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CORRESPONDENCE

The Finite Absorption Time (FAT) concept en route to PBPK modeling and pharmacometrics

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Abstract
The concept of Finite Absorption Time (FAT) for oral drug administration is set to affect pharmacokinetic analyses, Physiologically-based Pharmacokinetics simulations, and Pharmacometrics.

According to Ioannidis [1] "the ability to self-correct is considered a hallmark of science; however, self-correction does not always happen to scientific evidence by default". This is particularly so when replication efforts are missing and the scientists left with unconfirmed discoveries and unchallenged fallacies. This is the case for the dogma of first-order kinetics applied in oral drug absorption since the inception of pharmacokinetics in 1953 by Dost [2].

Unveiling the wrong assumption that breaks oral pharmacokinetics

At the turn of the previous century Harry Bateman, a Cambridge mathematician solved systems of differential equations [3] discovered by Rutherford [4] which describe radio-active decay. In nuclear physics, the Bateman equation is a mathematical model describing abundances and activities in a decay chain as a function of time, based on the decay rates and initial abundances. The model was formulated by Ernest Rutherford [4] and the analytical solution was provided by Harry Bateman [3]. For the simple case of a chain of three isotopes (mother, daughter, grand-daughter), Fig. 1a, the corresponding Bateman equation reduces to an equation with two exponentials for the abundance of the daughter species N_{daugther}:

$$N_{\text{daughter}} = \frac{N_{\text{m0}}\lambda_{\text{m}}}{\lambda_{\text{m}} - \lambda_{\text{d}}}\left(e^{-\lambda_{\text{d}}t} - e^{-\lambda_{\text{m}}t}\right) \quad (1)$$

where λ_{m} and λ_{d} are first-order rate constants for the transition of the mother to daughter species and the transition from the daughter to grand-daughter species, respectively; N_{m0} is the initial abundance of the mother species. Figure 1b shows in a comparative manner Dost's kinetic considerations describing oral drug absorption for the gastrointestinal tract. Equation 2 describes the concentration of drug in blood $C(t)$ as a function of time for the linear one-compartment model with first-order absorption and elimination

$$C(t) = \frac{FDk_{\text{a}}}{V_{\text{d}}(k_{\text{a}} - k_{\text{el}})}\left(e^{-k_{\text{el}}t} - e^{-k_{\text{a}}t}\right) \quad (2)$$

where F is the bioavailable fraction of dose D, V_{d} is the volume of distribution, k_{a} is the first-order rate constant of absorption and k_{el} is the elimination first-order rate constant. In fact, Dost [2] replaced the abundance of the daughter species with the concentration of drug in blood, Fig. 1.

The development of the Finite Absorption Time (FAT) concept

The first-order drug absorption is synonymous with a process running for infinite time, which never happens in real world of oral drug absorption phenomena, i.e., it does

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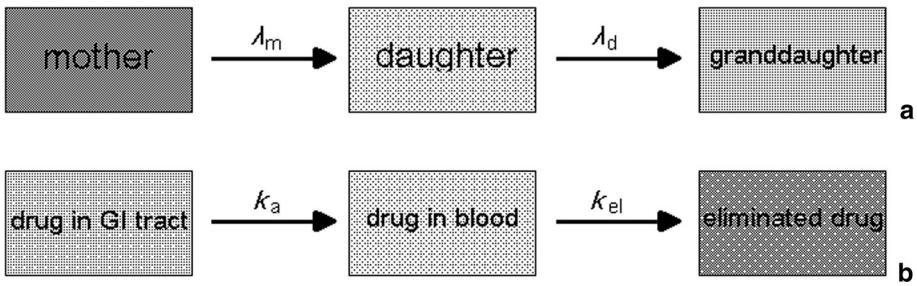

Fig. 1 **a** The model for a chain of three isotopes studied in 1910 by Bateman [3]. **b** Dost's corresponding drug kinetics considerations published in 1953 [2]. Redrawn from [5]

not seem to have any theoretical support. We initially questioned the validity of the first-order absorption assumption as unphysical [6]. We then developed a minimal FAT model of drug absorption [5]. Drugs are absorbed passively under sink conditions with the limiting property solubility (Class II drugs) or permeability (Class III drugs) or solubility/permeability (Class IV drugs) driving one to three sequential constant input rates for a certain period of time τ, which is subject to physiological gastrointestinal transit time constraints [5–7]. Apart from the above biopharmaceutical reasons, the high blood flow rate in the vena cava (20–40 cm/s) [5, 7, 8] also ensures drug transport under sink conditions. The pertinent physiologically based finite time pharmacokinetic (PBFTPK) models developed [9] were used for the analysis of a plethora of blood concentration, time data; meaningful parameter estimates for the duration of drug absorption, and drug input rate(s) were derived [9, 10]. In all cases, the PBFTPK models were superior compared to the classical models with first-order absorption in all fitting metrics [9, 10]. Besides, the implications associated with the valid use of bioavailability parameters $[AUC]_0^\infty$ and $C_{\max}$ for the assessment of bioequivalence were considered [7, 11, 12] since drug absorption terminates at time τ (FAT).

Basically, our work [5, 7, 9–13] demonstrates that "drugs are absorbed passively under sink conditions for a certain period of time, τ (FAT)". The sink conditions are associated with the prevailing rate limiting step, namely, slow dissolution because of the low drug solubility (Class II drugs) or slow permeation because of the low drug permeability (Class III drugs) or both (Class IV drugs). The sink conditions are maintained throughout the absorption process since the blood flow in the vena cava ensures the rapid removal of drug towards the liver. Besides, the FAT reflects the transit time for the drug passage from the absorptive sites of the gastrointestinal tract. The latter are primarily located in the small intestines and therefore the estimates for τ are, in most cases lower than 3 h [5, 7, 9–13]. However, complex absorption kinetics is frequently encountered and linked with either dissolution, e.g., precipitation, re-dissolution, supersaturation, or permeability, e.g., selective permeability. In these situations, more than one input rate can be identified; in fact, this has been verified using the developed PBFTPK models in the analysis of almotriptan, ibuprofen and the reference formulation of cyclosporine data [9]. Besides, it was found [7] that Class I drugs like theophylline are absorbed rapidly and the $t_{\max}$ coincides with the end of the completion of the absorption process. Overall, the drug concentration measured in plasma is correlated with the drug concentration in the lumen with the input and the elimination rates being the controlling factors. This was found in the first application of the FAT concept in the PBPK modeling since correlations were developed between the simulated solubility of drug in the lumen and $[\mathrm{AUC}]_0^\tau$ [14].

Although the FAT concept was formally introduced in [5], it has been proposed long time ago by Lovering et al. [15] in the context of the use of the ratio of the areas under the truncated C, t curves as measures of bioequivalence. It was found that for the ten drugs studied, the ratio of the truncated areas of test/reference was constant beyond a certain time point, τ, which obviously denotes the completion of the absorption for both test and the reference formulations. Besides, the FAT concept can be found in the work of Sugano [16, 17] since he has used models with drug absorption taking place for a certain period of time in conjunction with Eq. 2.

PBPK versus PBFTPK models

Since the PBFTPK models are "top-down", while the currently used Physiologically-Based Pharmacokinetics (PBPK) models are "bottom-up" models, their application to the same dataset will enhance our understanding of drug absorption phenomena. The first such application using six Merck drugs [14] revealed correlations between the simulated luminal drug concentrations from the PBPK model with the absorption rate estimates derived from the PBFTPK models using the same datasets. This finding is fundamental and in accord with the basic biopharmaceutical-physiological principles of PBFTPK models [5]. In addition, both models resulted in absorption time estimates within the small intestinal transit time, with PBFTPK models generally providing shorter time estimates. This should be attributed to the Gastro Plus software used for

the estimation of drug absorbed over time curve; accordingly, Gastro Plus utilizes simulation of absorption with differential equations based on indefinite integral and not finite integral with a time limit (FAT). It should be noted here that this "first-order approach" contradicts with the quantification of uptake rate in PBPK models on the basis of permeability estimates. We hope these observations will open further investigation for the predicted %absorbed versus time curves derived from the various software. In the same vein, combinatory applications of PBPK/PBFTPK modes for studies involving modified release formulations are anticipated. The PBFTPK models can provide estimates for the "prolonged" duration of drug absorption as well as drug's input rate(s), i.e., the two principal components of drug absorption from modified release formulations. Other potential applications of PBFTPK models can be envisaged in interspecies or paediatric pharmacokinetic scaling studies, which focus on bioavailability.

We are now working on a modified PBPK type software to be used for the development of drugs/generics in conjunction with the PBFTPK models. For the modified PBPK type software, the finite time concept will be embedded in the dissolution process utilizing modified versions of Noyes–Whitney equation and the Weibull function [18]. The dissolution (bioequivalence) safe space will be centered around the relative magnitude of finite time of drug dissolution and the FAT value. The development of adjusted algorithms to describe more physiologically sound absorption processes can support biopharmaceutical drug development, and complement existing PBPK models.

Pharmacometrics

Since the early days of NONMEM (Non Linear Mixed Effect Modelling) software [19–21], population approaches have been applied extensively in numerous oral, pulmonary and intranasal PK, PD, PK-PD studies, all of which involve absorption step(s). These studies have interpreted drugs' kinetics-dynamics as well as the variability associated with the parameters on the basis what we call "a valid population model". However, this vast literature relies on structural models, which are invariably mostly using either one- or two-compartment disposition model "*with a first-order absorption rate constant,* k_a*"* governing the absorption process. In fact, Fig. 2 provides a global view of the plot of citations for "the absorption rate constant" as a function of time in PUBMED from the beginning of its use circa 1964 and covers both the pre-NONMEM and the meta-NONMEM era. The increase after 2005 is most likely associated with the explosion of pharmacometric studies and the development of PBPK, pharmacometric software packages close to the turn of the century. It is widely understood that these commonly utilized models of drug absorption in population pharmacokinetics, with and without lag time or with transit compartments [22], often estimate large variabilities associated with k_a, which are unrealistic. In this context, it is not uncommon to see "impossible" k_a estimates submitted to and accepted by Drug Agencies since physically/physiologically sound alternatives do not exist.

During the ensuing years there were attempts to discontinue the perpetuation of the fallacious first-order drug absorption use. The first theoretically justified questioning of the validity of k_a as a single parameter describing oral drug absorption was based on fractal kinetic principles [23, 24]. Since drug dissolution, transit and uptake in the gastrointestinal tract take place at interfaces of different phases under variable stirring conditions, a time dependent coefficient, k, and not a rate constant was suggested as a better descriptor of the absorption kinetics

$$k = k_1 t^{-h} \tag{3}$$

where h is the different than zero fractal exponent of time t and k_1 is a constant expressed in $(time)^{h-1}$ units. Although this approach found extensive applications for the description of dissolution and release kinetics under in vitro conditions [25], it was not adopted in pharmacokinetics.

However, one can also see pharmacometricians replacing the models with first-order rate constant assuming complex absorption kinetics [26]. Common examples are mixed first-order and zero-order absorptions, either sequentially or simultaneously, and fast and slow parallel first-order absorptions, e.g., [27, 28]. Although these models provide better fits in comparison with their single first-order absorption counterparts, the physical/physiological meaning of the first-order parameters do not comply with the passive or active drug transport operating for time τ in accord with the FAT concept [5, 7, 9, 13]. Thanks to an insightful comment of an anonymous reviewer we analyzed, using PBFTPK models, nine sets of PK data from a mavoglurant population study whose complex absorption processes have been modeled with a sum of two or three inverse Gaussian functions [29]. PBFTPK models with one, two, three, or four constant successive input rates and two compartment model disposition were used as described in [9]. Figure 3 presents the successful fitting results of PBFTPK models to four out of nine sets of data in three subjects.

Figure 3 shows that mavoglurant absorption from the immediate release formulation exhibits one, three and four absorption phases for subjects S16, S18 and S38 respectively. The absorption of mavoglurant from the modified release formulation administered to the fasted subject S16 has one single phase of absorption, i.e., it is quite similar to

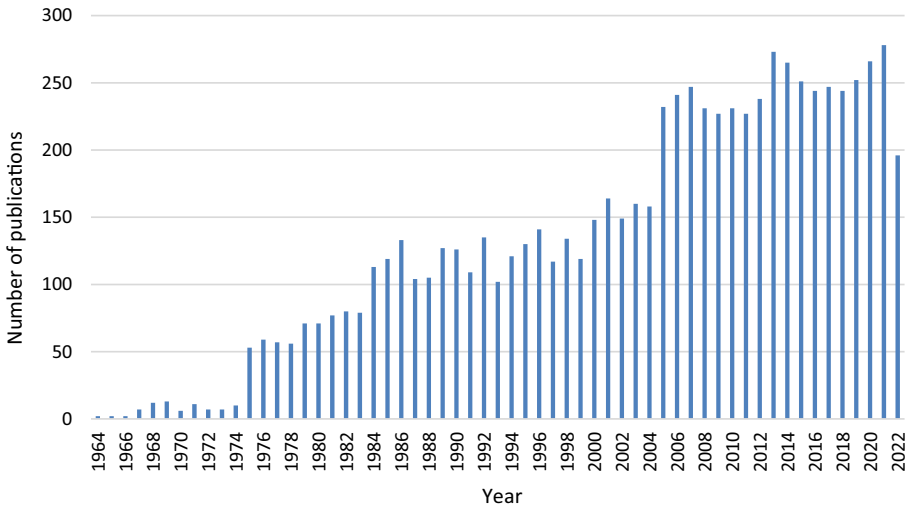

Fig. 2 Number of citations for "the absorption rate constant" per year in PUBMED (accessed 9/9/2022)

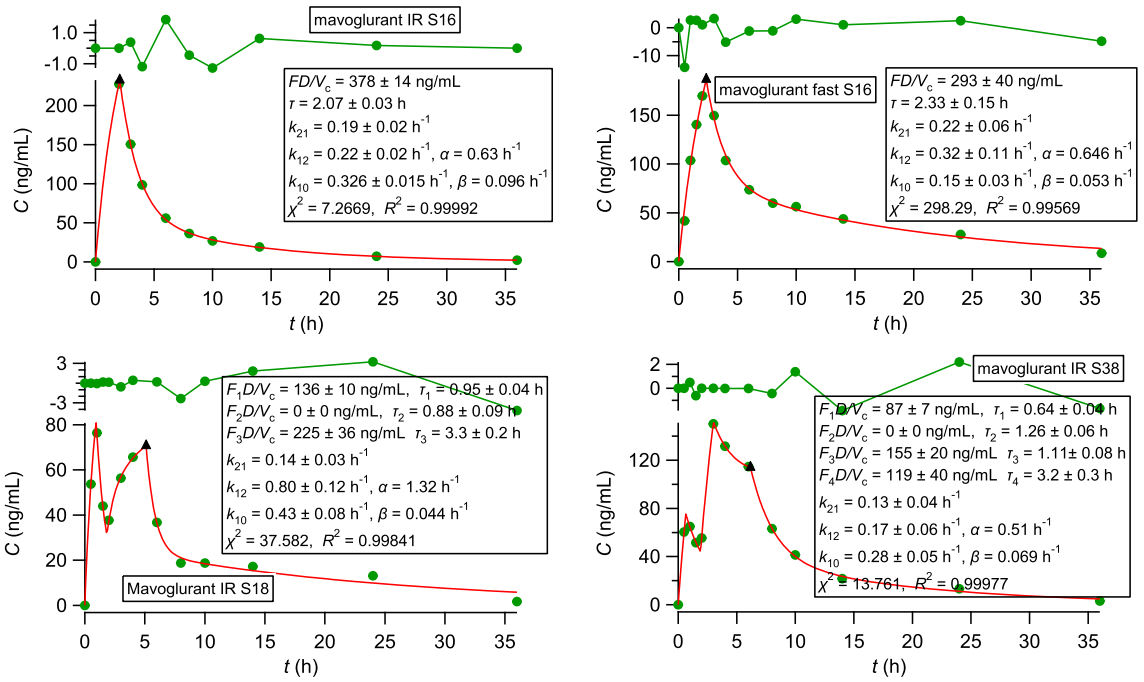

Fig. 3 Fitting results of a PBFTPK model with one (top panels) or three (bottom left panel) or four (bottom right panel) constant input rates of a specific time total duration, τ and two compartment model disposition to four sets of mavoglurant data [29]. Parameter estimates for τ, the concentration factor FD/V_c [9] and the compartmental constants are shown in each inset. Upper left and bottom panels: Immediate release (IR) formulation administered to subjects S16, S18 and S38 [29]. Top right panel: oral administration of modified release formulation to fasted subject S16. The solid triangles denote the end of the absorption process. The upper portion of each graph shows the fit residuals

the absorption profile with the immediate release formulation in the same subject. Based on the total time of drug duration quoted in Fig. 3, mavoglurant absorption from the immediate release formulation terminates at the upper part of the small intestine (τ = 2.07 h) for subject S16, close to the ileocecal valve that separates the small intestine from the large intestine (τ = 5.13 h) for subject S18 and the beginning of the ascending colon for subject S38 (τ = 6.21 h). For fitting purposes and in order to avoid negative values for the input rate, the mavoglurant input rate was set equal to zero during the declining portion of the absorption phase, Fig. 3. The unsuccessful fittings of the PBFTPK models to the rest of five sets of data, which provide unreliable parameter estimates are presented in the supplementary material. It can been seen again that mavoglurant is absorbed in successive input stages; however, the large variability of data coupled with the small number of data points compared to the large number of

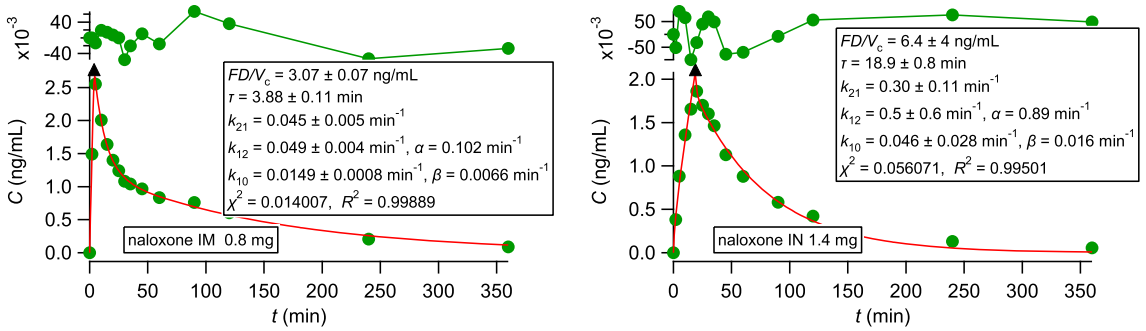

Fig. 4 Fitting results of a PBFTPK model with a constant input rate of a specific time duration, τ and two compartment model disposition to two sets of naloxone data [31]. Parameter estimates for τ, the concentration factor FD/V_c and the compartmental constants are shown in each inset. Left panel: intramuscular administration of 0.8 mg naloxone. Right panel: intranasal administration of 1.4 mg naloxone. The solid triangles denote the end of the absorption process. The upper portion of each graph shows the fit residuals

estimated parameters result in large uncertainties for the parameter estimates. Absolute bioavailability parameters were also derived for all data sets analyzed by integrating the best fit function of the PBFTPK models in each case. Initially, the classical bi-exponential equation $C(t) = Aexp(-\alpha t) + Bexp(-\beta t)$ was fitted to a number of digitized intravenous mavoglurant data points of 50 mg reported in the top panel of Fig. 3 in Ref [29]. From the estimated parameters, the area under the intravenous curve was found to be equal to 1902 ng h/mL using the classical equation $[\mathrm{AUC}]_0^\infty = \frac{A}{\alpha} + \frac{B}{\beta}$. This value was coupled with each one of the numerically integrated PBFTPK functions of the nine sets of data (Fig. 3 and supplementary material) for the estimation of $[\mathrm{AUC}]_0^\infty$ of the orally administered formulations. Upon dose correction, the following absolute bioavailability parameters were derived for the immediate release (IR) and modified release (MR) formulations: 0.296 (IR S16), 0.431 (MR-fasted S16), 0.502 (MR-fed S16), 0.184 (IR S18), 0.384 (MR-fasted S18), 0.576 (MR-fed S18), 0.323 (IR S38), 0.460 (MR-fasted S38), 0.665 (MR-fed S38). These estimates were found to be very similar (less than 9% difference) from those derived from empirical calculations based on the data points using the trapezoidal rule; an example is presented in the supplementary material for the immediate release formulation administered to subject S38 (Fig. S2). A direct comparison of these estimates with the corresponding estimates reported in Table IV of Ref. 29 cannot be made since the latter are derived from a population analysis using two or three inverse Gaussian functions, two compartment disposition and represent "average behavior". However, the most extensive absorption of mavoglurant from the MR formulation under fed conditions [29] is confirmed since the mean estimate from the three subjects is 0.582 compared to the mean estimates 0.268 for the IR formulation and 0.425 for the MR formulation under fasted conditions.

Apart from the application of the FAT concept to oral [5, 7, 9–13] and pulmonary [7] studies, this concept can be also applied to other routes of drug administration. For obvious anatomical and physiological reasons, intranasal administration should last for a certain period of time. Similarly, intramuscular injection in the deltoid muscle should result in rapid absorption in accord with the FAT concept due to the rich vasculature of the deltoid muscle [30]. We tested these hypotheses for the intranasal and intramuscular administration of naloxone used as an antidote in opioid intoxication [31]. We present fitting results of the PBFTPK models to two sets of PK data [31] using the PBFTPK software [9], Fig. 4. Both sets show the termination of naloxone absorption, at 18.9 ± 0.8 min for the intranasal administration of 1.4 mg naloxone and at 3.88 ± 0.11 min for the intramuscular administration of 0.8 mg naloxone. This permits an easy comparison of the two routes of administration in terms of the rate of naloxone absorption. Accordingly, population PK studies using PBFTPK as structural models can be also developed for intranasal and intramuscular administration to deltoid muscle.

The development of the FAT concept has led to a paradigm shift in oral pharmacokinetics [10, 13]. It is hoped that the application of FAT in PBPK modeling and pharmacometrics will place an end to the perpetuation of infinite oral drug absorption fallacy. Overall, the envisioned new technology based on PBFTPK models would ultimately lead to better population approaches in dosage regimen design adjustment in various therapeutic areas and speed up the development of generic medicines.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1007/s10928-022-09832-w.

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