small intestinal transit time distribution in humans. *Int. J. Pharm.* 171, 157–163. [https://doi.org/10.1016/S0378-5173\(98\)00174-4](https://doi.org/10.1016/S0378-5173(98)00174-4).