



Physiologically based Pharmacokinetic Models under the Prism of the Finite Absorption Time Concept

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Abstract

To date, mechanistic modeling of oral drug absorption has been achieved via the use of physiologically based pharmacokinetic (PBPK) modeling, and more specifically, physiologically based biopharmaceutics model (PBBM). The concept of finite absorption time (FAT) has been developed recently and the application of the relevant physiologically based finite time pharmacokinetic (PBFTP) models to experimental data provides explicit evidence that drug absorption terminates at a specific time point. In this manuscript, we explored how PBBM and PBFTP models compare when applied to the same dataset. A set of six compounds with clinical data from immediate-release formulation were selected. Both models resulted in absorption time estimates within the small intestinal transit time, with PBFTP models generally providing shorter time estimates. A clear relationship between the absorption rate and the product of permeability and luminal concentration was observed, in concurrence with the fundamental assumptions of PBFTP models. We propose that future research on the synergy between the two modeling approaches can lead to both improvements in the initial parameterization of PBPK/PBBM models but to also expand mechanistic oral absorption concepts to more traditional pharmacometrics applications.

Keywords correlation · finite absorption time · oral absorption · PBFTP · PBPK modeling

Introduction

The physiologically based pharmacokinetic (PBPK)¹ modeling work relies on detailed mechanistic representations, which reduce the complex drug processes of the biological systems. In this context, the PBPK models integrate both drug-dependent parameters (physicochemical properties) and drug-independent (species-specific anatomy, physiology, and biochemistry) as well as combined, such as parameters related to biotransformation and excretion [1–3].

One of the most important applications of PBPK modeling is in oral drug absorption. Thus, hot themes in oral drug absorption such as specific patient populations, regional differences in the gastrointestinal tract, advanced formulations, and food-drug interactions have been reviewed recently [4]. In parallel, the concept of finite absorption time (FAT) has been developed recently and the application of the relevant physiologically based finite time pharmacokinetic (PBFTP) models to experimental data provides explicit evidence that drug absorption terminates at a specific time point, τ [5–9]. In fact this is true because drug absorption takes place under sink conditions for physicochemical and physiological reasons. Thus, for BCS class II, III and IV drugs with low solubility and/or low permeability drug concentration in the GI tract remains essentially constant; in parallel, high blood flow in the vena cava, 20–40 cm/s [10] imposes sink conditions for the drug transfer rate. For class I drugs with high solubility and high permeability, absorption

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¹ Abbreviations: AUC: area under the curve, BCS: biopharmaceutics classification system, CMC: chemistry, manufacturing and controls, FAT: finite absorption time, IVIVC: *in vitro in vivo* correlation, PBBM: physiologically based biopharmaceutics model, PBFTP: physiologically based finite time pharmacokinetic, PBPK: physiologically based pharmacokinetic, PE: prediction error

is very rapid and is completed in very short time. For one-compartment model drugs with a one-input rate, the value of τ coincides with t_{\max} (the time corresponding to the maximum concentration, C_{\max}) [9]. In all other cases, simulations show that τ can be equal to or higher than t_{\max} [9].

PBPK models of oral drug absorption utilize specific transit times in the compartments of the gastrointestinal tract and often rely on the passive drug diffusion mechanism under sink conditions since the blood on the basolateral side of the membrane is regarded as an ideal sink [2]. The PBFTP models [5, 7–9] rely on the same principles: i) finite absorption time, τ for drug absorption processes and ii) zero-order drug input (single or multiple) or first-order [11–13] as a result of the passive drug absorption under sink conditions. This resemblance in the fundamental characteristics (transit and rate of drug input) prompted us to couple the simulated drug absorption profile derived from the PBPK models with the analysis of the *in vivo* data based on PBFTP models to get a better understanding of the kinetics of drug absorption. Furthermore, we explore the relationships, if any, between physicochemical and pharmacokinetic parameters, e.g., rate of drug input.

Materials and Methods

Compounds

Six compounds, including etoricoxib, gaboxadol, dipyrindamole, pioglitazone, compound C and losartan, were selected in this study to explore the relationship between biopharmaceutics and pharmacokinetic (PK) parameters. The key physicochemical and PK parameters are included in Table I. The selected compounds range from BCS I–III and are considered with a moderate to high fraction of absorption (F_a) for oral formulations [14–17]; the compounds were selected based on the availability of PO/IV data and PBPK models that were needed for this analysis.

PBPK Modeling Development

PBPK models for six selected compounds were developed as previously described [14–17]. The key physicochemical and pharmacokinetic parameters used as model input for each compound are summarized in Table I. When dissolution data were used, dissolution profile input was either entered as is or used a z-factor dissolution model [18] as input. Particle size based simulations used the Hintz-Johnson model [19]. Given that many of the compounds in this work are highly soluble in the stomach, the simulations are not very sensitive to the dissolution model selected. For compounds where precipitation was not observed *in vitro*, precipitation time (i.e. reciprocal of precipitation rate) was set to a high value as

not to impact the simulation. Most models estimated human effective permeability from *in vitro* data which is a common practice [20]. Pharmacokinetic parameters for systemic disposition were obtained from previous publications where they were estimated by fitting intravenous PK data using either Phoenix WinNonlin (Certara, Princeton, NJ) or with the build-in PK-Plus module in GastroPlus™ (Simulations Plus, Lancaster, CA). Specific model settings or optimized parameters for model development were included in Table I. Since the purpose of this study is to use the estimates of *in vivo* absorption for comparison to the PBFTP models, and the published models were within desired model acceptance criteria in terms of describing the clinical data, no further parameter optimization or change in the model setting was conducted in this manuscript; Table I indicates whether the original model was a bottom-up or middle-out approach, sources of parameters and fitted parameters when applicable.

All simulations were conducted using GastroPlus® software v9.8. The PBPK models used default fasted human physiology settings unless otherwise stated in the Table I. Opt logD model SA/V 6.1 was used as the absorption scale factor (ASF) model.

PBFTP Model Fittings

The model equations [9] were fitted to experimental PK data [14–17]. The PBFTP software used in all model fittings relies on user-defined functions in Igor programming environment. In this implementation, we adapted its versatile built-in least-squares algorithm which allows, among other features, restrictions to parameter values, the use of statistical weights and data sub-sets, calculation of parameter covariance matrix, and easy graphical representation of results. Due to the complex form of the model equations and the convoluted shape of the resulting χ^2 hypersurface in parameter space with numerous local minima, the determination of initial trial parameter values was crucial and required manual adjustments.

Exploring Relationships between Biopharmaceutics Properties and Pharmacokinetic Parameters

The absorption kinetics can be described by the rate of penetration [5, 7].

$$\text{Rate of Penetration} = P_{\text{eff}}(SA) (C_{GI}) = \frac{F_a D}{\tau} \quad (1)$$

where P_{eff} is the effective permeability of the drug expressed in velocity units (length/time), SA is the surface area of the membrane in (length)² units, C_{GI} is drug concentration in the gastrointestinal (GI) lumen, F_a is the fraction of dose (D) absorbed and τ is the duration of the absorption phase.

Table 1 PBBM Input Parameters of Tested Compounds

Parameter	Etoricoxib [15, 27]	Gaboxadol [16]	Dipyridamole [17]	Pioglitazone [14]	Compound C [14]	Losartan [14]
BCS	II	I	II	II	II	III
Dose used for the modeling and analysis (mg)	120	10	50	30	100	50
Molecular weight (g/mol)	358.85	140.14	504.6	356	504	423
Log P/Log D	2.28	-0.61	3.95 (pH 7)	2.9	2.1 (pH 7.0)	6.1
pKa	4.5 (basic)	4.3 (acidic), 8.3 (basic)	6.4 (basic)	4.8 (basic)	6.9 (acidic)	2.95 (basic), 4.25 (acidic) [28]
pH – solubility profile (mg/mL)	pH 2.0: 25.1 pH 3.07: 2.01 pH 3.54: 0.7 pH 4.01: 0.3 pH 4.54: 0.14 pH 5.03: 0.09 pH 5.47: 0.08 pH 6.8: 0.073	30 across pH (HCl salt form)	pH 3.0: 5 pH 5.0: 0.13 pH 7.5: 0.005 SGF (pH 1.3): 8.0 FaSSiF (pH 6.0–7.0): 0.012	pH 1.8: 0.38 pH 2.6: 0.03 pH > 6: 0.0003 salt form: pH 1.4: ~1.3	pH 2.1: 0.3 pH 4: 0.28 pH 6.9: 0.48 pH 7.7: 1.31	1.6 across pH to simulate as BCS III
Effective human permeability (cm/s)	4.48×10^{-4}	5×10^{-4} (topdown optimized due to active transport) [29])	2.5×10^{-4}	4×10^{-4}	2.5×10^{-4}	1.15×10^{-4}
Precipitation time (s)	10,000 (set to remove precipitation based on in vitro data)	900 (default, no impact on simulation due to high solubility)	120,000 (set to remove precipitation based on in vitro data)	10,000 (value needed to fit observed data)	900 (default, no impact on simulation as compound is an acid)	900 (default, no impact on simulation due to high solubility)
Dissolution model	z-factor Surface pH correction was conducted for pH 2 dissolution media, to pH 2.85 [15]. (no significant impact to the PK prediction due to very high stomach solubility)	N/A solution formulation	z-factor	Hintz-Johnson	Hintz-Johnson	Direct input
Dissolution method media	Multimedia (pH 2, pH 6.8) [15]	N/A solution formulation	SGF [17]	NA, PSD based simulation	FaSSiF [14]	SGF [14]

Table I (continued)

Parameter	Etoricoxib [15, 27]	Gabaxadol [16]	Dipyridamole [17]	Pioglitazone [14]	Compound C [14]	Losartan [14]
Disposition parameters	Vc = 35.49 L Cl = 3.19 L/hr. K12 = 0.62 1/hr. K21 = 0.28 1/hr. FPE liver = 0% as 100% bioavailability [27, 30]	Vc = 0.22 L/kg Cl = 0.43 L/h/kg K12 = 3.00 1/hr. K21 = 1.65 1/hr. FPE = 8% as 92% bioavailability [16, 31]	Vc = 0.0869 L/kg CL = 0.104 L/h/kg K12 = 2.38 1/hr. K21 = 3.63 1/hr. K13 = 0.50 1/hr. K31 = 0.074 1/hr. FPE liver = 8% Intestinal Bioavailability%: 37–66% [17, 32]	Vc = 0.253 L/kg Cl = 2.4 L/h FPE = 3% Bioavailability%: >80% [14, 33]	Vc = 11.8 L K12 = 3.4 1/hr. K21 = 2.0 1/hr. K13 = 0.09 1/hr. K31 = 0.08 1/hr. FPE liver = 41.4% Intestinal extraction = 13% Bioavailability%: ~46% [14, 34]	Vc = 28.7 L Cl = 21.7 L/h Bioavailability%: 33% [14]
Simulated fraction of absorption (%Fa)	99%	99%	94%	88%	99%	99%
Specific physiology settings	N/A	N/A	N/A	N/A	No colonic absorption (no significant impact to the PK prediction at 100 mg dose) Small intestine water content was set to 15%	N/A
Bottom up or Middle Out	Bottom Up	Middle Out – Fitting of intestinal permeability required due to active uptake	Bottom Up	Middle Out – Precipitation time fit to clinical data	Middle Out – intestinal volumes adjusted based on clinical data	Bottom Up

Table II Comparison of Observed and Predicted Pharmacokinetic Parameters (AUC, C_{max}) for Tested Compounds and PBFTPK Fitting (R²) of Tested Compounds

Test compounds	C _{max_obs} (ng/mL)	C _{max_pred} (ng/mL)	% PE*	AUC _{0-t_obs} (ng-h/mL)	AUC _{0-t_pred} (ng-h/mL)	% PE*	R ² of PBFTPK model fitting**
Etoricoxib	1886.8	1853.9	1.74	39594	35829	9.51	0.994
Gaboxadol	189.67	159.90	15.7	300.33	303.08	0.916	0.998
Dipyridamole	1774.9	1679.8	5.36	4550.9	5615.9	23.4	0.923
Pioglitazone	1111.0	1189.8	7.09	14290	10605	25.8	0.998
Compound C	561.10	582.20	3.76	1683.2	1797.3	6.78	0.994
Losartan	147.00	152.98	4.08	556.58	551.05	0.997	0.992

*%prediction error (%PE) = [(Observed value – Predicted value)/ Observed value] × 100

**R²: coefficient of determination. R² = 1 - (sum of squares of residuals/total sum of squares)

The relationship between biopharmaceutics properties (e.g., P_{eff} and solubility) and $(AUC)_{0-\tau}$ for one zero-order input rate was discussed previously [5, 7].

$$(AUC)_{0-\tau} = \frac{FD}{\tau} \frac{1}{V_d k_{el}} \left(\tau - \frac{1 - e^{-k_{el}\tau}}{k_{el}} \right) \quad (2)$$

where F is the bioavailable fraction of dose D , V_d is the volume of distribution and k_{el} is the elimination rate constant. Time τ denotes either the passage of the drug beyond the absorptive sites or the completion of the absorption process since no more dissolved drug is available for absorption. $(AUC)_{0-\tau}$ is the area under the curve from time 0 to τ .

$(AUC)_{0-\tau}$ represents the exposure of the compound in a certain time period and is a combining consideration of absorption rate and elimination rate. By replacing the FD/τ assuming *no first pass effect* with Eq. 1, a relationship among $(AUC)_{0-\tau}$, P_{eff} , gastrointestinal concentration, and elimination parameters is established. In this study, correlation analysis was conducted between physicochemical properties such as P_{eff} , C_{lumen} , and pharmacokinetics parameters such as τ , elimination rate, and $(AUC)_{0-\tau}$. For compounds, such as gaboxadol and pioglitazone, which require a second stage of zero-order kinetics, τ_1 and corresponding $(AUC)_{0-\tau_1}$ were used for analysis. In this manuscript, the term “ $(AUC)_{0-\tau}$ ” and “ τ ” were used for all the compounds.

All the selected compounds in this study are dissolved in solution after dosing and remain supersaturated in the GI tract, thus duodenum and jejunum lumen drug concentrations, estimated from PBPK modeling [14–17], were used for correlation analysis. Relevant PK parameters and absorption parameters were generated from PBFTPK fitting including τ , $(AUC)_{0-\tau}$ and elimination rate constant (k_{el}). Effective human permeability (P_{eff}) values for tested compounds were gathered from previously published papers [14–17].

Results

PBPK Modeling

Detailed model development and validation can be found in previous publications [14–17]. Overall, the developed models can reasonably describe the observed pharmacokinetic profiles for the tested compounds. The percentage of prediction errors (%PE) for C_{max} and AUC are within the typically acceptable criteria (%PE < 25%), as shown in Table II. Observed *versus* predicted plasma concentration-time profiles for each compound are presented in Fig. 1. Hence, the models are considered valid and robust, and suitable for further data analysis in this study.

Fittings of PBFTPK Models to *In Vivo* Data

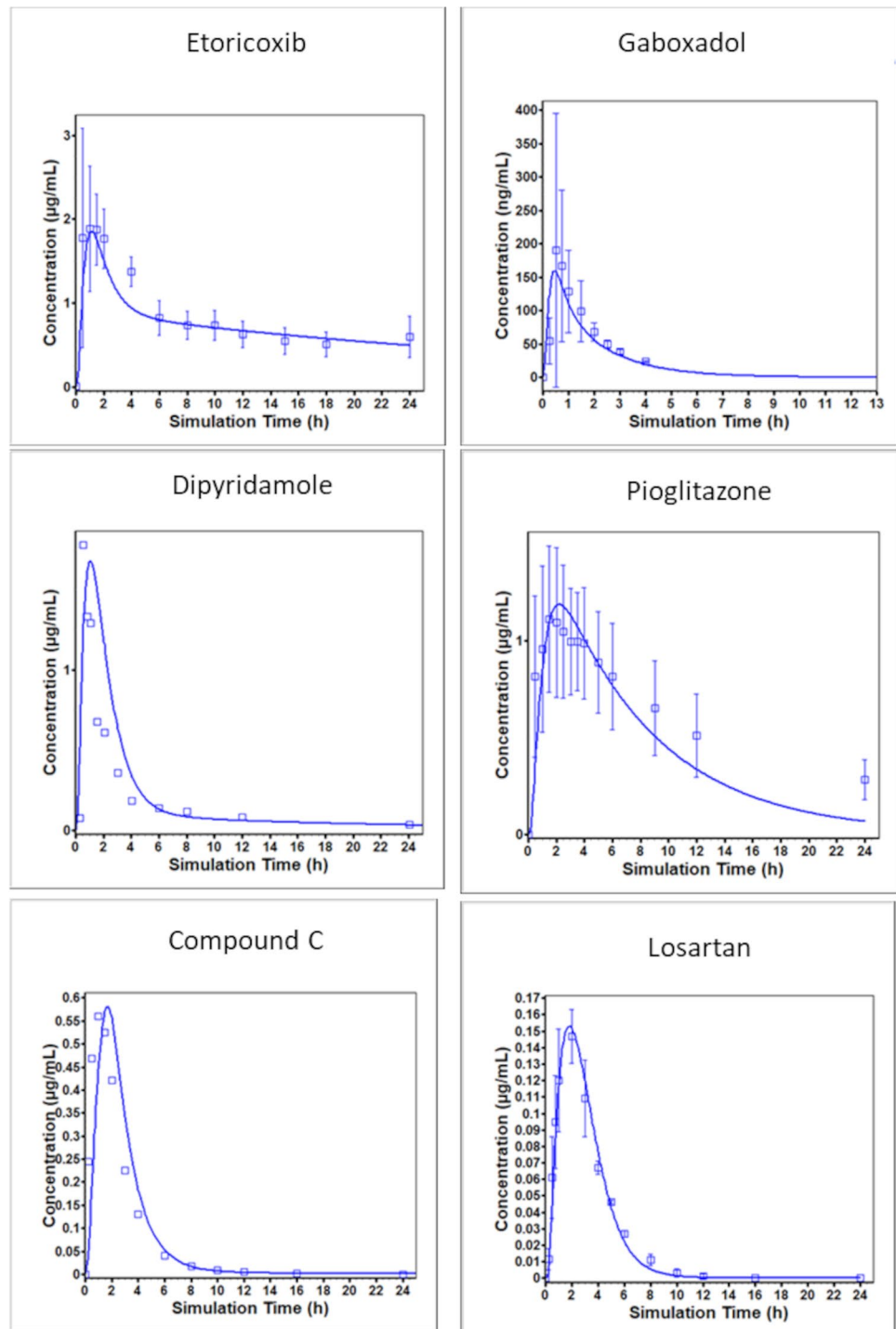
A variety of models [9] were tested on the experimental data of the six formulations. Fits were attempted with one or two zero-order input stages for one or two compartment disposition models. Figure 2 shows the best fit for each drug product. Details and parameter values are also given in Fig. 2 for each drug.

Figure 3 shows a plot of the disposition parameters *versus* the finite time absorption time τ estimates for the six drugs studied. All of them, except the borderline losartan, belong to the very rapidly absorbed drug class [9].

Exploring Relationships between Biopharmaceutical Properties and Pharmacokinetic Parameters

Physicochemical and PK parameters, including effective permeability (P_{eff}), maximum drug lumen concentration in duodenum and jejunum, absorption termination time (τ), $AUC_{0-\tau}$, and elimination rate (k_{el} or β), for data analysis, are included in Table III.

Fig. 1 Observed (dot) versus simulated (line) drug plasma concentration versus time from PBPK model simulation for (A) Etoricoxib [15, 27] (B) Gaboxadol [16] (C) Dipyridamole [17] (D) Pioglitazone [14] (E) Compound C [14] and (F) Losartan [14] (figures modified from references [14–17]).



Given the limited dataset, fully exploring relationships between PBFTPk parameters and PBBM input/output is not practical. Exploratory plots (data not shown) on, e.g., $AUC_{0-\tau}$ vs P_{eff} or C_s did not result in specific trends. We explore two relationships below.

1) D/τ vs $P_{\text{eff}} \cdot \max(C_{\text{lumen}})$

D/τ which is used as a measure of absorption rate showed a positive correlation with $P_{\text{eff}} \cdot C_{\text{lumen}}$ using either the maximum luminal concentration in the jejunum or duodenum, as shown in Fig. 4.

2) $k_{\text{el}} (\beta)$ vs. $AUC_{0-\tau}$

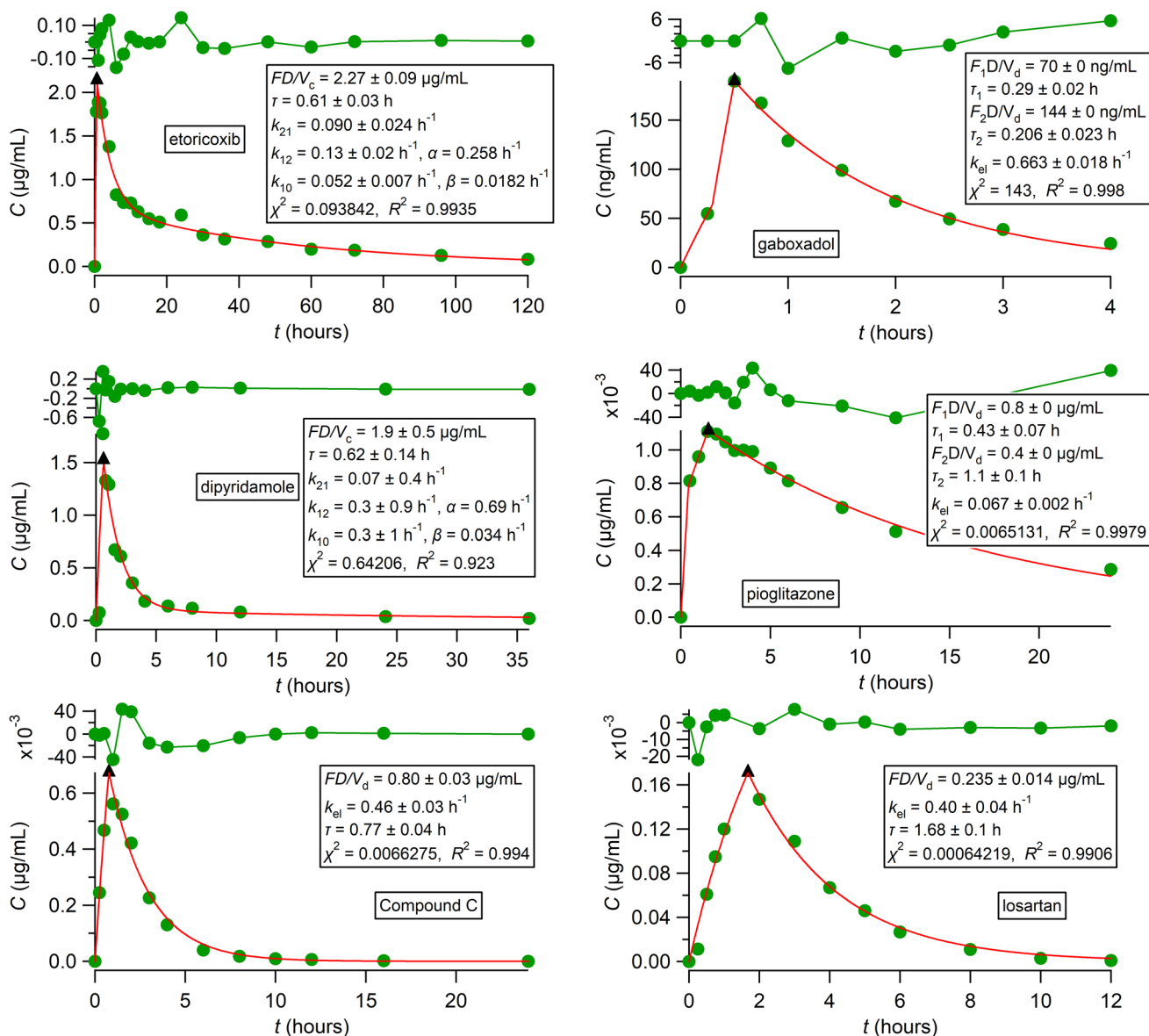


Fig. 2 Model fits to pharmacokinetic data for 6 oral formulations. Losartan and Compound C formulations are best described by a one-compartment model with a single stage of zero-order input kinetics [Eqs. 29–30 in [9]]. Gaboxadol and pioglitazone require a second stage of zero-order kinetics [Eqs. 31–33 in [9]]. Etoricoxib and dipyridamole are best described by a two-compartment model with one stage of zero-order kinetics [Eqs. 38–40 in [9]]. Optimized parameters are shown in the insets of each graph along with χ^2 and R^2 for each fit. Note: Fits for gaboxadol and pioglitazone were restricted to reduce parameter correlations. A solid triangle marks the end of any absorption stage, which in the cases presented happens to coincide with C_{max} .

Values for k_{el} or β were generated from PBFTPK model fitting, as shown in Fig. 2. Based on Eq. 2, elimination parameters (k_{el} , clearance, β) are expected to exhibit a negative relationship with $AUC_{0-\tau}$. As shown in Fig. 5, a negative correlation between k_{el} (or β for etoricoxib) and $AUC_{0-\tau}$ was observed.

Discussion

The two modeling approaches utilized in the present study were based on PBPK and PBFTPK models. This allows us, for the first time, to explore potential relationships

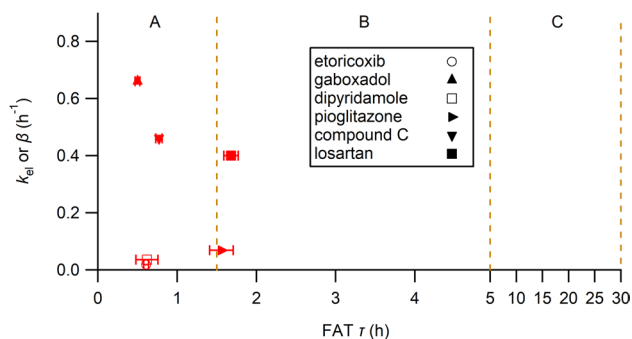


Fig. 3 Grouping of formulations based on ranges of elimination rate constants one-compartment model drugs (β rate constants for two-compartment drugs) and FATS. Open symbols refer to two-compartment models.

between the biopharmaceutics properties, solubility, and permeability with the pharmacokinetic parameters. This is so since the drug's passive absorption under sink conditions kinetics can be described by the rate of penetration (Eq. 1) [5].

To the best of our knowledge, this is the first attempt to explore PBPK (and more specifically PBBM) and PBFTPK models for the same clinical datasets. The two modeling approaches have currently distinct application and focus. PBBM primarily focuses on simulation/prediction of oral absorption for a diverse set of applications during discovery and CMC activities (e.g., formulation development, dissolution specifications) and during clinical development (e.g., pH-dependent drug-drug interaction prediction, food effect prediction) [21]. The outcome is dictated by the input parameters, while the observed data are used for model validation as demonstrated in Table II. PBFTPK models on the other hand focus on the characterization of oral absorption based on the fitting of observed data. This difference in focus is also reflected in the outcomes shown in the examples herein, where the PBBM models show some deviations from the clinical data and somewhat different estimations of, e.g., termination of absorption time compared to the PBFTPK model.

Despite the currently different focus, we believe that synergies exist for their application in oral absorption modeling, derived from the common denominator that is the finite absorption time concept. As is evident from Figs. 1 and 2 for all the compounds studied, absorption is essentially complete within the small intestinal transit time as estimated by either model. The estimates of absorption time were generally shorter using the PBFTPK model compared to the PBBM model. This is perhaps not surprising as the PBBM models incorporate additional first-order processes to simulate gastrointestinal transit resulting in absorption curves that show curvature at ~80% of the maximum absorption point; for the earlier points, the absorption rate is very close to zero-order as assumed in the PBFTPK models.

Based on Eqs. 1 and 2, in this manuscript, we attempted to explore the relationship between PBFTPK estimated parameters and input parameters or outputs for PBBM models. For such analysis to result in actionable correlations to single physicochemical properties (e.g., P_{eff}) it will require significantly larger datasets, most likely of compounds of similar class. Within the limited dataset explored, a clear relationship between D/τ and $P_{\text{eff}} \cdot C_{\text{lumen}}$ using either the maximum duodenum or jejunum concentrations was observed (Fig. 4). This relationship (Eq. 1) is fundamental and in accord with the basic principles of PBFTPK [5]. According to the drug's biopharmaceutics properties, the rate-limiting property solubility or permeability will control the rate of drug penetration. However, the analysis of the data of this study demonstrates that the product $P_{\text{eff}} \cdot C_{\text{lumen}}$ is correlated with the rate of drug input. This finding is in accord with the fundamental principles of the absorption potential concept [22, 23] used prior to the introduction of BCS for the biopharmaceutics classification of drugs.

According to Eq. 2, $(AUC)_{0-\tau}$ is increasing when k_{el} is decreasing. As shown in Fig. 5, this trend was indeed observable. It should also be emphasized that the partial area $(AUC)_{0-\tau}$ is used today as an early exposure metric [24]; however, what it represents, under the prism of the finite absorption time concept [7], is the fundamental extent of the

Table III Biopharmaceutics Parameters (Dose, C_{lumen} , P_{eff}) and PK Parameters (AUC , τ , D/τ , and k_{el}) for Data Analysis

Compounds	Dose (mg)	P_{eff} ($\text{cm/s} \times 10^{-4}$)	Max duodenum lumen conc (mg/mL)	Max jejunum lumen conc (mg/mL)	t_{max}	τ (h)	$AUC_{0-\tau}$ (h $\mu\text{g/mL}$)	D/τ (mg/h)	k_{el} (β) (1/h)
Etoricoxib	120	4.48	0.69	0.12	1	0.61	0.67	197	0.018
Gaboxadol	10	5	0.095	0.014	0.5	0.29	0.016	34.5	0.66
Dipyridamole	50	2.5	0.34	0.074	0.6	0.62	0.50	80.7	0.036
Pioglitazone	30	4	0.23	0.056	1.5	0.43	1.1	69.8	0.069
Compound C	100	2.5	0.41	0.18	1	0.77	0.27	130	0.46
Losartan	50	1.15	0.42	0.12	2	1.68	0.16	29.8	0.40

Fig. 4 Correlation between D/τ and $P_{eff} * C_{lumen}$. Open circle: etoricoxib, open triangle: gaboxadol, open square: dipyridamole, open diamond: pioglitazone, closed circle: compound C, closed square: losartan. For compounds, such as gaboxadol and pioglitazone, which require a second stage of zero-order kinetics, τ_1 was used for analysis.

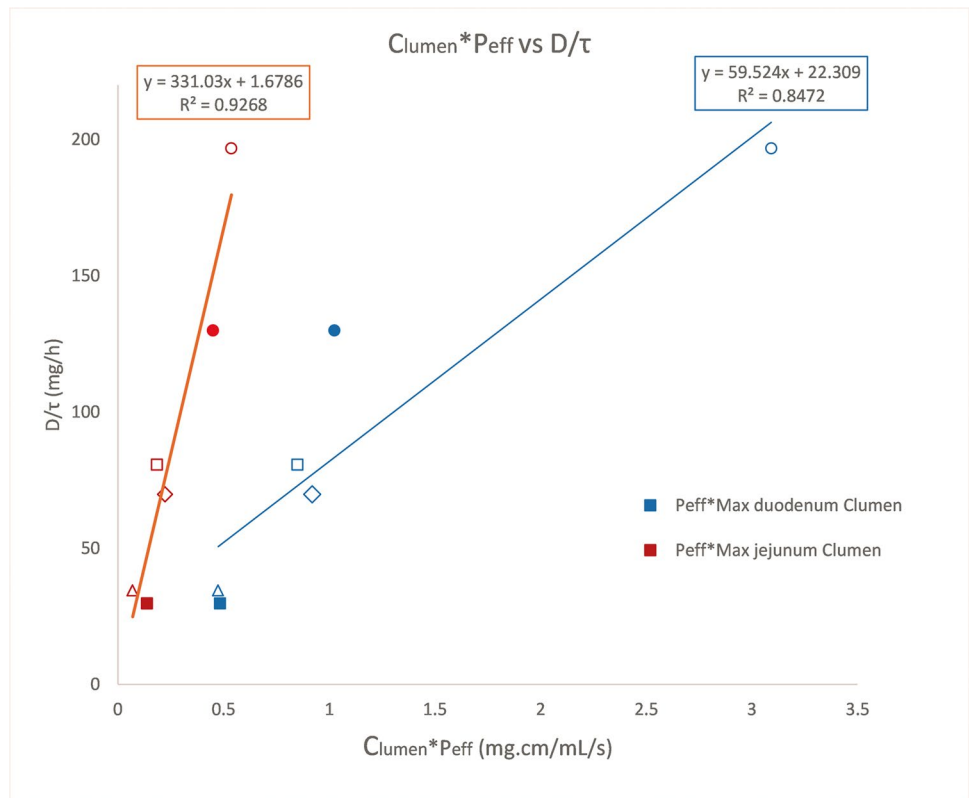
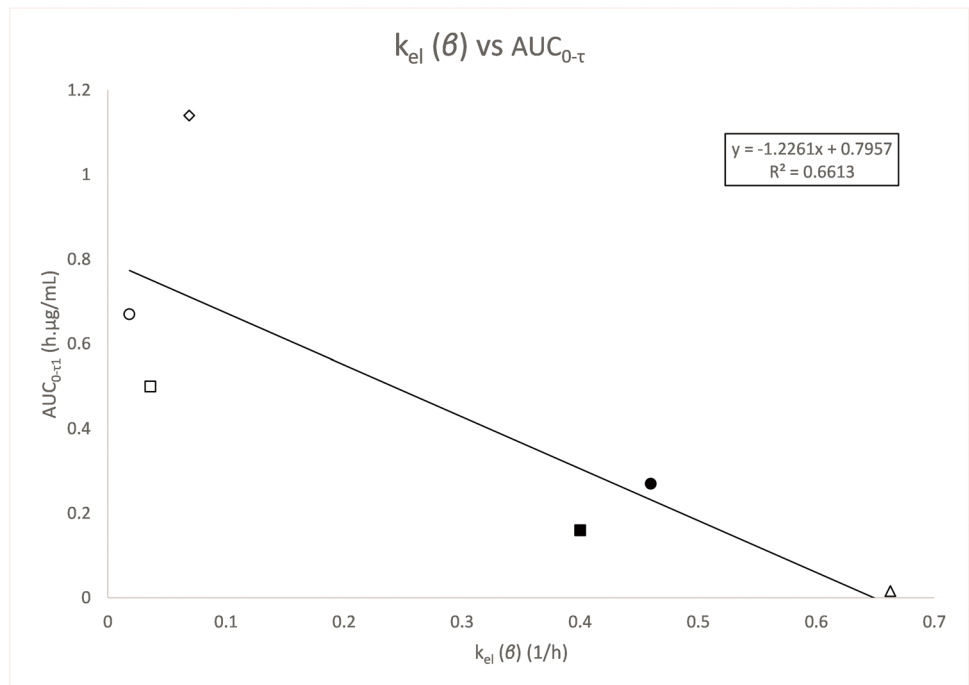


Fig. 5 Correlation between elimination parameter (k_{el} or β) and $AUC_{0-\tau}$. Open circle: etoricoxib, open triangle: gaboxadol, open square: dipyridamole, open diamond: pioglitazone, closed circle: compound C, closed square: losartan.



absorption metric since it is linearly related (Eq. 2) with the dose (D) absorbed at time τ , namely, the end of the absorption processes.

While the intent of this manuscript was to simply serve as a starting point for exploring the relationship of PBPK and PBFTP models, we envision some broader areas for

additional synergy of PBBM and PBFTP models that could be considered as areas of future research.

- PBFTP models allow for the estimation of bioavailability-corrected disposition parameters without the need for IV data [7] at an individual level basis. Current PBBM models are often developed either without IV data being available or with IV data coming from an independent study, thus introducing between-study variability uncertainty. Especially for compounds where absorption is close to complete and thus the bioavailability correction only reflects first-pass metabolism, PBFTP estimated disposition parameters could facilitate the development of PBBM models on an individual basis, allowing for better capturing of the variability of absorption processes, an important consideration, especially for virtual bioequivalence applications.
- It has been reported in the literature that “default” parameters for colonic permeability in PBPK models may overestimate the contribution of colonic absorption [15]. Given the ability of PBFTP models to readily estimate termination of absorption, this knowledge can help parameterization of regional dependent absorption for PBPK and IVIVC-PBPK models, especially for MR formulations. This could be accomplished by estimating τ from high dose arms of single ascending dose studies, where for BCS II/IV compounds, absorption is likely not to be complete.
- Estimation of different absorption time periods (i.e. τ_1 and τ_2) may also provide insights into *in vivo* processes that are currently difficult to predict via *in vitro* data, e.g., precipitation. Recent workshops have discussed these challenges as well as the importance of the use of biopredictive dissolution methods for PBPK models [20, 25]. Thus, an early estimation of τ , based on FIH data could facilitate the development of such dissolution methods.
- Currently, population pharmacokinetics (popPK) models generally rely on an empirical simulation of absorption using k_a/t_{lag} or transit compartment constructs without the necessary consideration of physiological constraints [26]. The potential of adoption of PBFTP model structure for popPK applications may allow to better connect findings from popPK models to mechanistic simulation via PBPK/PBBM in related applications (e.g., characterization of DDI with acid-reducing agents).

Conclusion

For the first time we report the application of PBBM and PBFTP models on the same clinical datasets. Both models support the concept of finite absorption time, which has

been somewhat underappreciated in traditional pharmacokinetic/pharmacometrics applications. The estimates of luminal concentration from PBPK model were correlated to the absorption rate estimates from PBFTP models. We propose that additional synergies should be explored moving forward to bring a more mechanistic modeling of the absorption process not only as part of core PBPK models, but incorporate these principles also in modeling applications that currently largely rely on compartmental models.

Declarations

Conflict of Interest The authors declare no competing interests. Filippos Kesisoglou and Di Wu are employees of Merck Sharp & Dohme LLC, a subsidiary of Merck & Co., Inc., Rahway, NJ, USA and may own stock or hold stock options in Merck & Co., Inc., Rahway, NJ, US.

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