Journal of
Food and Pharmaceutical Sciences

Review Article

Application in Silico Modeling Simulation in Bioequivalence Studies: A Review

Sekar Ayu Pawestri*

Department of Pharmaceutics, Faculty of Pharmacy, Universitas Gadjah Mada, Yogyakarta, Indonesia
*Corresponding author: Sekar Ayu Pawestri | Email: sekar.ayu.p@ugm.ac.id

Received: 21 October 2022; Revised: 3 February 2023; Accepted: 2 March 2023; Published: 31 March 2023

Abstract: Bioequivalence testing aims to ensure that the therapeutic performance of the drug is consistent and reproducible when it is administrated. Modeling and simulation in silico methods are currently performed to conduct virtual bioequivalence studies. Various computer simulation software is used to generate the simulation and model input data. This review summarizes the software used for predicting in vivo performance which supports the analysis of virtual bioequivalence testing. GastroPlus™ and SimCyp® are widely used platforms in generating data for virtual bioequivalence studies. The studies suggest that the validity procedure is necessary for modeling and simulation. The in silico method has become a valuable tool in bioequivalence studies as supporting extension of the biowaiver drug list and contributing to future drug development.

Keywords: modeling; simulation; bioequivalence; biowaiver; in silico

1. INTRODUCTION

The bioequivalence test is a standardized test to ensure the therapeutic equivalence of drug products before being marketed [1]. Drug products are said bioequivalent when geometric ratio of area under the blood concentration–time curve (AUC) and the maximum blood concentration (Cmax) as surrogate measure of the pharmacokinetic profile lie within 0.8 and 1.25 in the 90% confidence interval to fulfil the bioequivalence criterion [2]. It indicated that the rate and extent of drug absorption into systemic circulation are considered equivalent [3]. In the actual bioequivalence test, the design experiment is preferred using cross-over design which assigns the healthy volunteer (and patients, in the specific case) into two groups or sequences. Specifically, the subjects in each group received two formulation products: a test product and a reference product and administrated in two periods with sufficient wash-out time [1,4].

Nowadays, the exemption of bioequivalence studies, called biowaiver, is still limited to only some drugs which included to Biopharmaceutics Classification System (BCS) Class I (high solubility, high permeability) and class III (high solubility, low permeability) [5]. It based on the drug could exhibit rapid or very rapid in vitro dissolution according to the recommended test method. However, an extension biowaiver drug list is needed as biowaiver offers to save time and reduces cost because experiment in human testing is unnecessary.

Recently, in silico modeling and simulation using software have a significant role in predicting human drug exposure. Platforms such as SimCyp®, NONMEM®, and PK-Sim® are reported to be capable of carrying out those predictions [5]. Those platforms could reduce effort, cost, and time in conducting virtual bioequivalence, especially for the supporting extension biowaiver and

developing drug products. This review will discuss about the application of those platforms on the bioequivalence studies.

2. METHODS

The articles related to the modeling simulation using computer simulation in bioequivalence studies was identified and selected from the databases. The databases used in this review were ScienceDirect, and PubMed with keywords of modeling+ simulation+ bioequivalence. Inclusion criteria for the articles were in English, open access, and published in the last 10 years.

3. RESULTS AND DISCUSSION

In the bioequivalence studies, comparing two drug products (reference and test product) with the same active substance indicate they will have similar dispositions but will be different in the absorption process due to the different formulation and excipient used. Therefore, evaluating the in vitro drug release performance become the critical factor in measuring the equivalent of both products. In silico mathematical modeling and simulation are valuable tools in the early stage of drug development for optimizing the design dosage form. This method uses software to input model data including the in vitro data of the drug and simulates the data to predict the pharmacokinetic profile [6]. The application of computer simulation recently involved in analyzing about physiologically based pharmacokinetic (PBPK) models, predicting the pharmacokinetics profile of certain drugs (e.g, inhalers), and predict bioequivalence using virtual subjects [5,7–9]. Some platforms are generally applied in silico bioequivalence study is presented in Table 1.

Table 1. Computer software used in simulation and modeling for bioequivalence study.

Computer software/In Vitro	Application	References
GastroPlus™	Using the built-in module, it can simulate the plasma concentration–time curves for the population virtual subjects, combining physiology and pharmacokinetic variability considering the input data of drug database	[10–19]
SimCyp®	a) developing a mechanistic gastrointestinal simulation in estimating absorption model b) establishing the IVIVCs using two-stage approach of IVIVC module c) modeling the drug dissolution and absorption using the Advanced Dissolution, Absorption and Metabolism (ADAM) model d) quantifying description of drug absorption through the skin using the multi-phase multi-layer (MPML) MechDermA model e) simulating virtual bioequivalence studies	[20–26]
NONMEM®	a) performing the Monte Carlo simulations of bioequivalence studies b) performing virtual bioequivalence studies	[1,27,28]
MATLAB®	a) developing an in vitro–in vivo simulation (IVIVS) approach to predict the outcome of a bioequivalence study b) constructing the compartmental absorption and transit (CAT) model to simulate the drug concentrations in plasma	[6,29]
Stella® Professional	a) developing in silico drug absorption model b) developing a physiologically based biopharmaceutics (PBBM)	[30,31]
B^2O simulator	Constructing PBPK model by integrating clinical and nonclinical data to predict the bioequivalence using different dissolution profiles data	[32]
PK-Sim®	Coupling in vitro biorelevant dissolution testing in USP-4 Apparatus (flow-through cell) with PBPK modeling to predict the bioequivalence of oral drug products	[33]

3.1. GastroPlus™

GastroPlus™ is a computer program that uses PBPK models to simulate and predict absorption-distribution-metabolism- excretion (ADME) processes and generates pharmacokinetic profiles. The model is built by inputting the appropriate data, such as physicochemical properties of the drug (e.g., solubility, log P, permeability), physiological variables (e.g., the volume of gastrointestinal compartments, pH of transit time), pharmacokinetic parameters (e.g., clearance, the volume of distribution), etc. GastroPlus™ is widely used in early development stages to predict bioavailability from in vitro data, simulate plasma concentration profiles, perform virtual bioequivalent studies justify biowaivers, etc. [7,34].

Mitra et al. developed the absorption modeling to predict the bioequivalence of etoricoxib tablets manufactured at two sites using Gastroplus™. This drug is classified as a BCS Class II drug due to has low solubility but is rapidly absorbed orally. During developing the absorption model, Mitra et al. slightly modified increase the absorption scale factors (ASF) in duodenum from the default value of 2.794 to 3.794 and jejunum from the default value of 2.750 to 3.750 considering within possible ranges for in vivo deviation of parameters merely relying on in vitro measurements. The development resulting from virtual trials in a single simulation using the 0,01 N HCl dissolution showed the similarity prediction in AUC and Cmax for the tablet batches. Those predicted had verified with definite bioequivalence study, and it can be concluded that both the tablets manufactured at the two sites are bioequivalent [16].

GastroPlus™ is also employed for predicting the effect of food on the pharmacokinetics of generic and reference drug products (BCS Class II) using modeling and simulation. Rebeka et al. built a PBPK model to predict the fed bioequivalence outcome with virtual trials. The developed model showed that it could predict the food effect with up to 10% prediction error. Virtual bioequivalence trials confirmed the bioequivalence of drug products in the fed state [17].

However, there is still a shortcoming of this method. Before simulating plasma concentration, the input data were from various knowledgebase such as from literature and prediction of ADMET Predictor™ (one of the module in the Gastroplus) [5,10]. It might be resulting different outputs between researchers as standardized references are still unavailable. Moreover, the simple fitting of parameters, as with other platforms in predicting bioequivalence profiles, may cause the work to be subjective and questionable. Therefore, validating is necessary by conducting a prospective study in which the platform's results are validated by in vivo evaluation to be within much smaller tolerances than those commonly reported in the literature [5].

3.2. SimCyp®

SimCyp® is a population-based simulator involving demographic, physiologic, and genomic databases to consider patient variability [5]. Doki et al. examined the bioequivalence outcome of levothyroxine and nifedipine based on PBPK modeling in achlorhydria conditions. The model was built using the Advanced Dissolution, Absorption, and Metabolism (ADAM) model to construct the drug dissolution and absorption model. The ADAM model is within the Simcyp Simulator [21]. Another report also used Simcyp® Simulator to perform virtual bioequivalence of naproxen, a BCS class II weak acid. The in vitro data of biorelevant solubility and dissolution were input to the PBPK model. The result of the virtual bioequivalence study indicating in vitro dissolution of naproxen reaching 85% dissolved within 90 min comfortably lie within the bioequivalence limits for Cmax and AUC [22].

Mittapelly and Polak developed a model to characterize the skin absorption of Nimesulide in both in vitro and in vivo subjects. The PBPK modeling was carried out using a multilayer mechanistic dermal absorption (MPML MechDermA) model within the Simcyp Simulator software, which can simulate drug permeation through the skin. A virtual bioequivalence study using the PBPK model was conducted at systemic and local exposure (dermal concentration). After performing in vitro/in vivo extrapolation (IVIVE) to assess the model's predictability for studying nimesulide's in vivo pharmacokinetics, the resulting analysis indicated that these formulations were concluded to be bioequivalent. In this study, demographic information was available in simulations, but default

settings were used if the information was not available. Considering several parameter values for simulation in studies mentioned above, either by default or prediction in SimCyp®, it possibility reducing the reliability of the results [24,35].

3.3. NONMEM®

The NONlinear Mixed Effects Modeling (NONMEM®) is a computer program developed by Lewis Sheiner, Stuart Beal, and the NONMEM Project Group at the University of California. This program can fit models to a wide variety of data. Many reports have recently used NONMEM® as a tool for population pharmacokinetic-pharmacodynamic analysis [36]. This software could be used to perform the Monte Carlo simulations of bioequivalence studies. Mangas-Sanjuan et al. explored which analyte (parent drug or any of its active metabolites) is the most sensitive to drug formulation changes. The results from different studied scenarios demonstrated the parent drug was the most sensitive analyte for bioequivalence trials [1].

Cuesta-Gragera et al. tested the validity of the developed semi-physiologic pharmacokinetic model, which is applied in NONMEM to simulate bioequivalence trials of acetylsalicylic acid and compared against acetylsalicylic acid human experimental data. The validation results exhibited that the simulated concentration-time curves closely predicted the published experimental data [27].

Hsieh and Hsu employed a simulation in virtual bioequivalence studies using NONMEM to investigate which analyte of ezetimibe (e.g., ezetimibe alone, ezetimibe-glucuronide alone, total form alone, or combination of ezetimibe and total form) was more sensitive to detect the changes in the rate of absorption as a bioequivalence indicator. Based on the results of those simulations, none of the single analytes (ezetimibe alone, ezetimibe-glucuronide alone, total form alone) provide clear advantages in detecting differences in the rate of absorption; therefore, a combination of ezetimibe and total form should be considered in the bioequivalence evaluation [28].

3.4. The other in silico platform

There are also reports of using other software to simulate the model, such as MATLAB®. Kortejärvi et al. examine the dissolution acceptance criteria for BCS I and III biowaivers and MDR-1 efflux in substrate bioequivalence using the Compartmental Absorption and Transport Model (CAT) by one or two systemic compartments constructed in the MATLAB® program [29]. Vlacho and Karalis were developing a novel in vitro in vivo simulation (IVIVS) approach for a new generic amlodipine/irbesartan/hydrochlorothiazide combination products and programming in MATLAB®. This approach allows for predicting the probability of success in bioequivalence studies [6]. Another several platforms also have been applicated by other researchers such as Stella® Professional, B^2O simulator and PK-Sim® which may not being applied as much as compared to the previously mentioned.

Several benefit of closing the gap between in silico, in vitro, and in vivo by establishing mechanistic absorption model and combining with a population PBPK model are they could predict the clinical outcome, hepful in decision-making of regulatory and allow regulatory flexibility (e.g., the extension of some BCS class II biowaivers). Certainly, they also reduce product development time and cost by replacing unnecessary clinical trials. Nevertheless, mechanistic extrapolation of in vitro data (such as dissolution) to the in vivo performance is essential conducted for the validating and interpreting results from virtual bioequivalence studies. Further validation is needed to increase confidence and evaluate the power of mechanistic absorption modeling and PBPK in designing formulation and regulation [22,23].

4. CONCLUSION

The use of computer simulation to predict the pharmacokinetic profiles based on the physicochemical properties of substance and physiological-absorption input model data was currently implemented to conduct virtual bioequivalence study. This method potentially supports the extension of the biowaiver drug list, especially for the drug besides BCS Class I. The benefit of the method certainly reduces time and associated costs compared with the actual bioequivalence study.

Various platform is available to simulate the data. GastroPlus™ and SimCyp® are widely used platforms in generating data for virtual bioequivalence studies. However, to continuously use this in silico method in the studies, the regulatory agencies need to validate the simulation procedure and the platform experiences.

Funding: This research received no external funding.
Acknowledgments: -
Conflicts of interest: The authors declare no conflict of interest.

References

1. Mangas-Sanjuan V, Navarro-Fontestad C, García-Arieta A, Trocóniz IF, Bermejo M. Computer simulations for bioequivalence trials: Selection of analyte in BCS class II and IV drugs with first-pass metabolism, two metabolic pathways and intestinal efflux transporter. Eur J Pharm Sci. 2018 May;117:193–203.
2. EMA. Investigation of bioequivalence [Internet]. European Medicines Agency. 2018 [cited 2022 Oct 19]. Available from: https://www.ema.europa.eu/en/investigation-bioequivalence
3. Gajjar P, Dickinson J, Dickinson H, Ruston L, Mistry HB, Patterson C, et al. Determining bioequivalence possibilities of long acting injectables through population PK modelling. Eur J Pharm Sci. 2022 Dec;179:106296.
4. Hyodo M, Onobuchi A, Kurakami H. An approximate multivariate asymptotic expansion-based test for population bioequivalence. J Stat Plan Inference. 2019 May;200:74–86.
5. Al-Tabakha MM, Alomar MJ. In Vitro Dissolution and in Silico Modeling Shortcuts in Bioequivalence Testing. Pharmaceutics. 2020 Jan 4;12(1):45.
6. Vlachou M, Karalis V. An In Vitro–In Vivo Simulation Approach for the Prediction of Bioequivalence. Materials. 2021 Jan 24;14(3):555.
7. GastroPlus® PBPK & PBBM Modeling and Simulation [Internet]. [cited 2022 Oct 18]. Available from: https://www.simulations-plus.com/software/gastroplus/
8. NONMEM | Nonlinear Mixed Effects Modelling | ICON plc [Internet]. [cited 2022 Oct 18]. Available from: https://iconplc.com/innovation/nonmem/
9. Simcyp PBPK [Internet]. Certara. [cited 2022 Oct 18]. Available from: https://www.certara.com/software/simcyp-pbpk/
10. Duque MD, Silva DA, Issa MG, Porta V, Löbenberg R, Ferraz HG. In Silico Prediction of Plasma Concentrations of Fluconazole Capsules with Different Dissolution Profiles and Bioequivalence Study Using Population Simulation. Pharmaceutics. 2019 May 5;11(5):215.
11. García MA, Bolger MB, Suarez-Sharp S, Langguth P. Predicting Pharmacokinetics of Multisource Acyclovir Oral Products Through Physiologically Based Biopharmaceutics Modeling. J Pharm Sci. 2022 Jan;111(1):262–73.
12. Jereb R, Kristl A, Mitra A. Prediction of fasted and fed bioequivalence for immediate release drug products using physiologically based biopharmaceutics modeling (PBBM). Eur J Pharm Sci. 2020 Dec;155:105554.
13. Kato T, Nakagawa H, Mikkaichi T, Miyano T, Matsumoto Y, Ando S. Establishment of a clinically relevant specification for dissolution testing using physiologically based pharmacokinetic (PBPK) modeling approaches. Eur J Pharm Biopharm. 2020 Jun;151:45–52.

14. Laisney M, Heimbach T, Mueller-Zsigmondy M, Blumenstein L, Costa R, Ji Y. Physiologically Based Biopharmaceutics Modeling to Demonstrate Virtual Bioequivalence and Bioequivalence Safe-space for Ribociclib which has Permeation Rate-controlled Absorption. J Pharm Sci. 2022 Jan;111(1):274–84.
15. Li X, Liang E, Hong X, Han X, Li C, Wang Y, et al. In Vitro and In Vivo Bioequivalence Study of 3D-Printed Instant-Dissolving Levetiracetam Tablets and Subsequent Personalized Dosing for Chinese Children Based on Physiological Pharmacokinetic Modeling. Pharmaceutics. 2021 Dec 22;14(1):20.
16. Mitra A, Kesisoglou F, Dogterom P. Application of Absorption Modeling to Predict Bioequivalence Outcome of Two Batches of Etoricoxib Tablets. AAPS PharmSciTech. 2015 Feb;16(1):76–84.
17. Rebeka J, Jerneja O, Igor L, Boštjan P, Aleksander B, Simon Ž, et al. PBPK Absorption Modeling of Food Effect and Bioequivalence in Fed State for Two Formulations with Crystalline and Amorphous Forms of BCS 2 Class Drug in Generic Drug Development. AAPS PharmSciTech. 2019 Feb;20(2):59.
18. Tang C, Ou-yang C xi, Chen W jing, Zou C, Huang J, Cui C, et al. Prediction of pharmacokinetic parameters of inhaled indacaterol formulation in healthy volunteers using physiologically-based pharmacokinetic (PBPK) model. Eur J Pharm Sci. 2022 Jan;168:106055.
19. Yang B, Wu C, Ji B, Wu M, He Z, Shang L, et al. Virtual population pharmacokinetic using physiologically based pharmacokinetic model for evaluating bioequivalence of oral lacidipine formulations in dogs. Asian J Pharm Sci. 2017 Jan;12(1):98–104.
20. Beloica S, Cvijić S, Bogataj M, Parojčić J. In vitro-in vivo-in silico approach in biopharmaceutical characterization of ibuprofen IR and SR tablets. Eur J Pharm Sci. 2015 Jul;75:151–9.
21. Doki K, Darwich AS, Patel N, Rostami-Hodjegan A. Virtual bioequivalence for achlorhydric subjects: The use of PBPK modelling to assess the formulation-dependent effect of achlorhydria. Eur J Pharm Sci. 2017 Nov;109:111–20.
22. Loisios-Konstantinidis I, Cristofoletti R, Fotaki N, Turner DB, Dressman J. Establishing virtual bioequivalence and clinically relevant specifications using in vitro biorelevant dissolution testing and physiologically-based population pharmacokinetic modeling. case example: Naproxen. Eur J Pharm Sci. 2020 Feb;143:105170.
23. Loisios-Konstantinidis I, Hens B, Mitra A, Kim S, Chiann C, Cristofoletti R. Using Physiologically Based Pharmacokinetic Modeling to Assess the Risks of Failing Bioequivalence Criteria: a Tale of Two Ibuprofen Products. AAPS J. 2020 Sep;22(5):113.
24. Mittapelly N, Polak S. Modelling and simulation approaches to support formulation optimization, clinical development and regulatory assessment of the topically applied formulations – Nimesulide solution gel case study. Eur J Pharm Biopharm. 2022 Sep;178:140–9.
25. Tsakalozou E, Babiskin A, Zhao L. Physiologically-based pharmacokinetic modeling to support bioequivalence and approval of generic products: A case for diclofenac sodium topical gel, 1%. CPT Pharmacomet Syst Pharmacol. 2021;10(5):399–411.
26. Zhang X, Wen H, Fan J, Vince B, Li T, Gao W, et al. Integrating In Vitro,Modeling, and In Vivo Approaches to Investigate Warfarin Bioequivalence: Investigate Warfarin Bioequivalence. CPT Pharmacomet Syst Pharmacol. 2017 Aug;6(8):523–31.

27. Cuesta-Gragera A, Navarro-Fontestad C, Mangas-Sanjuan V, González-Álvarez I, García-Arieta A, Trocóniz IF, et al. Semi-physiologic model validation and bioequivalence trials simulation to select the best analyte for acetylsalicylic acid. Eur J Pharm Sci. 2015 Jul;74:86–94.
28. Hsieh CM, Hsu LF. Investigation of the discriminatory ability of analytes for the bioequivalence assessment of ezetimibe: Parent drug, metabolite, total form, and combination of parent drug and total form. Eur J Pharm Sci. 2022 Jul;174:106192.
29. Kortejärvi H, Malkki J, Shawahna R, Scherrmann JM, Urtti A, Yliperttula M. Pharmacokinetic simulations to explore dissolution criteria of BCS I and III biowaivers with and without MDR-1 efflux transporter. Eur J Pharm Sci. 2014 Sep;61:18–26.
30. Kambayashi A, Dressman JB. Towards Virtual Bioequivalence Studies for Oral Dosage Forms Containing Poorly Water-Soluble Drugs: A Physiologically Based Biopharmaceutics Modeling (PBBM) Approach. J Pharm Sci. 2022 Jan;111(1):135–45.
31. Kambayashi A, Yomota C. Exploring clinically relevant dissolution specifications for oral solid dosage forms of weak acid drugs using an in silico modeling and simulation approach. Eur J Pharm Sci. 2021 Apr;159:105728.
32. Zhang F, Zhou Y, Wu N, Jia R, Liu A, Liu B, et al. In silico prediction of bioequivalence of Isosorbide Mononitrate tablets with different dissolution profiles using PBPK modeling and simulation. Eur J Pharm Sci. 2021 Feb;157:105618.
33. Ibarra M, Valiante C, Sopeña P, Schiavo A, Lorier M, Vázquez M, et al. Integration of in vitro biorelevant dissolution and in silico PBPK model of carvedilol to predict bioequivalence of oral drug products. Eur J Pharm Sci. 2018 Jun;118:176–82.
34. Flanagan T, Van Peer A, Lindahl A. Use of physiologically relevant biopharmaceutics tools within the pharmaceutical industry and in regulatory sciences: Where are we now and what are the gaps? Eur J Pharm Sci. 2016 Aug 25;91:84–90.
35. Patel N, Clarke JF, Salem F, Abdulla T, Martins F, Arora S, et al. Multi-phase multi-layer mechanistic dermal absorption (MPML MechDermA) model to predict local and systemic exposure of drug products applied on skin. CPT Pharmacomet Syst Pharmacol. 2022 Aug;11(8):1060–84.
36. Bauer RJ. NONMEM Tutorial Part I: Description of Commands and Options, With Simple Examples of Population Analysis. CPT Pharmacomet Syst Pharmacol. 2019 Aug;8(8):525–37.