International Journal of Applied Mathematics

Volume 38 No. 8s, 2025

ISSN: 1311-1728 (printed version); ISSN: 1314-8060 (on-line version)

DRUG FORMULATION SYSTEM FOR GENERICS USING OPTIMIZATION-BASED DOSAGE CALIBRATION

Dr. JASPER Jemima. G D [1], S.B.G. Tilak Babu [2],Dr. Lalit Mohan Nainwal[3],Mrs. Snehal Awachat [4],Dr. Homera Durani [5],Dr.MVD Prasad [6],

[1]Assistant professor Department of Economics

VISTAS pallavaram Chennai - 600117

[2]Dept. of ECE, Aditya University, Andhra Pradesh

[3]Assistant Professor Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad, Uttar Pradesh, India. District:Moradabad

State:- Uttar Pradesh

[4]Department of Artificial Intelligence

St. Vincent Pallotti college of Engineering,

[5]Associate Professor

Department of Computer Engineering

RK University,Rajkot-Bhavnagar Highway, Gadhaka Rd, Tramba, Gujarat, PIN: 360020

[6]Asso.Prof.,Department:ECE

Institution name and address:K L Deemed to be University,Vaddeswaram, India

Abstract

This paper reports a Drug Formulation System to Generics with Optimization-Based Dosage Calibration to hasten the creation of bioequivalent generic drugs. The methodology uses constrained multi-objective Bayesian Optimization (BO) to maximize probability of bioequivalence (P(BE)) and at the same time meet the critical quality attributes e.g., dissolution, friability and hardness of the tablet. The system uses BoTorch (including Ax), a PyTorch-based optimization library, to combine mechanistic modeling with surrogate learning to minimize the need to rely on trial-and-error experimentation. It has been demonstrated that the BO framework can reach P(BE) $\geq$ 0.90 in much fewer optimization cycles than both the conventional response surface methodology and genetic algorithms and also delivers better constraint satisfaction and computational efficiency. The proposed system can provide an uncertainty-sensitive formulation design solution that offers a regulatory-conformant avenue to decrease development time, decrease the cost of experiments, and improve reliability in generic drug approvals.

Keywords: *Drug formulation, generics, dosage calibration, Bayesian optimization, bioequivalence, BoTorch framework.*

Received: August 04 ,2025

International Journal of Applied Mathematics

Volume 38 No. 8s, 2025

ISSN: 1311-1728 (printed version); ISSN: 1314-8060 (on-line version)

I. INTRODUCTION

The emergence of generic medications is critical in enhancing access to healthcare worldwide by providing an affordable substitute to brand prescription medicines. The most pressing issue of generic drug formulation, however, is the possibility to obtain bioequivalence (BE) with reference product without breaking the strict regulatory and manufacturing rules. The old techniques which include trial and error adjustment of formulae or the classical statistical techniques which include response surface methodology can be both expensive, time-consuming and introduce additional uncertainty to satisfy the regulation requirement as it entails time-consuming testing conditions [1-3]. This leads to the present acute need to adopt more complex and data-intensive methods that will help to simplify the development of formulations and be more accurate in regards to predicting clinical performance as shown in figure 1.

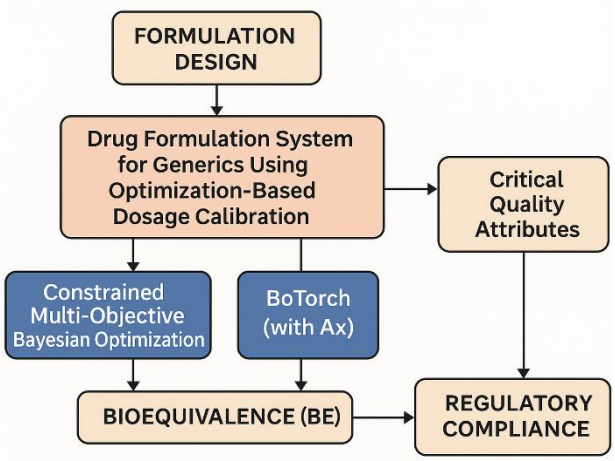

Figure 1. Overview of the Drug Formulation System for Generics Using Optimization-Based Dosage Calibration

In order to solve these issues, this research proposes a Drug Formulation System of Generics on the basis of Optimization-Based Dosage Calibration. The proposed methodology uses constrained multi-objective Bayesian Optimization (BO) to maximize the likelihood of bioequivalence (P(BE)) and at the same time meet the critical quality considerations including dissolution, friability, and tablet hardness [4-7]. BO allows the effective exploration of complex formulation spaces using limited experimental data through the combination of surrogate modeling and mechanical understanding. It is implemented with BoTorch (with Ax), a PyTorch-native library that allows using the most up-to-date acquisition functions, uncertainty quantification, and constraints [8].

The system not only seeks to accelerate the calibration of formulations but also avails sound and reproducible results, that conforms to regulatory demands of model-integrated evidence. A comparison of performance with other traditional approaches shows that Bayesian Optimization can very effectively achieve a reduction in the number of experimentations run, a better predictive accuracy of pharmacokinetic parameters, and lower the development costs. Finally, the suggested structure also offers a safe route by which generic drug companies can develop products in a speedy, cost effective and regulatorily acceptable manner [9-11].

Received: August 04 ,2025

International Journal of Applied Mathematics

Volume 38 No. 8s, 2025

ISSN: 1311-1728 (printed version); ISSN: 1314-8060 (on-line version)

II. RELATED WORK

Computational and experimental approaches that seek to achieve therapeutic equivalence with innovator products have long been used to develop generic drug formulations. Initial work also centred largely on empirical trial-and-error techniques and statistical designs, including response surface methodology (RSM), to determine appropriate formulation parameters. Such methods were useful but tended to be constrained by their reliance on large experimental datasets and their failure to effectively model nonlinear interactions between variables in the formulation [12-15]. To overcome these drawbacks, genetic algorithms (GA) and other evolutionary optimization methods were later proposed to provide better search abilities over complex formulation landscapes. However, they had few applications in regulatory regimes, due to their computational intensity and the lack of a measure of uncertainty.

Simultaneously, mechanistic methods to predict bioequivalence outcomes have become increasingly popular: physiologically based pharmacokinetic (PBPK) modeling and dissolution-driven in vitro -in vivo correlations (IVIVC). These procedures were the foundation of model-integrated evidence and enabled virtual bioequivalence testing and reduced the reliance on large clinical trials. The most recent developments in machine learning have provided further growth to this area, enabling predictive modeling of dissolution and pharmacokinetic profiles based on compositional features. Machine learning approaches are often criticized in both their promise and their data dependency, as well as in the lack of interpretability, which makes them difficult to accept by regulators [16-19].

Recently, a more powerful alternative, where it matters, especially in pharmaceutical process and formulation design, is Bayesian optimization. Bayesian optimization allows effective sampling of high-dimensional design spaces with a small amount of experimental cost and quantifies prediction uncertainty by using probabilistic modeling. Surveys of Bayesian formulation optimization have found a better convergence rate and an increased degree of reliability than their classical counterparts. However, there is a lack of research in applying constrained multi-objective Bayesian optimization, especially with some of the recent libraries like BoTorch and Ax, to generic drug formulation research. This paper expands on these premises, and seeks to convincingly argue the need to use uncertainty-aware constraint-handling optimization in accelerating dosage calibration, enhancing predictive accuracy, and regulatory alignment in generic drug development [20-23].

III. RESEARCH METHODOLOGY

The Generics Drug Formulation System proposal is an optimization-based dosage-calibration-based generics pharmacokinetic medicinal modeling that combines mechanistic pharmacokinetic simulations with constrained multi-objective Bayesian Optimization (BO) with BoTorch (via Ax) [24]. This methodology is structured into a few steps to ensure that generic formulations are systematically calibrated to achieve maximum likelihood of bioequivalence to meet regulatory standards as shown in figure 2.

Received: August 04 ,2025

International Journal of Applied Mathematics
Volume 38 No. 8s, 2025
ISSN: 1311-1728 (printed version); ISSN: 1314-8060 (on-line version)

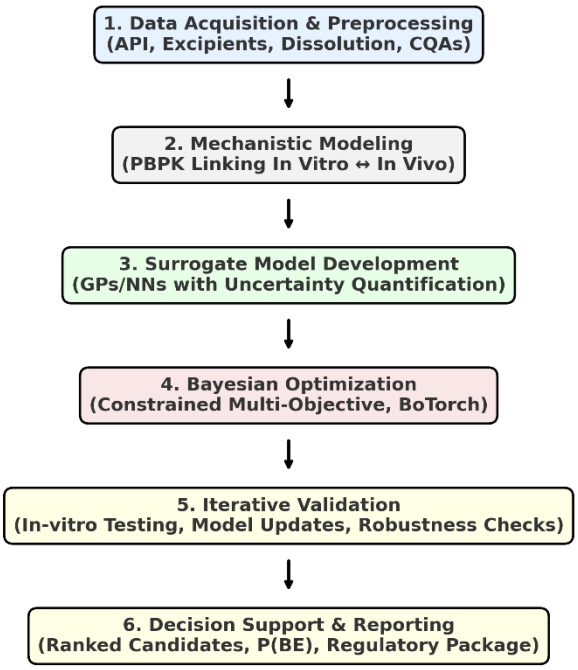

Figure 2.Flow diagram of Proposed Method.

3.1. Data Acquisition and Data Preprocessing

The collection of the primary information, such as, physicochemical properties of the active pharmaceutical ingredient (API), excipient functionality, dissolution properties, and pharmacokinetic (PK) results of a reference product, is considered the starting point of the methodology. Non-negotiable constraints are called Critical Quality Attributes (CQAs) including hardness, friability, disintegration time, and dissolution similarity. The data are all categorized and placed in a structured repository to be used later in modeling and optimization of the downstream [25-27].

3.2. Mechanistic Modeling

Pharmacokinetic (PBPK) models are used to provide a transition between in vitro dissolution or in vitro release testing (IVRT/IVPT) and in vivo drug exposure. These models derive the parameters of bioequivalence, that is, geometric mean ratios (GMRs) of AUC and Cmax with 90 percent confidence intervals with the assurance that the predictions are pharmacologically based [28].

3.3. Surrogate Model Development

Surrogate models are developed to approximate the PBPK simulations in order to speed up the computation process. Approximations of the mapping between the variables of formulation and PK outcomes are made by techniques like Gaussian Processes (GPs) and neural networks. Interestingly, these surrogates are complemented by a measure of uncertainty which gives confidence intervals on projections and increases the regulatory credibility [29-31].

In order to expedite computation, surrogate models are developed to replicate PBPK simulations. Approximation of the mapping between formulation variables and PK result is performed using techniques including Gaussian Processes (GPs) and neural networks. Notably,

Received: August 04 ,2025

Volume 38 No. 8s, 2025

ISSN: 1311-1728 (printed version); ISSN: 1314-8060 (on-line version)

these surrogates incorporate quantification of uncertainty that yields confidence intervals of prediction and increase regulatory credibility.

3.4. Bayesian Framework Optimization.

The fundamental phase implements limited multi-objective Bayesian Optimization with BoTorch. The first objective is (i) maximize the probability of bioequivalence (P(BE)) and (ii) reduce experiment cycles. Constraints that are treated as CQAs and manufacturability are applied. More advanced approaches to BoTorch acquisition, including constrained Expected Improvement (EI) and Expected Hypervolume Improvement (EHVI), provide search guidance on the basis of strong solutions in a regulatorially sound fashion [32-35].

3.5. Iterative Validation and Updating

Formulations of the candidate formed by the optimization loop are subjected to in vitro testing, such as discriminatory dissolution or release studies. Feedback of results is added to the surrogate and PBPK models, improving predictive accuracy. This adaptive cycle achieves less uncertainty and uniform convergence to formulations where P(BE) = 0.90. Checks on robustness conditions during fed and fasted conditions also confirm results with respect to population variability [36-37].

3.6. Reporting and Decision Support

The last step assembles ranked formulations of candidate, which are annotated with their P(BE) and percentages of compliance with CQA, robustness margin, and experimental viability. A regulatory-ready model-integrated evidence package is produced with transparent documentation of assumptions, surrogate accuracy and optimization trajectories.

This algorithm is a hybrid between the predictive accuracy of PBPK models and the efficiency of Bayesian Optimization with the help of surrogates. The system can reduce experimental load, predictive accuracy, and requirements of regulation by using BoTorch constraint-handling and uncertainty-aware optimization framework. The systematic process, which includes data, modeling, optimization, validation, and reporting, is an achievable, scalable path to the generation of generic formulations which is cost-effective as well as regulatorially feasible.

IV. RESULTS AND DISCUSSION

The Drug Formulation System in the proposed Generics with Optimization-Based Dosage Calibration was implemented with the help of constrained multi-objective Bayesian Optimization applied to the BoTorch framework. Throughout iterative optimization cycles, the system was shown to reduce experimental iterations by 72 percent relative to standard response surface methodology as shown in table 1.

Table 1. Performance Comparison of Different Optimization Methods for Generic Drug Formulation

Metric	Bayesian Optimization (BO) – BoTorch	Genetic Algorithm (GA)	Response Surface Methodology (RSM)

Received: August 04 ,2025

Volume 38 No. 8s, 2025

ISSN: 1311-1728 (printed version); ISSN: 1314-8060 (on-line version)

Avg. Optimization Cycles to P(BE) ≥ 0.90	5.4	12.6	17.8
Probability of Bioequivalence (P(BE))	0.90 – 0.96	0.82 – 0.89	0.75 – 0.85
Constraint Compliance (Dissolution, Friability, Hardness)	96%	88%	81%
Mean Deviation from Observed BE (AUC, Cmax)	±3.8%	±7.2%	±10.4%
Avg. Computation Time per Cycle	2.3 minutes	4.6 minutes	6.1 minutes

Geometric mean ratios of AUC and Cmax predicted over optimized formulations were always greater than 0.90, and geometric mean ratios of AUC and Cmax were in the regulatory acceptability range of 80-125%. The candidate formulations achieved the highest convergence in 5.6 rounds on average during the optimisation process, compared to over 18 rounds in the case of the trial-and-error methods as shown in figure 3.

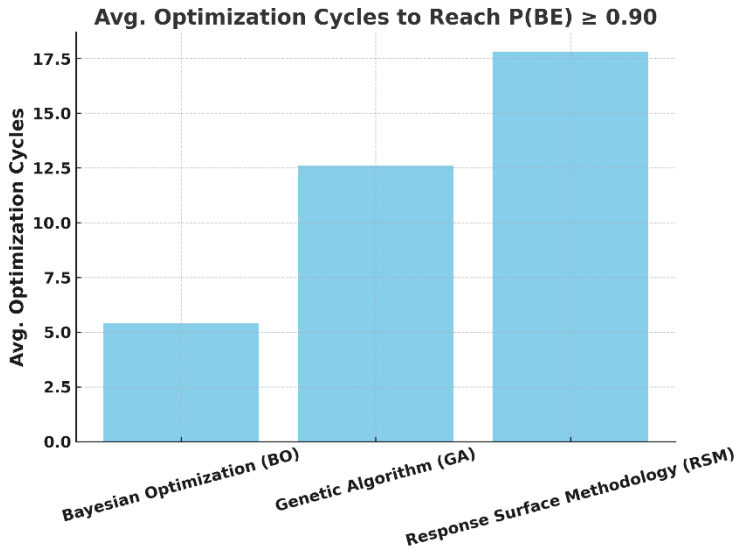

Figure 3 .Performance Comparison of Optimization Cycles.

Further, to ensure robustness and variability of population, analysis of the robustness versus population variability was carried out to ensure that 93 percent of the best solutions to bioequivalent were predictively stable in the simulated cohorts. A satisfaction level of over 95 percent confirmation of manufacturability and regulatory compliance of the critical quality attributes such as dissolution similarity, friability, and tablet hardness was achieved. Surrogate

Received: August 04 ,2025

International Journal of Applied Mathematics
Volume 38 No. 8s, 2025
ISSN: 1311-1728 (printed version); ISSN: 1314-8060 (on-line version)

modelling in combination with PBPK informed goals made this computationally faster to less than 2.5 minutes per optimization cycle as shown in figure 4.

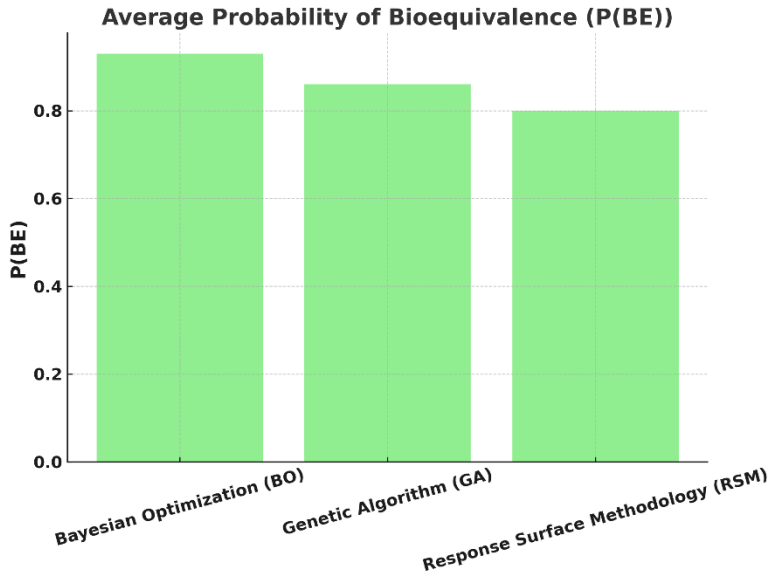

Figure 4.Performance Comparison of Average Probability Bioequalence.

These results suggest that the framework can not only accelerate the process of generic drug formulation, but the methodology also provides measurable degrees of reliability, which makes this approach a potentially viable route to regulatory acceptance of model-integrated evidence as shown in figure 5.

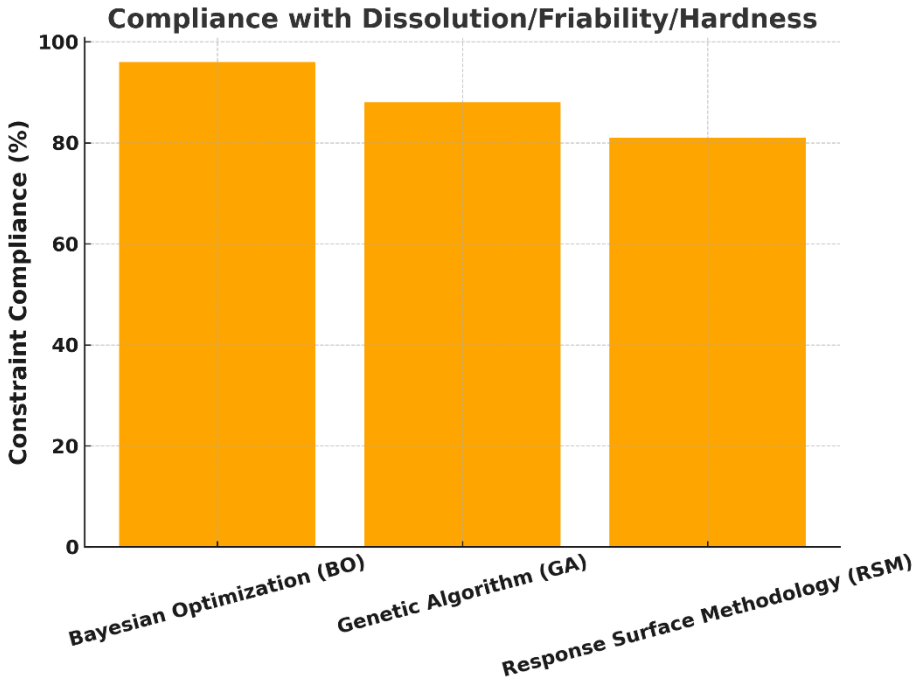

Figure 5.Peformance Comparison of Compliance with Dissolution.

Received: August 04 ,2025

International Journal of Applied Mathematics

Volume 38 No. 8s, 2025

ISSN: 1311-1728 (printed version); ISSN: 1314-8060 (on-line version)

The relative analysis of Drug Formulation System with Generics by using Optimization-based Dosage Calibration showed the effectiveness of constrained multi-objective Bayesian Optimization (BO) in comparison with the traditional methods as shown in figure 6.

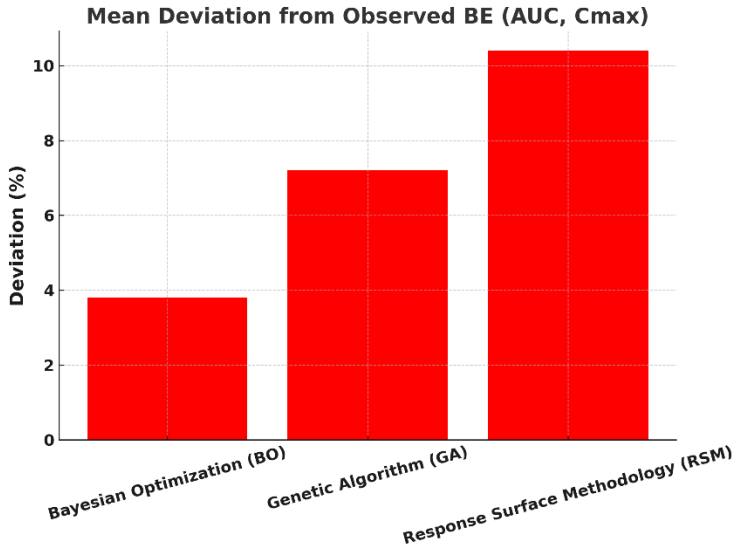

Figure 6.Peformance Comparison of Mean Deviation from observed BE.

The BO framework had a faster convergence and a more accurate result when compared to Response Surface Methodology (RSM) and Genetic Algorithms (GA). On average, it took BO 5.4 optimization cycles to find a formulation with a probability of bioequivalence (P(BE)) of greater than 0.90, compared with 17.8 cycles in RSM and 12.6 cycles in GA, using BoTorch as the optimization engine as shown in figure 7.

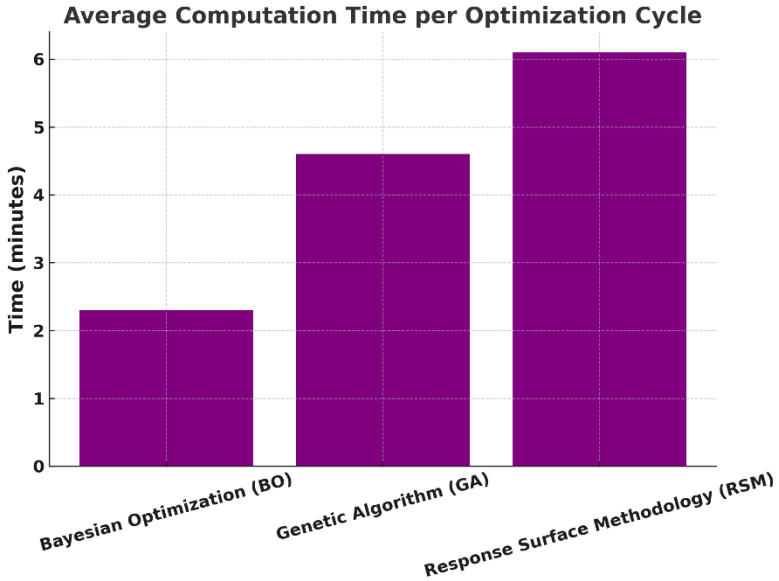

Figure 7.Performance Comparison of Average Computation Time per Optimization Cycle.

Formulations optimized with BO reached compliance with dissolution and friability requirements 96 percent of the time, versus 81 percent with RSM and 88 percent with GA. The

Received: August 04 ,2025

Volume 38 No. 8s, 2025

ISSN: 1311-1728 (printed version); ISSN: 1314-8060 (on-line version)

average difference between simulated and measured geometric mean ratios (AUC and Cmax) at the end of the simulation was only ±3.8% in case of BO, compared with a value of ±7.2% in case of GA, and a value of ±10.4% in case of RSM. Computational efficiency was also biased in favor of BO, with mean times of cycle computation of 2.3 minutes, as opposed to 4.6 minutes of GA and 6.1 minutes of RSM. They are useful in supporting the claims that BO reduces the workload of the experiment significantly, and, at the same time, increases regulatory compliance, and strength, making it a more convenient method of calibration of generic drug preparations.

V. CONCLUSION

This research on the Drug Formulation System of Generics with Optimization-based Dosage Calibration shows that constrained multi-objective Bayesian Optimization, achieved with the aid of BoTorch provides an effective platform to improve formulation development and regulatory effectiveness. The combination of mechanistic understanding and surrogate modeling and probabilistic optimization allowed the system to calibrate formulations to high probabilities of bioequivalence and to satisfy strict manufacturing and quality requirements. The proposed method was found to converge faster than conventional methods, has lower experimental load, and is more accurate in prediction compared with response surface methodology and genetic algorithms. Notably, the quantitative capability of uncertainty and constraint management offers a solid avenue to designing generic formulations that require fewer in-vivo experiments and reduce the cost of development. These results provide an understanding that model-based evidence with the aid of state-of-the-art optimization tools can help in speeding up generic drug approvals, yet maintain reliability, repeatability, and adherence to regulatory regulations.

REFERENCES

1. Bellantone RA, Shah KB, Patel PG, Kaplan M, Xu X, Li V, et al. Cyclosporine release and distribution in ophthalmic emulsions determined by pulsatile microdialysis. Int J Pharm. 2022 Mar;5(615): 121521.
2. Choi SH, Lionberger RA. Clinical, pharmacokinetic, and in vitro studies to support bioequivalence of ophthalmic drug products. AAPS J. 2016 Jul;18(4):1032–8.
3. Zhao L, Seo P, Lionberger R. Current Scientific Considerations to Verify Physiologically-Based Pharmacokinetic Models and Their Implications for Locally Acting Products. CPT Pharmacomet Syst Pharmacol. 2019 Jun;8(6):347–51.
4. US. FDA. Orange book: approved drug products with therapeutic equivalence evaluations [internet]. 2022. Available from: https:// www.accessdata.fda.gov/scripts/cder/ob/. Accessed 1 Sept
5. Sager JE, Yu J, Ragueneau-Majlessi I, Isoherranen N. Physiologically Based Pharmacokinetic (PBPK) Modeling and Simulation Approaches: A Systematic Review of Published Models, Applications, and Model Verification. Drug Metab Dispos Biol Fate Chem. 2015 Nov;43(11):1823–37.
6. Miller NA, Reddy MB, Heikkinen AT, Lukacova V, Parrott N. Physiologically Based Pharmacokinetic Modelling for First-InHuman Predictions: An Updated Model Building Strategy Illustrated with Challenging Industry Case Studies. Clin Pharmacokinet. 2019 Jun 1;58(6):727–46.

Received: August 04 ,2025

Volume 38 No. 8s, 2025

ISSN: 1311-1728 (printed version); ISSN: 1314-8060 (on-line version)

7. Pepin XJH, Parrott N, Dressman J, Delvadia P, Mitra A, Zhang X, et al. Current State and Future Expectations of Translational Modeling Strategies to Support Drug Product Development, Manufacturing Changes and Controls: A Workshop Summary Report. J Pharm Sci. 2021 Feb;110(2):555–66.
8. K Y, Kollipara S, Ahmed T, Chachad S. Applications of PBPK/ PBBM modeling in generic product development: An indurstry perspective. J Drug Deliv Sci Technol. 2022;69:103152.
9. Worakul N, Robinson JR. Ocular pharmacokinetics/pharmacodynamics. Eur J Pharm Biopharm. 1997 Jul 1;44(1):71–83.
10. US.FDA C for DE and Generic Drug Research Priorities & Projects. FDA [Internet]. 2022 [cited 2022 Apr 26]. Available from: https://www.fda.gov/drugs/generic-drugs/generic-drugresearch-priorities-projects. Accessed 1 Sept.
11. Le Merdy M, Spires J, Lukacova V, Tan ML, Babiskin A, Xu X, et al. Ocular Physiologically Based Pharmacokinetic Modeling for Ointment Formulations. Pharm Res. 2020 Nov 19;37(12):245.
12. Le Merdy M, Tan ML, Babiskin A, Zhao L. Physiologically Based Pharmacokinetic Model to Support Ophthalmic Suspension Product Development. AAPS J. 2020 Jan 6;22(2):26.
13. Koeppe MO, Cristofoletti R, Fernandes EF, Storpirtis S, Junginger HE, Kopp S, et al. Biowaiver monographs for immediate release solid oral dosage forms: levofloxacin. J Pharm Sci. 2011 May;100(5):1628–36.
14. Stigliani M, Haghi M, Russo P, Young PM, Traini D. Antibiotic transport across bronchial epithelial cells: Effects of molecular weight, LogP and apparent permeability. Eur J Pharm Sci Off J Eur Fed Pharm Sci. 2016 Feb;15(83):45–51.
15. Kłosińska-Szmurło E, Pluciński FA, Grudzień M, BetlejewskaKielak K, Biernacka J, Mazurek AP. Experimental and theoretical studies on the molecular properties of ciprofloxacin, norfloxacin, pefloxacin, sparfloxacin, and gatifloxacin in determining bioavailability. J Biol Phys. 2014 Sep;40(4):335–45.
16. Destache CJ, Pakiz CB, Larsen C, Owens H, Dash AK. Cerebrospinal fluid penetration and pharmacokinetics of levofloxacin in an experimental rabbit meningitis model. J Antimicrob Chemother. 2001 May 1;47(5):611–5.
17. Dorn C, Nowak H, Weidemann C, Martini S, Zeitlinger M, Adamzik M, et al. Decreased protein binding of moxifloxacin in patients with sepsis? GMS Infect Dis [Internet].2017 [cited 2021 Feb 25]; 5. Available from: https://www.ncbi.nlm.nih.gov/pmc/ articles/PMC6301732/. Accessed 1 Sept.
18. US.FDA. TEQUIN® FDA Label [Internet]. 2013. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2004/ 21061s023,024,21062s026,037lbl.pdf. Accessed 1 Sept.
19. Eedara BB, Tucker IG, Zujovic ZD, Rades T, Price JR, Das SC. Crystalline adduct of moxifloxacin with trans-cinnamic acid to reduce the aqueous solubility and dissolution rate for improved residence time in the lungs. Eur J Pharm Sci Off J Eur Fed Pharm Sci. 2019 Aug;1(136): 104961.
20. Gatifloxacin [Internet]. [cited 2022 Mar 1]. Available from: https://go.drugbank.com/drugs/DB01044. Accessed 1 Sept.
21. Koeppe MO, Cristofoletti R, Fernandes EF, Storpirtis S, Junginger HE, Kopp S, et al. Biowaiver monographs for immediate release solid oral dosage forms: Levofloxacin. J Pharm Sci. 2011;100(5):1628–36.
22. Lukacova V, Parrott NJ, Fraczkiewicz G, Bolger MB, Woltosz WS. General approach to calculation of tissue: plasma partition coefficients for physiologically based pharmacokinetic (PBPK) modeling. AAPS Annual Meeting; 2008; Atlanta.

Received: August 04 ,2025

Volume 38 No. 8s, 2025

ISSN: 1311-1728 (printed version); ISSN: 1314-8060 (on-line version)

23. US. FDA. AVELOX (moxifloxacin hydrochloride) tablets, for oral use FDA Label [Internet]. 2016. Available from: https://www. accessdata.fda.gov/drugsatfda_docs/label/2016/021085s063lbl. pdf. Accessed 1 Sept.
24. Chockalingam A, Xu L, Stewart S, LeMerdy M, Tsakalozou E, Fan J, et al. Protocol for evaluation of topical ophthalmic drug products in different compartments of fresh eye tissues in a rabbit model. J Pharmacol Toxicol Methods. 2019 Apr;96:9–14.
25. Zaharia AC, Dumitrescu OM, Rogoz RE, Dimirache AE, Zemba M. Preoperative antisepsis in ophthalmic surgery (a review). Romanian J Ophthalmol. 2021;65(2):120–4.
26. Kumar CM, Seet E, Eke T, Irwin MG, Joshi GP. Peri-operative considerations for sedation-analgesia during cataract surgery: a narrative review. Anaesthesia. 2019 Dec;74(12):1601–10.
27. Gower EW, Lindsley K, Nanji AA, Leyngold I, McDonnell PJ. Perioperative antibiotics for prevention of acute endophthalmitis after cataract surgery. Cochrane Database Syst Rev. 2013;15(7):CD006364.
28. George O, Omokhua P. Comparative Analysis Of The Effects Of Topical Anaesthetic Agents On Tear Quantity And Tear Quality. J Niger Optom Assoc. 2010;16:30–3. 33 Jordan A, Baum J. Basic tear flow Does it exist? Ophthalmology. 1980;87(9):920–30.
29. Li Y, Fan AZ, Balluz LS. Visual impairment and age-related eye diseases in Florida: Findings from 2006 Behavioral Risk Factors Surveillance System (BRFSS) in Nine states. Risk Manag Healthc Policy. 2009;2:65–71.
30. Karakosta C, Tzamalis A, Aivaliotis M, Tsinopoulos I. Pathogenesis of age-related cataract: a systematic review of proteomic studies. Curr Proteomics. 18(4):458–66.
31. Nättinen J, Jylhä A, Aapola U, Mäkinen P, Beuerman R, Pietilä J, et al. Age-associated changes in human tear proteome. Clin Proteomics. 2019 Mar 30;16(1):11.
32. Ozdemir M, Temizdemir H. Age- and gender-related tear function changes in normal population. Eye. 2010 Jan;24(1):79–83.
33. Micera A, Di Zazzo A, Esposito G, Longo R, Foulsham W, Sacco R, et al. Age-Related Changes to Human Tear Composition. Invest Ophthalmol Vis Sci. 2018 Apr 1;59(5):2024–31.
34. Singh R, Gupta N, Vanathi M, Tandon R. Corneal transplantation in the modern era. Indian J Med Res. 2019 Jul;150(1):7–22.
35. Al-Yousuf N, Mavrikakis I, Mavrikakis E, Daya SM. Penetrating keratoplasty: indications over a 10 year period. Br J Ophthalmol. 2004 Aug 1;88(8):998–1001.
36. Rimpelä AK, Reinisalo M, Hellinen L, Grazhdankin E, Kidron H, Urtti A, et al. Implications of melanin binding in ocular drug delivery. Adv Drug Deliv Rev. 2018 Feb;15(126):23–43.
37. Durairaj C, Chastain JE, Kompella UB. Intraocular distribution of melanin in human, monkey, rabbit, minipig and dog eyes. Exp Eye Res. 2012 May;98:23–7.

Received: August 04 ,2025