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Review

Columbus' egg: Oral drugs are absorbed in finite time

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ABSTRACT

The infinite time of oral drug absorption was conceived from the first day of the birth of pharmacokinetics when H. Dost introduced the term pharmacokinetics in his book published in 1953. He adopted the function developed by H. Bateman back in 1908 for the decay of the nuclei isotopes to describe oral drug absorption as a first-order process. We unveiled this false hypothesis relying on common wisdom i.e. drugs are absorbed in finite time. This false assumption had dramatic effects on the evolution of oral pharmacokinetics but most importantly on the bioavailability and bioequivalence concepts and metrics. This work focuses on the finite absorption time (FAT) concept, the relevant Physiologically Based Finite Time (PBFTPK) models developed and their applications in oral pharmacokinetics, bioavailability and bioequivalence. The crux of the matter is that drug absorption from the gastrointestinal tract takes place under sink conditions because of the high blood flow rate in the vena cava. The termination of oral, pulmonary and intranasal drug absorption at a specific time point, calls for regulatory changes in bioavailability and bioequivalence studies in terms of the study design and metrics used for the bioequivalence assessment.

1. Introduction

Although the view that "drugs are absorbed in finite time" relies on common and scientific wisdom, pharmacokinetics since its inception (Dost, 1953) has been built on the opposite concept, namely, that oral drug absorption follows an infinite time pattern. In fact, this is like a dogma in contemporary pharmacokinetics and software. Besides, FDA founded the relevant fields of bioavailability and bioequivalence in January 7, 1977 relying on the concept of infinite absorption time. In this vein, the current FDA (FDA, 2017) and EMA (EMA, 2010) guidelines utilize the gold standard metric for the extent of absorption, namely, the area under the blood drug concentration, C time, t curve extrapolated to infinite time $[AUC]_0^\infty$, as a logical consequence of this dogma. This parameter implies infinite time for absorption, which never happens in the real world.

2. Drugs are absorbed in finite time: The Finite Absorption Time (FAT) concept

Recently, the finite absorption time (FAT) concept was developed (Macheras, 2019; Macheras and Chryssafidis, 2020; Chryssafidis et al., 2020; Tsekouras and Macheras, 2021; Chryssafidis et al., 2022) and the relevant physiologically based finite time (PBFTPK) models were successfully fitted to experimental data; reliable estimates for FAT and the other model parameters were derived (Chryssafidis et al., 2022). The FAT concept causes a paradigm shift in oral drug absorption. This is shown diagrammatically in a schematic for the underlying processes in the gastrointestinal (GI) membrane/vena cava (V.C.) region which are supportive of the FAT concept (Fig. 1a). Furthermore, panels b, c and d of Fig. 1 show the resulting variations of drug concentration in the blood.

We consider Fig. 1a as a "Columbus egg" since the underlying microscopic processes were not known at the beginning of pharmacokinetics (Dost, 1953), but they have been very well known for several decades now. However, it was only recently realized that the high blood flow (20−40 cm/s) in vena cava ensures sink conditions for the drug transfer (Chryssafidis et al., 2022; Iranpour et al., 2016). In fact, this blood flow rate is five orders of magnitude higher than the usual drug effective permeability estimates $\sim 10^{-4}$cm/sec. Hence, the rate of presentation of drug to the liver is the product of this blood flow and the drug's concentration in blood which changes linearly in accord with its permeability expressed in velocity units (cm/s), Fig. 1a. Plausibly, this

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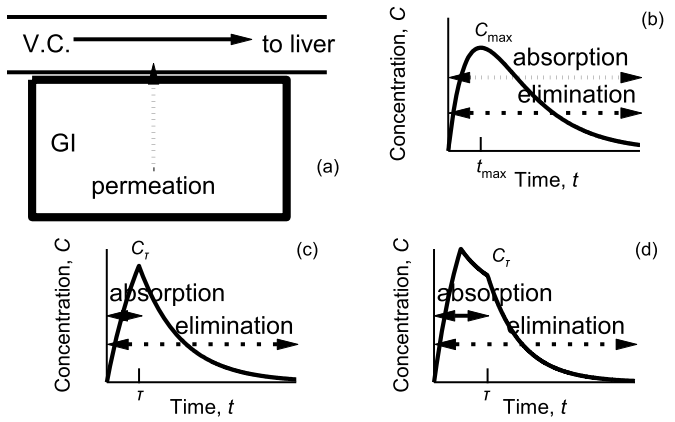

Fig. 1. A paradigm shift in oral drug absorption. (a) The passive transport of drug molecules (vertical arrow) from the GI tract to blood in vena cava (V.C.) always takes place under sink conditions, since the blood flow rate is very high, 20-40 cm/s (Inapour et al. 2016) (horizontal arrow), resulting in constant drug input rate to the liver. (b) According to the established view, drug absorption and elimination operate concurrently from zero time to infinity (Dost, 1953). (c, d) According to the FAT concept (Macheras and Chryssafidis, 2020; Chryssafidis et al., 2020; Tsekouras and Macheras, 2021; Chryssafidis et al., 2022), drug absorption and elimination operate concurrently from zero to τ, while only elimination continues to operate until infinity. Two different profiles can be observed with (c) $t_{max} = \tau$ and (d) $t_{max} < \tau$. Such behavior has been observed in a number of drugs (Chryssafidis et al., 2022) including paracetamol, cyclosporine and in axitinib (Alimpertis et al., 2022) formulations, respectively.

constant drug input entry to the liver terminates, when either the drug has been completely absorbed prior to its passage from the absorptive sites in the intestines or the dissolved and undissolved drug species pass beyond the absorptive sites; the latter, in the great majority of cases, are located in the small intestines. Accordingly, beyond time τ only drug elimination is operating, Fig. 1c and d.

It should be noted that permeability estimates have been measured for a large number of drugs since permeability is one of the two properties (together with solubility) used for biopharmaceutical classification purposes in the relevant FDA (FDA, 2017) and EMA (EMA, 2010) guidelines. For example, due to its permeability metoprolol is widely reported in the literature as a high permeability model compound and used as such by FDA.

All the work published so far on the FAT concept and PBFTPK models has focused on passively absorbed drugs. Prompted by an insightful comment of a reviewer, we consider briefly the application of the FAT concept to drugs following carrier-mediated transport assuming one compartment model disposition, first-order elimination kinetics and a single input rate following Michaelis–Menten saturation kinetics operating for time τ. In such a case, it is not possible to arrive at an analytic expression for the drug concentration in the blood as a function of time, but the situation can be remedied with a numerical approach whose main disadvantage is that it is not as elegant, but equally valid. As expected the general form of the resulting curve has the familiar form of a rising and a falling part, with the details depending on the duration of input stage and the values of the model parameters, namely, the maximum transport velocity, the Michaelis constant for the drug transport, and the elimination rate constant.

3. Bioavailability/bioequivalence implications

The results of the recent study (Chryssafidis et al., 2022) provide conclusive evidence that in all experimental sets examined, drug absorption from the gastrointestinal tract takes place in finite time, τ. Accordingly, the corresponding area $(AUC)_{0\text{-}\tau}$ and not $(AUC)_{0\text{-}\infty}$ is the appropriate metric for a drug's extent of absorption. This has been theoretically explained on the basis of FAT concept (Chryssafidis et al., 2021) and it was verified (Tsekouras and Macheras, 2021) using digoxin data from a bioavailability study carried out in 1973 (Sanches, 1973) and a bioequivalence study analyzed by FDA (Center for Drug Evaluation and Research, 2002). The termination of digoxin absorption in the former study was estimated to be at 1 and 3 h under fasting and fed conditions, respectively (Tsekouras and Macheras, 2021). Using the pertinent AUC ratios, i.e., $\frac{[(AUC)_{0-1}\,fasted]}{[(AUC)_{0-3}\,fed]}$ we found the same result (equal bioavailability) with the results derived from the cumulative five day urinary excretion of digoxin. Similarly, the duration of drug absorption in the 1992 bioequivalence study under fasting and fed conditions was found to be 1 and 1.5 h, respectively; the corresponding ratios $\frac{[(AUC)_{0-1}\,fasted,test]}{[(AUC)_{0-1}\,fasted,reference]}$, $\frac{[(AUC)_{0-1.5}\,fed,test]}{[(AUC)_{0-1.5}\,fed,reference]}$ were quite similar with the classical comparison of AUCs calculated up to the very end of the sampling scheme (144 h) and infinity, namely, $(AUC)_{0\text{–}144}$ and $(AUC)_{0\text{-}\infty}$, reported in the FDA document.

The take home message from these findings is that $(AUC)_{0\text{-}\tau}$ can replace $(AUC)_{0\text{-}\infty}$ in bioequivalence studies, as a more proper indicator of the extent of absorption, while $(AUC)_{0\text{-}\infty}$ can be maintained as an exposure metric. Several aspects of the current FDA (FDA, 2017) and EMA (EMA, 2010) guidelines concerning the sampling period of the study for a reliable estimation of $(AUC)_{0\text{-}\infty}$ are not in accord with the FAT concept; e.g., the sampling schedule required to be long enough to achieve $(AUC)_{0\text{-}t}$ covers at least 80% of $(AUC)_{0\text{-}\infty}$. Moreover, the recommended time limit of 72 h for the truncated AUC, namely, $(AUC)_{0\text{-}72}$ to be used as an alternative to $(AUC)_{0\text{-}t}$, is much longer than the physiological FAT limit of ~30 h (Macheras and Chryssafidis, 2021; Abuhelwa et al., 2016) for immediate release formulations.

A long time ago an experimental study (Lovering et al., 1975) and more recent simulation studies (Sugano, 2021; Sugano, 2012; Endrenyi and Tothfalusi, 1997) focused on the use of truncated concentration-time curves for bioequivalence assessment; albeit the first-order character of gastrointestinal absorption was maintained, in all cases (Lovering et al., 1975; Sugano, 2021; Sugano, 2012; Endrenyi and Tothfalusi, 1997), the experimental and simulation results validated the use of the truncated areas for bioequivalence assessment. In the same vein, our work (Macheras and Chryssafidis, 2020; Chryssafidis et al., 2020; Tsekouras and Macheras, 2021; Chryssafidis et al., 2022) not only provides conclusive evidence that truncated concentration-time curves can be used reliably for bioequivalence assessment, but also the ideal metric is $(AUC)_{0\text{-}\tau}$ since time τ denotes the termination of drug's absorption, Fig. 1c and d.

Concern is also arising for C_{max} (Fig. 1b) which is currently used as an absorption rate metric. Under the FAT concept (Chryssafidis et al., 2021; Tsekouras and Macheras, 2021; Chryssafidis et al., 2022), C_τ (Fig. 1c and d) simply corresponds to blood drug concentration at the termination of the drug absorption process at time τ. In this vein, the numerical value of the observed maximum blood drug concentration equal to or greater than C_τ (Chryssafidis et al., 2022) should be used as such; thus, the magnitude of its difference between reference and test formulations in bioequivalence studies should be specified on pharmacological-pharmacodynamic basis for each one of the drugs examined. For example, critical dose drugs with narrow therapeutic index, e.g., cyclosporine, can have a smaller absolute difference and/or an upper/lower boundary for the test and reference formulations.

4. Epilogue

We envisage applications of the FAT concept and the relevant PBFTPK models in pulmonary and intranasal pharmacokinetic, pharmacokinetic-pharmacodynamic (PK-PD) studies, which involve drug absorption step(s). In the same vein, PBFTPK models can be applied in oral pulmonary and intranasal population PK-PD studies. In parallel, the obvious complementarity of PBPK (Sjögren et al., 2013; Sager et al., 2015; Charalabidis et al., 2019) and PBFTPK models will enhance the analytical power of modeling and simulation studies in oral drug

absorption. Moreover, methodologies for the estimation of absolute bioavailability from oral data exclusively (Chryssafidis et al., 2021) (a fact, which is unthinkable today) can be expanded to two compartment model drugs; this can lead to the abolishment of the invasive, laborious and expensive microdosing studies (van Andel et al., 2018; Zajic et al., 2016) at the early phases of drug development.

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Declaration of Competing Interest

None.

Data availability

Data will be made available on request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ejps.2022.106265.

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