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Drugs are Absorbed in Finite Time: A New Era in Biopharmaceutics and Pharmacokinetics

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1. Introduction

From the early days of Pharmacokinetics (1) drug absorption was modeled as a first-order process implying an infinite time for drug absorption. According to the current scientific knowledge and common wisdom, drugs are absorbed passively in finite time.

The concept of "finite time" of absorption has been used in various Physiologically Based Pharmacokinetic (PBPK) models. However, the formal development of Physiologically Based Finite Time Pharmacokinetic (PBFTPK) models was published recently (2-5). The PBFTPK models were built on two principles: i) drugs are absorbed passively for a finite period of time, τ and ii) time absorption constrains linked with the gastrointestinal transit times of drug in the stomach, the small intestines and the colon were applied (2-5). Zero- or first-order input is used for the $(PBFTPK)_0$ and $(PBFTPK)_1$ models, respectively.

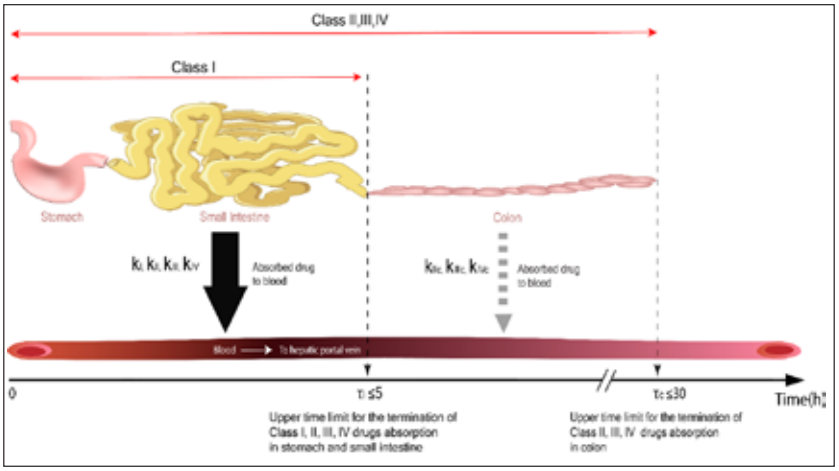

Figure 1 *A schematic of the biopharmaceutical/physiological drug absorption model, which relies on the transit times of the drug along the gastrointestinal tract (3). For Class I drugs, the completion of absorption (F > 0.90) ceases in a shorter time than the duration of the stomach and small intestine transit 4.86 h (7). For Class II,III and IV drugs, the limited overall absorption (F < 0.90) can be continued beyond the ileocecal valve and lasts not more than the whole gut transit time e.g. 29.81 h (7). The thick black arrow denotes the major site of drug absorption, namely, the small intestine. The dashed arrow indicates the potentially limited drug absorption from the colon.*

2. Materials and methods

The $(PBFTPK)_0$ models were developed by coupling the drug properties solubility and permeability of the Biopharmaceutic Classification System (BCS) with the kinetics of drug uptake under sink conditions. The $(PBFTPK)_1$ models rely on first-order drug absorption which is terminated at time τ (6) when the drug either passes beyond the absorptive sites or no more soluble drug is available for absorption. Figure 1 shows the minimal physiological model used for the development of PBFTPK mathematical models (3).

3. Results

Various simulation scenarios were used to generate concentration (C_b) time data for Class I, II, III and IV drugs using $(PBFTPK)_0$ (3) and $(PBFTPK)_1$ (4) models The simulated data of the $(PBFTPK)_0$ models with multiple constant inputs exhibit rich dynamics encountered in complex drug absorption phenomena (4). Both $(PBFTPK)_1$ and $(PBFTPK)_0$ models result either in $C_{max} = C_b(\tau)$ or $C_{max} > C_b(\tau)$ for rapidly- and not rapidly-

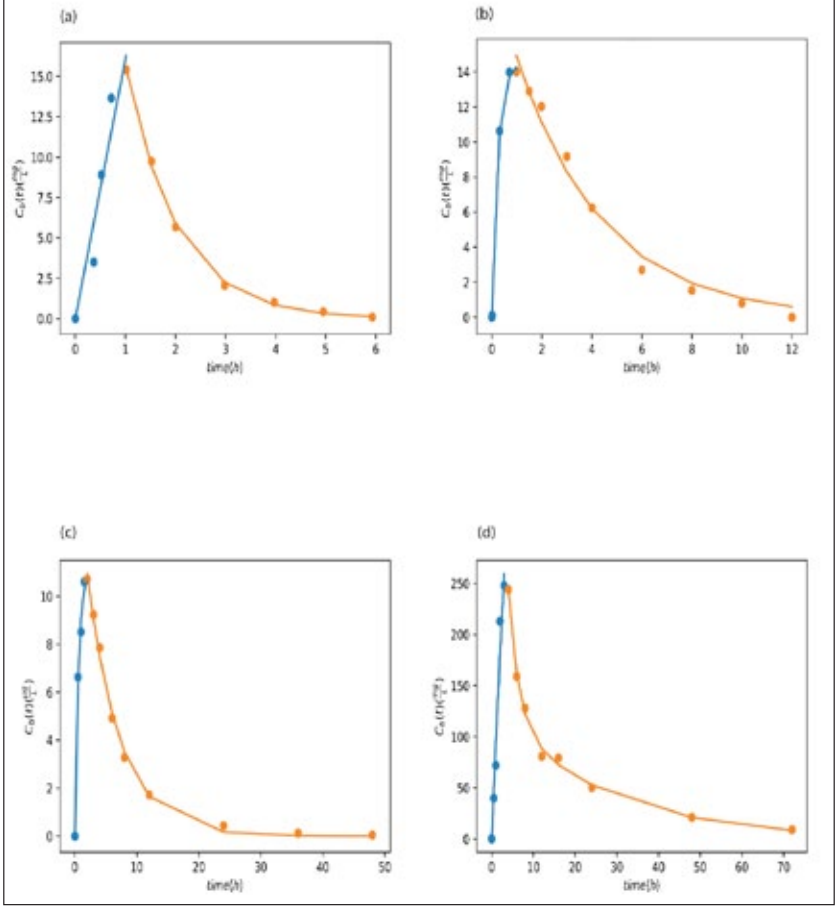

Figure 2 *Curve fitting of the $(PBFTPK)_0$ models to experimental data points (3). Key: (a) Cephradine. Dose = 500 mg, R^2 = 0.9723. (b) Ibuprofen, Dose = 200 mg, R^2 = 0.9961(c) Flurbiprofen, Dose = 100 mg, R^2 = 0.9908. (d) Itraconazole, Dose = 200 mg, R^2 = 0.9797. The blue lines correspond to drug absorption and the orange lines represent the drug's elimination phase.*

absorbed drugs, respectively; in the latter case, $C_b(\tau)$ and τ are meaningful parameters for drug's rate of exposure.

Fitting results (3) to experimental data using the model equations of $(PBFTPK)_0$ models are shown in Figure 2. A methodology for the estimation of absolute bioavailability, F, from oral data exclusively was developed (4). An estimate for F close to unity, based on theophylline bioequivalence data, was also derived from an areas proportionality (4)

4. Conclusions

The realization that the gastrointestinal absorption takes place in finite time and the development of $(PBFTPK)_0$ and $(PBFTPK)_1$ models open a new era in the scientific and regulatory aspects of biopharmaceutical sciences. Several areas of research such as *in vitro in vivo* correlations, interspecies pharmacokinetic scaling will be affected beyond the fundamental bioavailability and bioequivalence topics. Most importantly, the estimation of absolute bioavailability from oral data exclusively can lead to regulatory implications.

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