SEMINAR

PHYSIOLOGICALLY BASED FINITE TIME PHARMACOKINETIC (PBFTPK) MODELS EN ROUTE TO PBPK AND PHARMACOMETRICS: EMPHASIS ON DRUG ABSORPTION

27th June 2023, 9:00 am (A Coruna time)

Hotel Zenit Coruña
Comandante Fontanes 19, 15003, A Coruña (Galicia) +34 981 21 84 84

The Laboratory of Biopharmaceutics-Pharmacokinetics, Department of Pharmacy, National and Kapodistrian University of Athens, organizes a one day seminar on Tuesday, June 27, 2023 covering modelling approaches in oral drug absorption. Special emphasis is given to the novel concept of Finite Absorption Time (F.A.T.) and the relevant Physiologically Based Finite Time Pharmacokinetic (PBFTPK) models developed recently. The published papers along with the published book are quoted at the end of the Summary (1-10).

Summary

This one-day seminar is intended for academics, students or scientists working in academia, pharmaceutical industries, regulatory agencies, and contract research organizations.

The seminar will begin with a talk on in vivo predictive dissolution methods for the in vivo performance of oral dosage forms. Experimental models that incorporate relevant physiological variables and mathematical models describing the link between in vitro data and the in vivo processes (liberation and absorption) are used. Several examples of this approach will be presented showing the in vitro - in vivo correlations (IVIVC) with physiologically-based in vitro dissolution devices and in vivo plasma concentrations of the drug.
The second talk focuses on the modelling and simulation strategies for biopharmaceutics applications. The understanding of gastro-intestinal absorption related processes is crucial to ensure the successful development of complex oral formulations. In the recent years, modelling approaches have been gradually influencing decision making ability during pharmaceutical development. In this session we will revise several modelling and simulation approaches with specific case examples to demonstrate its utility during formulation development.
The third talk firstly reveals the unphysical assumption, introduced in 1953, of infinite time of drug absorption which breaks oral pharmacokinetics. Then, a minimal model of gastrointestinal drug absorption based on the Finite Absorption Time (F.A.T.) concept is described. The assumptions of the model are as follows: i) drugs are absorbed passively under sink conditions ii) physiological time limits were applied for drug

absorption in the small intestines or colon and iii) the limiting property is solubility and/or permeability in accordance with drug's BCS classification.
The fourth talk will focus on the development of **P**hysiologically **B**ased **F**inite **T**ime **P**harmaco**K**inetic (PBFTPK) models. Several case studies for data set analyses using the PBFTPK models will be presented. Data will represent the time evolution of drug concentration in the blood stream after oral administration of formulations. A step-by-step approach for each case will guide researchers in choosing the most appropriate model and determining the optimum and realistic parameters. Physiological constraints will be considered in guiding the selection of model parameters.

The fifth talk discusses the PBPK models under the prism of the Finite Absorption Time (F.A.T.) concept. PBPK and PBFTPK models rely on the same principles: i) finite absorption time for drug absorption processes and ii) zero-order drug input (single or multiple) rate as a result of the passive drug absorption under sink conditions. This resemblance in the fundamental characteristics (transit and rate of drug input) calls for a comparative analysis of the simulated drug absorption profile derived from the PBPK models with the analysis of the *in vivo* data based on PBFTPK models; this provides a better understanding of the kinetics of drug absorption.

The first part of the sixth talk explores the application of the parameters of the physiologically based finite time pharmacokinetic (PBFTPK) models to bioavailability and bioequivalence; a methodology for the estimation of absolute bioavailability from oral data exclusively is presented. The second part of this talk deals with the analysis of complex absorption of oxybutynin and mavoglurant PK and pharmacometric data using PBFTPK models. PBPK oxybutynin data and mavoglurant pharmacometric data are analyzed nicely using the PBFTPK models.

The seventh talk describes the complex absorption of amiloride after intranasal administration. Two absorption phases are observed. The first is associated with the intranasal absorption of amiloride and follows the finite absorption time concept. The second phase is attributed to gastrointestinal absorption of amiloride and is described with fractal kinetics principles.

The eight talk has three portions. The first is concerned with the analysis of intranasal and intramuscular naloxone data using PBFTPK models. This is followed by a short demonstration of PBFTPK Software, while attendees can bring their *C,t* PK data for analysis.

REFERENCES

1. P Macheras. On an unphysical hypothesis of Bateman equation and its implications for pharmacokinetics. *Pharmaceutical Research.* (2019) 36:94 https://doi.org/10.1007/s11095-019-2633-4

2. P. Macheras, P. Chryssafidis. Revising Pharmacokinetics of Oral Drug Absorption: I Models Based on Biopharmaceutical/Physiological and Finite Absorption Time Concepts. *Pharm Res* **37,** 187 (2020).

https://doi.org/10.1007/s11095-020-02894-w (cover page of the issue). Erratum/ *Pharm Res* **37,** 206 (2020). https://doi.org/10.1007/s11095-020-02935-4

3. P. Chryssafidis, A. A. Tsekouras, P. Macheras. Revising Pharmacokinetics of Oral Drug Absorption: II Bioavailability-Bioequivalence Considerations, *Pharmaceutical Research* 38, 1345–1356 (2021) [DOI: 10.1007/s11095-021-03078-w]

4. A. A. Tsekouras, P. Macheras. Re-examining digoxin bioavailability after half a century: Time for changes in the bioavailability concepts. *Pharmaceutical Research* (2021) [DOI: 10.1007/s11095-021-03121-w]

5. P. Chryssafidis, A. A. Tsekouras, P. Macheras. Re-writing oral pharmacokinetics using physiologically based finite time pharmacokinetic (PBFTPK) models. *Pharmaceutical Research*. 2022;39:. https://doi.org/10.1007/s11095-022-03230-0.

6. N. Alimpertis, A. A. Tsekouras, P. Macheras. Revising the assessment of bioequivalence in the light of finite absorption time (FAT) concept: The axitinib case. 30th PAGE meeting Ljubljana 28 June-1 July , 2022

7. D. Wu, A. A. Tsekouras, P. Macheras, F. Kesisoglou. Physiologically based pharmacokinetic models under the prism of the finite absorption time concept. Pharmaceutical Research 1-11 (2022)

8. A. A. Tsekouras, P. Macheras. Columbus' egg: Oral drugs are absorbed in finite time. *European Journal of pharmaceutical sciences* https://doi.org/10.1016/j.ejps.2022.106265

9. Macheras P, Tsekouras AA. The Finite Absorption Time (FAT) concept en route to PBPK modeling and pharmacometrics. J Pharmacokinet Pharmacodyn. 2022 Nov 11. doi: 10.1007/s10928-022-09832-w. Epub ahead of print. PMID: 36369406.

10. P. Macheras, A. A. Tsekouras. Revising Oral Pharmacokinetics, Bioavailability and Bioequivalence Based on the Finite Absorption Time Concept, Springer, Berlin. (2023)

11. A. A. Tsekouras, P. Macheras. Re-examining naloxone pharmacokinetics after intranasal and intramuscular administration using the finite absorption time concept. *Submitted*

Programme: Tuesday, 27 June 2023

A CORUNA TIME	SPEAKER	**TOPIC**
8:55 am	Panos Macheras, Department of Pharmacy, National and Kapodistrian University of Athens. ATHENA Research Center, Athens, Greece	Welcome
9:00 am	Marival Bermejo, Isabel Gonzalez-Alvarez. Pharmacokinetic and Pharmaceutical Technology, Miguel Hernandez University, Alicante, Spain	Examples of modelling intestinal absorption from in vitro models to in vivo predictions
9:45 am	Valvanera Vozmediano Center for Pharmacometrics and Systems Pharmacology, Department of Pharmaceutics, University of Florida, USA	Modeling and simulation as a tool to understand and guide formulation development
10:30 am	Panos Macheras, Department of Pharmacy, University of Athens. ATHENA Research Center, Athens, Greece.	From the unphysical hypothesis of infinite absorption time to the development of Finite Absorption Time (F.A.T.) concept
11:15 am	Coffee break	
11:45 am	Nikolaos Alimpertis Department of Pharmacy, University of Athens, Athens, Greece	The rise of Physiologically Based Finite Time Pharmacokinetic (PBFTPK) models
12:30 pm (zoom call presentation)	Di Wu Pharmaceutical Sciences and Clinical Supply, Merck & Co., Inc., Rahway, NJ, USA	Physiologically based pharmacokinetic (PBPK) models under the prism of the Finite Absorption Time (F.A.T.) concept
1:15 pm	Panos Macheras, Department of Pharmacy, University of Athens. ATHENA Research Center, Athens, Greece.	Applications of PBFTPK models to: 1. Bioavailability& Bioequivalence 2. Analysis of complex absorption of oxybutynin and mavoglurant PK and Pharmacometric data
2:00 pm	Light lunch	
2:30 pm	Venkata Yellepeddi Division of Clinical Pharmacology, School of Medicine and Department of Molecular Pharmaceutics, College of	Analysis of complex amiloride intranasal absorption based on the Finite Absorption Time (F.A.T.) concept

	Pharmacy, University of Utah, Salt Lake City, Utah, USA	
3:00-5:00 pm	Nikolaos Alimpertis Department of Pharmacy, National and Kapodistrian University of Athens, Athens, Greece	1. Analysis of intranasal and intramuscular naloxone data using PBFTPK models 2. Short demonstration of PBFTPK Software 3. Attendees can bring their C,t PK data for analysis

Registration-Fees

- Industry, CROs: €300
- Academia-Government: €150
- Student : €100