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ORIGINAL PAPER

Panos Macheras: a pioneering scientist in pharmaceutical science

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Abstract
Professor Panos Macheras is a pioneering scientist in pharmacokinetics, pharmacodynamics and biopharmaceutics. His many important contributions to pharmaceutical science are reviewed.

Keywords Pharmacokinetics · Pharmacodynamics · Biopharmaceutics · Bioequivalence · Fractal kinetics

Professor Panos Macheras is a prominent, pioneering scientist in pharmacokinetics, pharmacodynamics and biopharmaceutics. It is therefore fitting that a special issue of the Journal of Pharmacokinetics and Pharmacodynamics is devoted to celebrate Professor Macheras' 75th birthday and to pay tribute to his many seminal scientific contributions. Panos Macheras is Professor Emeritus in the Department of Pharmacy of the National and Kapodistrian University of Athens. He is also Head of the PharmaInformatics Unit of the Research Center ATHENA in Athens, Greece, an affiliated member of the Biomedical Research Foundation of the Academy of Athens, and an Adjunct Professor in the Department of Pharmaceutical Sciences in the State University of New York in Buffalo, NY.

Dr. Macheras received a B.Pharm. (1970) and Ph.D. degree (1977) in Pharmaceutical Chemistry from the University of Athens, Greece and a Ph.D. degree (1981) in Biopharmaceutics-Pharmacokinetics from King's College, University of London, U.K. He has published more than 160 journal articles and six books in the field of Biopharmaceutics-Pharmacokinetics and supervised 16 graduate students. Dr. Macheras serves on the Editorial Board of the journals: Pharmaceutical Research; International Journal of Pharmaceutics; and European Journal of Pharmaceutical Sciences. He has served as a member of the Scientific Committee of the Greek National Organization for Medicines and was vice-president from 1997 to 1998 as well as on the International Affairs Committee and the Pediatric Initiative Committee for the American Association of Pharmaceutical Scientists. Dr. Macheras has an h-index of 27 with his papers cited an average of 21 times and a total of over 2900 citations of his work over the span of his career) as shown in Fig. 1.

Panos Macheras' scientific work and leadership have been acknowledged by several honors and awards. The Republic of Greece bestowed on him the title and award of Commander in the Order of Honor of the Hellenic Republic (2015). He received honorary doctorate degrees from the Semmelweis University in Budapest, Hungary (2015) and from the University of Bucharest. He is a Fellow of the American Association of Pharmaceutical Scientists (AAPS) and of the American Society for Medical and Biological Engineering. He is recipient of the AAPS Dale E. Wurster Award in Pharmaceutics (2014), the Pharmaceutical Sciences World Congress Research Achievement Award (2010), and of the Xanthopoulos-

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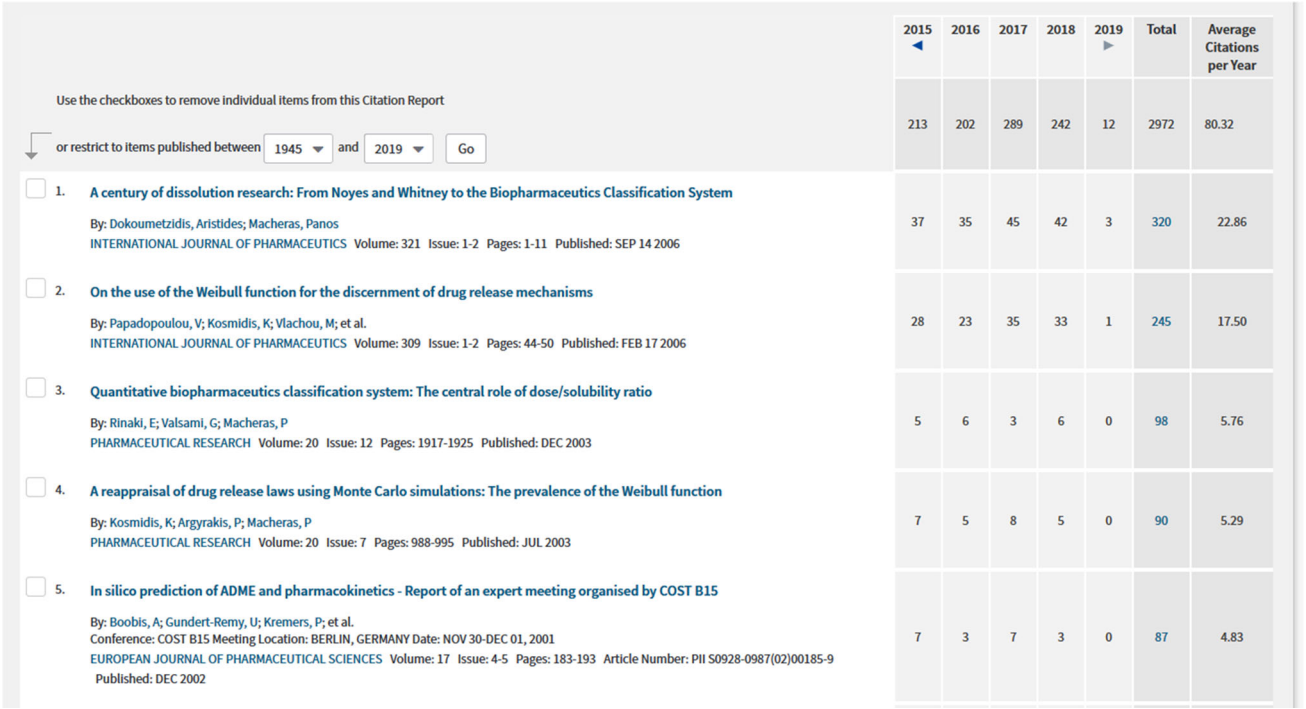

		2015 ◄	2016	2017	2018	2019 ►	Total	Average Citations per Year
Use the checkboxes to remove individual items from this Citation Report or restrict to items published between 1945 and 2019 Go		213	202	289	242	12	2972	80.32
1.	A century of dissolution research: From Noyes and Whitney to the Biopharmaceutics Classification System By: Dokoumetzidis, Aristides; Macheras, Panos INTERNATIONAL JOURNAL OF PHARMACEUTICS Volume: 321 Issue: 1-2 Pages: 1-11 Published: SEP 14 2006	37	35	45	42	3	320	22.86
2.	On the use of the Weibull function for the discernment of drug release mechanisms By: Papadopoulou, V; Kosmidis, K; Vlachou, M; et al. INTERNATIONAL JOURNAL OF PHARMACEUTICS Volume: 309 Issue: 1-2 Pages: 44-50 Published: FEB 17 2006	28	23	35	33	1	245	17.50
3.	Quantitative biopharmaceutics classification system: The central role of dose/solubility ratio By: Rinaki, E; Valsami, G; Macheras, P PHARMACEUTICAL RESEARCH Volume: 20 Issue: 12 Pages: 1917-1925 Published: DEC 2003	5	6	3	6	0	98	5.76
4.	A reappraisal of drug release laws using Monte Carlo simulations: The prevalence of the Weibull function By: Kosmidis, K; Argyrakis, P; Macheras, P PHARMACEUTICAL RESEARCH Volume: 20 Issue: 7 Pages: 988-995 Published: JUL 2003	7	5	8	5	0	90	5.29
5.	In silico prediction of ADME and pharmacokinetics - Report of an expert meeting organised by COST B15 By: Boobis, A; Gundert-Remy, U; Kremers, P; et al. Conference: COST B15 Meeting Location: BERLIN, GERMANY Date: NOV 30-DEC 01, 2001 EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES Volume: 17 Issue: 4-5 Pages: 183-193 Article Number: PII S0928-0987(02)00185-9 Published: DEC 2002	7	3	7	3	0	87	4.83

Fig. 1 Screen shot from Web of Science for top 5 cited papers accessed 1/31/2019 2:45 p.m.

Pneumatikos Award for outstanding academic teaching in Greece (2011).

Dr. Macheras' research has challenged the status quo, in particular the assumptions of homogeneity and acyclic linearity that pervade biopharmaceutics, pharmacokinetics and pharmacodynamics. The reliance of the field on assumptions of homogeneity has been useful in simplifying the representation of systems but has also hampered the ability to develop truly predictive constructs for assessing measurements and responses.

Dr. Macheras' scientific work has covered several areas of pharmacokinetics (PK) and biopharmaceutics with significant contributions to: modeling and simulation in drug dissolution and release; gastrointestinal absorption analysis-biopharmaceutics classification; gastrointestinal absorption analysis-biopharmaceutics classification; automated techniques for drug–cyclodextrin interactions, drug protein binding and dissolution studies; drug solubility, binding and dissolution studies in milk; freeze-dried drug–milk formulations, novel milk-based formulations; bioequivalence (BE) metrics and limits; and fractal, fractional and nonlinear dynamic aspects of drug disposition and response. His contributions to each of these areas is highlighted in the following sections.

Biopharmaceutics/pharmaceutics

Modeling and simulation in drug dissolution and release

Dr. Macheras used the concepts of heterogeneity in drug dissolution and release extended well mixed assumptions to improve on descriptions of these processes. This was accomplished using fractional kinetics and fractal concepts to determine the fractal reaction dimension in dissolution studies [1–3]. He discovered and provided an explanation for the ubiquitous presence of the Weibull function in dissolution studies using fractal kinetic concepts increasing our understanding of these processes. In parallel, he developed the population growth model of dissolution for heterogeneous media wherein the presuppositions of time continuity and Fick's law of diffusion are not applicable. This approach and his reaction-limited model of dissolution [4, 5] are the only that can mechanistically explain supersaturated dissolution data. In the field of drug release, he derived the equations of Case II drug transport with axial and radial release from cylinders. Also, he successfully used the power law for the entire release profile, an approach grounded in non-classical diffusion theory [6]. Fractional kinetics and Monte Carlo simulations were critical to his reassessment of the fundamental release laws. This work contributed to the verification of the conditions for the validity of the Higuchi law and demonstrating that

the Weibull function is the most powerful tool for the description of release kinetics in Euclidean and fractal spaces. These studies led him to the use of the Weibull function for the discernment of drug release mechanisms [7], resulting in one of the most cited articles in drug release today. In addition, his review on drug dissolution [8] is very highly cited (Fig. 2).

Gastrointestinal absorption analysis-biopharmaceutics classification

Dr. Macheras was the first to publish an explicit relationship between the fraction of dose absorbed and the physicochemical characteristics of drugs and he was the first to propose a classification scheme according to drugs' biopharmaceutical properties [9, 10]. Based on physical-physiological observations he has been able to analyze the heterogeneous character of drug dissolution, transit and uptake in the GI tract using fractal concepts. The results of this work in turn led him to the replacement of the "absorption rate constant" term with the "absorption rate coefficient" concept [11, 12]. This principle prompted him to develop the heterogeneous tube model for the study of small intestinal transit flow and intestinal drug absorption using probabilistic concepts. He also developed [13, 14] a quantitative version of the biopharmaceutics classification system (BCS) which places particular emphasis on dose/solubility ratio. Critically, he provided theoretical justification as well as practical examples for the existence of biowaivers among Class II drugs using NSAIDs as model drugs. His contributions included perspectives on the validity of the solubility and dissolution criteria of BCS FDA Guideline suggesting model independent parameters (mean times for dissolution and permeation) for biopharmaceutical classification purposes, recently elucidating the role of dose in the BCS and introducing the concepts of critical dose and effective in vivo solubility. Finally, he explained the physiological-dynamical reasons for the frequently observed (but not published) failure of the IVIVC and presented the theoretical basis for the development and the application of the power law IVIVC [15]. An invited critical review on the science and the regulation of oral drug absorption commemorating Professor Benet's contributions to science includes most of his work in GI absorption and bioequivalence [16].

Automated techniques for drug–cyclodextrin interactions, drug protein binding and dissolution studies

In this area, Dr. Macheras developed automated techniques using ion selective electrodes for the study of the complexation of drugs with cyclodextrins and the binding of drugs to plasma proteins. He also used flow injection analysis for the study of drug dissolution in complex media. This work has the potential to contribute significantly to the determination of the freely available drug improve interpretation of the active fraction of drug able to exert a pharmacodynamic effect.

Drug solubility, binding and dissolution studies in milk

In a highly cited article [17], Macheras revealed the unusual solubility behavior of cyclosporine (solubility decreases with increasing temperature). He also demonstrated that the increased bioavailability of cyclosporine in the presence of TPGS in cholestatic patients is associated with the solubilization effect of TPGS. The other papers listed above relate to his work on the understanding of drug–food interactions in the GI tract using milk as a model medium. The dissolution studies of immediate and controlled release formulations in milk are considered as the outset of dissolution studies in biorelevant media developed in the late '90s.

Freeze-dried drug–milk formulations, novel milk-based formulations

His original work on freeze-dried drug–milk formulations coupled with his extensive work on drug binding and solubility in milk lead Macheras to the development of novel milk-based formulations. This approach has been patented while its potential application to pediatric formulations has been recently proposed by the pediatric task force of AAPS.

Fig. 2 Screen shot from web of science (accessed 1/31/2019, 2:37 p.m.) showing citations for Ref. [8]

Pharmacokinetics

Bioequivalence (BE) metrics and limits

Dr. Macheras was one of the few who published on the problem of absorption rate metrics in BE studies. He calculated the most appropriate cut-off time point for the partial area method and improved the intercept method for the assessment of absorption rate in BE studies. He also introduced pharmacodynamic considerations for the BE assessment. In addition, he introduced novel scaled BE limits to tackle the problem of highly variable drugs (HVD) and was the first to introduce scaled BE limits with levelling-off properties [18, 19]. These type of BE limits were adopted by the EMA in their latest Guideline. He also compared the reference scaled BE semi-replicate method with other approaches and compared the performance of the current FDA vis-a-vis the current EMA approach for (HVD) and was one of the first to publish on the problem of two-stage design in BE studies.

Fractal, fractional and dynamic aspects of drug disposition

Based on fractal geometry, fractal-fractional kinetics and chaotic dynamics concepts, Dr. Macheras has offered new insights for the complex, drug kinetic and dynamic phenomena in the body [2, 3, 20–22]. A dichotomous branching network for the arterial and venous vessels was used to interpret calcium PK; an advanced version of this model was used to describe the materials' transport in the circulatory system and the calculation of recirculatory parameters. Moreover, he conceived the body as a fractal object with infinitely high surface to volume ratio and developed novel PK parameters, e.g., the fractal volume of drug distribution and fractal clearance. Also, he explained the unusual nonlinear PK of mibefradil, the erratic disposition of cyclosporine and the deviation of carrier mediated transport from Michaelis–Menten kinetics. Dr. Macheras introduced the concepts of nonlinear dynamics to biopharmaceutical sciences and developed a nonlinear dynamic model that exhibited chaotic behavior describing the erratic secretion of cortisol and its suppression by corticosteroids. This was illustrated by his use of return mapping to identify intrinsic dependence and periodicity in multiple dimensions (Fig. 3).

His use of fractional derivatives for the description of drug absorption and disposition processes explained the anomalous kinetics of amiodarone and resulted in the development of fractional multi-compartmental PK models. Finally, Dr. Macheras has a deep interest in population pharmacokinetics; he is now leading together with his colleague, ex-Ph.D. student Aris Dokoumetzidis, a project introducing population PK analysis in Greek hospitals for the purposes of therapeutic optimization.

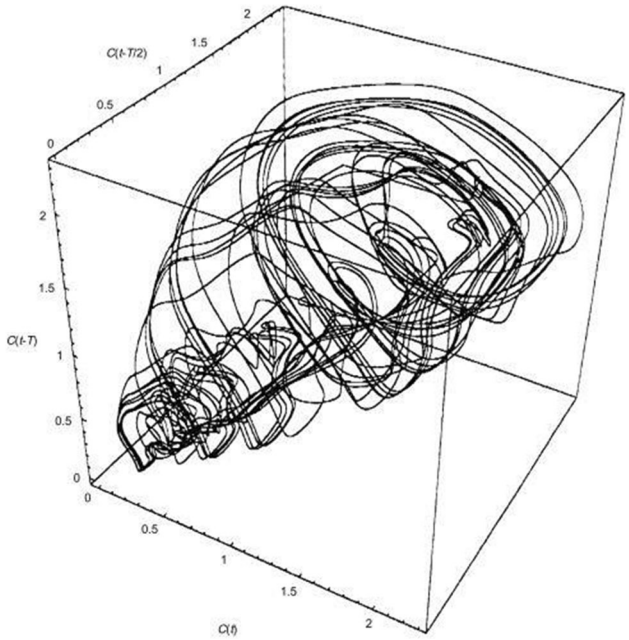

Fig. 3 A pseudo-phase space for the model of equations 1 and 2 using the variables $C(t)$, $C(t - T/2)$ and $C(t - T)$ expressed in μg 100 ml^{-1}. The real phase space is of infinite dimension, however, trajectories may be considered to lie in a low dimensional space (attractor). The model parameters take the same values as in Figure 2 and time runs for 10 days [24]. (Used with permission from BJCP Br J Clin Pharmacol. 2002 Jul; 54(1): 21–29)

Concluding remarks

Panos Macheras' investigations have significantly moved the frontiers of the fields of (1) bioequivalence (metrics and scaled limits), (2) oral drug absorption (modeling and simulation analysis of drug dissolution and release, biopharmaceutics classification, drug–milk interactions, novel milk based formulations), and (3) heterogeneous kinetics and dynamics (fractal and fractional kinetics as well as applications of nonlinear dynamics to biopharmaceutical systems).

He undertook both excellent experimental studies and innovative theoretical investigations. His development, method and applications of fractal and fractional analysis are groundbreaking. They have led to important advances in our understanding of the basic processes of gastrointestinal drug delivery from solid dosage forms and of the subsequent absorption into the systemic circulation.

Among the 6 books of Macheras, particularly remarkable is the groundbreaking Springer publication, written with A. Iliadis, entitled "Modeling in biopharmaceutics,

pharmacokinetics and pharmacodynamics: homogeneous and heterogeneous approaches" [23]. It received an Academy of Athens Award and has its second edition.

Panos Macheras is indeed a pioneer of pharmacokinetics, pharmacodynamics and biopharmaceutics. The many contributions herein reflect the innovative spirit that is the embodiment of Dr. Machers' career. It is fitting that this special issue should celebrate his 75th birthday.

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