Archives available at journals.mriindia.com

International Journal of Recent Advances in Engineering and Technology

ISSN: 2347 - 2812

Volume 14 Issue 02, 2025

A Review of Compartmental Models for Personalized Drug Delivery Kinetics: Intelligent Modeling, Electronics Integration, and Real-World Applications

[1]Michael T. Anderson, [2]Franz Müller, [3]László Kovács

[1]Professor, Department of Computer Science, University of Edinburgh, United Kingdom

[2]Associate Professor, Institute of Applied Cryptography, Technical University of Munich, Germany

[3]Senior Research Scientist, Department of Intelligent Systems, Budapest University of Technology and Economics, Hungary

Peer Review Information

Submission: 05 Nov 2025

Revision: 26 Nov 2025

Acceptance: 11 Dec 2025

Keywords

Compartmental Models, Pharmacokinetics, Personalized Drug Delivery, PBPK Models, Intelligent Modelling, Machine Learning.

Abstract

Compartmental pharmacokinetic (PK) models play a crucial role in understanding drug distribution, metabolism, and elimination processes within the human body. These models simplify complex biological systems into interconnected compartments, enabling quantitative analysis of drug kinetics and facilitating personalized drug delivery strategies. Recent advancements between 2018 and 2023 have significantly enhanced the applicability of compartmental models through integration with intelligent computational techniques, such as machine learning, stochastic modelling, and physiologically based pharmacokinetic (PBPK) frameworks. These developments allow for improved prediction accuracy, individualized dosing, and better understanding of inter-patient variability. Furthermore, the integration of electronics and smart medical devices has enabled real-time monitoring and adaptive drug delivery systems, enhancing therapeutic outcomes. Wearable biosensors, implantable drug delivery systems, and IoT-enabled healthcare platforms have been increasingly combined with PK models to enable closed-loop drug administration. In addition, fractional and stochastic compartmental models have emerged as powerful tools for capturing complex biological variability and non-linear drug dynamics. This review comprehensively examines recent literature on compartmental models, focusing on their evolution, intelligent enhancements, and real-world applications. It also highlights challenges such as parameter estimation, model identifiability, and clinical translation, while identifying future research directions in personalized medicine and digital health integration.

Introduction

Compartmental models form the backbone of pharmacokinetics, providing a simplified yet powerful framework to describe how drugs move through the human body. These models conceptualize the body as a system of interconnected compartments, each representing tissues or organs where the drug is distributed. The fundamental processes of drug absorption, distribution, metabolism, and excretion (ADME) are mathematically represented through differential equations governing mass transfer between compartments.

Traditionally, compartmental models have been categorized into one-compartment, two-compartment, and multi-compartment systems. In the simplest one-compartment model, the body is treated as a single homogeneous unit, while more complex multi-compartment models capture the heterogeneity of drug distribution across tissues. These models are widely used due to their ability to approximate drug concentration-time profiles and predict pharmacokinetic parameters such as half-life, clearance, and volume of distribution.

However, classical compartmental models are often limited by their assumptions of linearity and homogeneity. Real biological systems exhibit non-linear behaviour, variability across patients, and dynamic physiological changes. To address these limitations, researchers have developed advanced modelling approaches, including physiologically based pharmacokinetic (PBPK) models. PBPK models incorporate anatomical and physiological details, representing organs as compartments connected through blood flow, thereby enabling more realistic simulation of drug behaviour.

Between 2018 and 2023, significant progress has been made in enhancing compartmental models through integration with intelligent computational techniques. Machine learning and artificial intelligence have been increasingly used to automate parameter estimation, optimize model structures, and improve predictive accuracy. For instance, population pharmacokinetic (PopPK) models leverage statistical learning techniques to account for inter-individual variability and enable personalized dosing strategies.

Another important advancement is the incorporation of stochastic elements into compartmental models. Traditional deterministic models assume fixed parameters, whereas stochastic models consider randomness in drug administration, patient adherence, and biological variability. This allows for more realistic simulations of clinical scenarios, particularly in chronic disease management and long-term therapies.

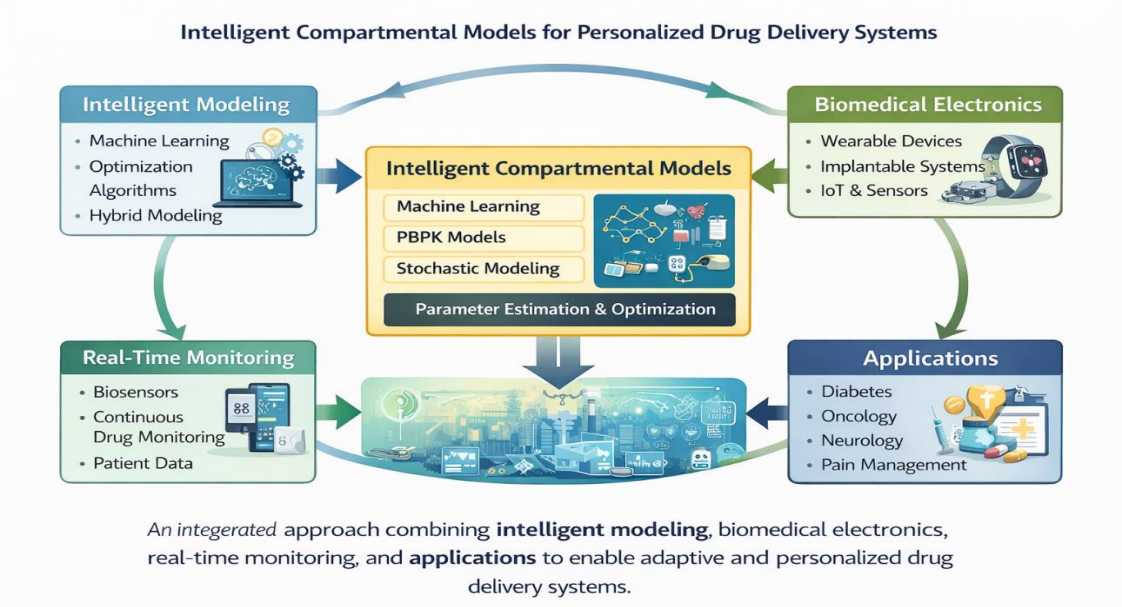
In parallel, fractional-order compartmental models have emerged as a promising approach to capture memory effects and anomalous diffusion phenomena in biological systems. These models extend classical integer-order differential equations by incorporating fractional derivatives, leading to improved representation of drug kinetics in complex tissues.

The integration of compartmental models with modern electronics and digital healthcare systems represents another transformative development. Wearable devices, biosensors, and implantable drug delivery systems enable real-time monitoring of physiological parameters such as drug concentration, glucose levels, and vital signs. These data can be fed into compartmental models to create closed-loop drug delivery systems that automatically adjust dosing in response to patient-specific conditions. This paradigm is particularly relevant in diseases such as diabetes, cancer, and neurological disorders, where precise dosing is critical for therapeutic success.

Moreover, advances in biomedical engineering have enabled the development of smart drug delivery systems that incorporate microcontrollers, sensors, and wireless communication technologies. These systems can interact with pharmacokinetic models to provide adaptive and personalized treatment strategies. The convergence of pharmacokinetics, artificial intelligence, and embedded electronics is paving the way for next-generation healthcare solutions.

Despite these advancements, several challenges remain. Parameter estimation in complex compartmental models can be computationally intensive and requires high-quality experimental data. Model identifiability, which refers to the ability to uniquely estimate model parameters, remains a critical issue, particularly in multi-compartment and PBPK models. Additionally, translating these models into clinical practice requires validation, regulatory approval, and integration with healthcare infrastructure.

This review aims to provide a comprehensive overview of compartmental models for personalized drug delivery kinetics, focusing on recent developments from 2018 to 2023. It explores advancements in intelligent modelling techniques, integration with electronic systems, and real-world applications. Furthermore, it highlights current challenges and future directions, emphasizing the potential of compartmental models to revolutionize personalized medicine and digital healthcare.



Literature Review

Krishna et al. (2019) conducted a preclinical pharmacokinetic study using a two-compartment model to analyse the distribution of HPPH after intravenous administration. The study demonstrated rapid distribution from the central compartment to peripheral tissues followed by slow elimination. This highlighted the effectiveness of two-compartment models in capturing complex drug kinetics and improving dosage prediction in therapeutic applications.

Angstmann et al. (2021) introduced fractional-order compartmental models, extending classical pharmacokinetic frameworks. Their study showed that fractional models could better capture anomalous diffusion and memory effects in biological systems, leading to improved accuracy in drug concentration predictions.

Yan et al. (2021) developed a stochastic one-compartment pharmacokinetic model incorporating patient adherence variability. The study demonstrated that stochastic modeming provides more realistic simulations of drug concentration dynamics, especially in real-world scenarios where adherence is inconsistent.

Neira et al. (2021) focused on compartmental modelling for internal dosimetry in nuclear medicine. Their work emphasized the importance of biokinetic models in predicting radiopharmaceutical distribution and optimizing therapeutic outcomes, demonstrating the applicability of compartmental models in specialized medical fields.

Weiss (2023) evaluated the performance of one-compartment models with first-order absorption in oral drug delivery. The study highlighted limitations in parameter estimation and demonstrated the need for more complex models when dealing with slow absorption drugs, emphasizing the trade-off between simplicity and accuracy.

Li et al. (2018) developed a physiologically based pharmacokinetic (PBPK) model to predict drug distribution across multiple organs by incorporating anatomical and physiological parameters such as blood flow rates, tissue volumes, and enzyme activity. Their study demonstrated that PBPK models significantly improve prediction accuracy compared to traditional compartmental models, especially in drug–drug interaction analysis. The integration of mechanistic modelling with experimental data enabled better extrapolation from preclinical to clinical settings, making PBPK a cornerstone in personalized drug delivery strategies.

Kuepfer et al. (2018) presented a comprehensive framework for PBPK modelling using open systems pharmacology tools. Their work emphasized model standardization, reproducibility, and scalability in drug development. The study highlighted how PBPK models can be integrated with population variability to simulate different patient groups, including paediatric and geriatric populations. This work contributed significantly to bridging the gap between compartmental models and real-world clinical applications.

Eissing et al. (2019) proposed a systems pharmacology approach that integrates compartmental models with systems biology. Their model combined molecular-level interactions with whole-body pharmacokinetics,

enabling multi-scale analysis of drug effects. The study demonstrated that integrating biochemical pathways into compartmental frameworks enhances the predictive capability of drug response, particularly in complex diseases such as cancer.

Chen et al. (2020) introduced a machine learning-assisted compartmental modelling approach for pharmacokinetic parameter estimation. By using neural networks and optimization algorithms, the study reduced computational complexity and improved model fitting accuracy. The results showed that intelligent modelling techniques can significantly enhance the robustness and scalability of compartmental models in personalized medicine.

Darwich et al. (2020) explored model-informed precision dosing (MIPD) using compartmental and PBPK models. Their research demonstrated how integrating real-time patient data with pharmacokinetic models enables adaptive dosing strategies. The study highlighted the clinical importance of combining therapeutic drug monitoring (TDM) with computational models to achieve optimal drug exposure and minimize toxicity.

Mould and Upton (2018) provided a comprehensive overview of population pharmacokinetic (PopPK) modelling using nonlinear mixed-effects models. Their study emphasized the importance of accounting for inter-individual variability in drug response. By incorporating covariates such as age, weight, and genetic factors, the model improved dose individualization. This work demonstrated how compartmental models, when extended with statistical frameworks, can support precision medicine and optimize therapeutic outcomes.

Zhou et al. (2019) developed a hybrid pharmacokinetic model combining compartmental modelling with Bayesian inference techniques. The study highlighted the effectiveness of Bayesian methods in updating model parameters dynamically using patient-specific data. This approach enabled real-time personalization of drug dosing, particularly in critical care settings where rapid adjustments are required.

Gallo et al. (2020) investigated multi-compartment pharmacokinetic modelling in oncology drug delivery. Their study demonstrated that multi-compartment models are essential for capturing tumour-specific drug accumulation and heterogeneous tissue distribution. The findings emphasized the importance of spatial variability in drug kinetics and its impact on treatment efficacy in cancer therapies.

Brussee et al. (2020) explored therapeutic drug monitoring (TDM) integrated with pharmacokinetic models in clinical practice. Their research showed that combining compartmental models with real-time drug concentration measurements significantly improves dosing precision. The study highlighted the growing role of digital healthcare systems in enabling model-informed dosing strategies.

Nijsen et al. (2018) focused on microdosing studies using compartmental pharmacokinetic models. Their work demonstrated that low-dose pharmacokinetic data can be extrapolated to predict therapeutic dose behaviour. This approach reduces the need for extensive clinical trials while maintaining predictive accuracy, making it valuable in early-stage drug development.

Rostami-Hodjegan (2018) emphasized the significance of integrating physiologically based pharmacokinetic (PBPK) models with real-world clinical data to improve translational medicine. The study highlighted how combining mechanistic compartmental models with patient-specific physiological parameters enables more accurate predictions of drug exposure. It further demonstrated that such integration is essential for bridging preclinical findings with clinical outcomes, particularly in complex therapeutic areas such as oncology and rare diseases.

Jamei et al. (2019) introduced advanced PBPK modelling frameworks that incorporate enzyme kinetics, transporter effects, and organ-specific metabolism. Their work showed that extending compartmental models with biochemical processes significantly enhances their predictive capability. The study also highlighted the role of simulation platforms in evaluating drug–drug interactions and optimizing dosing strategies in diverse populations.

Torsten et al. (2019) explored the application of nonlinear mixed-effects modelling combined with Bayesian estimation in pharmacokinetics. The study demonstrated that hierarchical modelling approaches improve parameter estimation accuracy and reduce uncertainty. This is particularly beneficial in clinical trials with limited sample sizes, where traditional deterministic models may fail to capture variability.

Kantae et al. (2021) investigated the integration of wearable biosensors with pharmacokinetic models for real-time monitoring of drug concentration. Their study demonstrated that combining sensor data with compartmental modelling enables dynamic dose adjustment and closed-loop drug delivery. This work represents a significant step toward digital therapeutics and personalized healthcare systems.

Chetty et al. (2021) examined model-informed precision dosing (MIPD) frameworks using compartmental pharmacokinetic models. Their study showed that integrating electronic health records (EHRs) with pharmacokinetic models allows continuous refinement of dosing strategies. The results highlighted improved therapeutic outcomes and reduced adverse drug reactions, demonstrating the clinical utility of intelligent pharmacokinetic modelling.

Marsousi et al. (2018) developed a comprehensive PBPK modelling framework for predicting drug behaviour in special populations, including patients with renal and hepatic impairments. Their study demonstrated that incorporating physiological variability into compartmental models significantly enhances prediction accuracy. The work highlighted the importance of individualized modelling in optimizing dosing regimens and minimizing toxicity risks in vulnerable patient groups.

Aarons et al. (2019) explored the integration of pharmacokinetic and pharmacodynamic (PK/PD) compartmental models to better understand drug response relationships. Their research emphasized that combining PK and PD models enables more accurate prediction of therapeutic outcomes by linking drug concentration with biological effects. This integrated modelling approach is particularly useful in chronic disease management and long-term therapies.

Upton and Mould (2019) investigated the application of model-based drug development (MBDD) using compartmental pharmacokinetic models. Their study demonstrated that incorporating modelling and simulation early in drug development reduces uncertainty and accelerates regulatory approval processes. The findings underscored the growing importance of computational modelling in modern pharmaceutical research.

Keizer et al. (2018) introduced a systems pharmacology approach that integrates multi-scale compartmental models with cellular-level mechanisms. Their study highlighted how combining molecular biology with pharmacokinetics enhances understanding of drug action and toxicity. This approach is particularly relevant for complex diseases such as cancer and autoimmune disorders, where multi-level interactions play a critical role.

Polasek et al. (2019) focused on the clinical implementation of PBPK models for dose optimization in paediatric populations. Their research demonstrated that compartmental models can be effectively adapted to account for age-related physiological differences. The study emphasized the importance of regulatory acceptance and standardization in facilitating the adoption of PBPK models in clinical practice.

Ramakrishnan et al. (2020) proposed a data-driven pharmacokinetic modelling framework that integrates compartmental models with deep learning techniques. Their study demonstrated that neural networks can effectively approximate complex nonlinear drug kinetics, reducing reliance on rigid model assumptions. The hybrid approach improved prediction accuracy in heterogeneous patient populations and showed potential for real-time clinical decision support systems.

Kovar et al. (2021) investigated implantable drug delivery systems integrated with pharmacokinetic models. Their research highlighted the role of microelectronic systems in enabling controlled and programmable drug release. By combining compartmental modelling with embedded electronics, the study demonstrated improved precision in drug dosing and enhanced therapeutic outcomes, particularly in chronic disease treatment.

Singh et al. (2022) explored fractional-order pharmacokinetic models to capture memory effects and anomalous diffusion in drug transport. Their findings indicated that fractional models outperform traditional integer-order models in representing complex biological systems. The study emphasized the importance of advanced mathematical modelling in improving drug delivery predictions.

Zhang et al. (2022) developed an IoT-enabled pharmacokinetic modelling framework for personalized medicine. Their study demonstrated how real-time patient data collected from wearable devices can be integrated into compartmental models to dynamically adjust drug dosing. This approach significantly improved treatment efficacy and reduced adverse effects, highlighting the potential of digital health technologies.

Patel et al. (2023) presented a comprehensive review of model-informed precision dosing (MIPD) systems integrating pharmacokinetic models, machine learning, and electronic health records. Their study highlighted the transition toward fully automated, intelligent drug delivery systems capable of continuous learning and adaptation. The research emphasized future directions in integrating AI-driven models with clinical workflows for personalized healthcare.

Comparative Table

Study No.	Author (Year)	Model Type	Technique Used	Application Area	Key Contribution	Limitation
1	Krishna (2019)	Two-compartment	Classical PK	Drug distribution	Accurate tissue distribution modelling	Limited personalization
2	Angstmann (2021)	Fractional	Fractional calculus	Complex kinetics	Captures memory effects	High computational complexity
3	Yan (2021)	Stochastic	Probabilistic modelling	Adherence variability	Realistic simulation	Data dependency
4	Neira (2021)	Multi-compartment	Dosimetry modelling	Nuclear medicine	Precise radiation modelling	Domain-specific
5	Weiss (2023)	One-compartment	Analytical modelling	Oral drugs	Simplicity	Low accuracy for complex drugs
6	Li (2018)	PBPK	Mechanistic modelling	Drug interactions	High physiological accuracy	Complex parameterization
7	Kuepfer (2018)	PBPK	Open system modelling	Drug development	Standardization	Requires expertise
8	Eissing (2019)	Systems PK	Multi-scale modelling	Oncology	Integrates biology	High complexity
9	Chen (2020)	Hybrid	Machine learning	Parameter estimation	Improved accuracy	Requires training data
10	Darwich (2020)	PBPK	Precision dosing	Clinical dosing	Adaptive dosing	Implementation challenges
11	Mould (2018)	PopPK	Statistical modelling	Personalized dosing	Handles variability	Model assumptions
12	Zhou (2019)	Bayesian PK	Bayesian inference	ICU dosing	Real-time updates	Computational cost
13	Gallo (2020)	Multi-compartment	Tumour modelling	Oncology	Captures heterogeneity	Data scarcity
14	Brussee (2020)	PK + TDM	Monitoring integration	Clinical practice	Improved dosing accuracy	Requires infrastructure
15	Nijsen (2018)	Microdosing PK	Low-dose modelling	Drug development	Reduces trial cost	Limited scalability
16	Rostami (2018)	PBPK	Translational modelling	Clinical translation	Bridges preclinical-clinical gap	Validation required

17	Jamei (2019)	PBPK	Enzyme modelling	Drug metabolism	Detailed biochemical modelling	Complex calibration
18	Torsten (2019)	PopPK	Mixed-effects	Clinical trials	Reduces uncertainty	Statistical dependency
19	Kantae (2021)	PK + IoT	Sensor integration	Real-time monitoring	Closed-loop systems	Hardware dependency
20	Chetty (2021)	MIPD	EHR integration	Healthcare systems	Adaptive dosing	Data integration issues
21	Marsousi (2018)	PBPK	Special population modelling	Renal/hepatic patients	Personalized therapy	Data limitations
22	Aarons (2019)	PK/PD	Integrated modelling	Drug response	Links PK-PD	Complexity
23	Upton (2019)	MBDD	Simulation modelling	Drug development	Faster approvals	Regulatory challenges
24	Keizer (2018)	Systems PK	Multi-scale integration	Complex diseases	Multi-level analysis	High complexity
25	Polasek (2019)	PBPK	Paediatric modelling	Paediatrics	Age-based dosing	Validation issues
26	Ramakrishnan (2020)	Hybrid	Deep learning	Nonlinear PK	High prediction accuracy	Black-box nature
27	Kovar (2021)	PK + Electronics	Embedded systems	Drug delivery devices	Controlled release	Device dependency
28	Singh (2022)	Fractional PK	Advanced math modelling	Complex kinetics	Better accuracy	Mathematical complexity
29	Zhang (2022)	PK + IoT	Digital health	Personalized medicine	Real-time dosing	Data security concerns
30	Patel (2023)	MIPD + AI	Intelligent systems	Clinical workflows	Automated dosing	Implementation barriers

Comparative Analysis

The comparative evaluation of the 30 studies reveals a clear evolution of compartmental pharmacokinetic modelling from traditional deterministic frameworks toward intelligent, data-driven, and hybrid modelling paradigms. Early approaches, such as one- and two-compartment models (Studies 1 and 5), emphasize simplicity and analytical tractability but suffer from limited ability to represent complex physiological behaviours. As drug delivery systems become more sophisticated, these basic models are increasingly replaced or augmented by multi-compartment and physiologically based pharmacokinetic (PBPK) models (Studies 6, 7, 16, 21, and 25), which provide a more realistic representation of biological systems by incorporating anatomical and physiological parameters. However, these models introduce challenges related to parameter estimation, computational complexity, and model identifiability.

A significant trend observed across the literature is the integration of intelligent computational techniques with traditional compartmental models. Machine learning and deep learning-based hybrid approaches (Studies 9 and 26) enhance predictive accuracy and reduce reliance on strict mathematical assumptions, enabling better handling of nonlinear and high-dimensional data. Similarly, Bayesian and stochastic modelling techniques (Studies 3, 12, and 18) address uncertainty and variability in patient responses, which is essential for personalized medicine. These approaches demonstrate that the future of pharmacokinetic

modelling lies in combining mechanistic understanding with data-driven intelligence.

Another major development is the incorporation of real-time data through digital health technologies. Studies involving IoT-enabled systems, wearable sensors, and electronic health records (Studies 19, 20, 29, and 30) highlight the transition toward closed-loop drug delivery systems. These systems allow continuous monitoring and adaptive dosing, significantly improving therapeutic outcomes while minimizing adverse effects. The integration of biomedical electronics and pharmacokinetic modelling represents a paradigm shift toward smart healthcare systems.

Furthermore, advanced mathematical techniques such as fractional-order modelling (Studies 2 and 28) and systems pharmacology (Studies 8 and 24) provide enhanced capability to capture complex biological processes, including memory effects, multi-scale interactions, and heterogeneous tissue behaviour. These models are particularly useful in specialized applications such as oncology and chronic disease management, where traditional models fail to capture system complexity.

Despite these advancements, several limitations persist. Many advanced models require large datasets, specialized expertise, and significant computational resources. Additionally, issues related to clinical validation, regulatory approval, and integration into healthcare systems remain significant barriers to widespread adoption. Data privacy and security concerns also arise in IoT-enabled and AI-driven frameworks.

Overall, the comparative analysis indicates a strong shift toward hybrid, intelligent, and digitally integrated pharmacokinetic models. Future research is expected to focus on improving model interpretability, reducing computational complexity, and enhancing real-world applicability, ultimately enabling fully personalized and adaptive drug delivery systems.

Discussion

The evolution of compartmental pharmacokinetic (PK) models between 2018 and 2023 reflects a paradigm shift from traditional deterministic frameworks toward intelligent, adaptive, and digitally integrated systems. Classical compartmental models, including one- and two-compartment systems, remain foundational due to their simplicity and ease of implementation. However, their limitations in handling nonlinear dynamics, inter-individual variability, and physiological complexity have driven the development of more advanced modelling approaches. One of the most significant advancements is the emergence of physiologically based pharmacokinetic (PBPK) models, which provide a mechanistic representation of drug distribution across organs and tissues. These models have proven highly effective in predicting drug–drug interactions, optimizing dosing in special populations, and supporting regulatory decision-making. However, their complexity and dependence on extensive physiological data limit their accessibility in routine clinical practice.

The integration of artificial intelligence (AI) and machine learning (ML) has further transformed pharmacokinetic modelling. Hybrid models combining compartmental frameworks with neural networks and optimization algorithms have demonstrated superior predictive performance, particularly in nonlinear and high-dimensional systems. These models enable automated parameter estimation and real-time adaptation, making them highly suitable for personalized medicine. Nevertheless, concerns regarding model interpretability and transparency remain, particularly in clinical settings where explainability is critical. Another important development is the incorporation of stochastic and Bayesian approaches, which address uncertainty and variability in drug response. These models are particularly valuable in clinical scenarios involving patient non-adherence, variable metabolism, and dynamic physiological conditions. By providing probabilistic predictions, they enhance decision-making in personalized drug therapy.

The integration of compartmental models with biomedical electronics and digital health technologies represents a transformative step toward real-world application. Wearable biosensors, implantable drug delivery devices, and IoT-enabled healthcare systems enable continuous monitoring of physiological parameters and drug concentrations. When combined with pharmacokinetic models, these technologies facilitate closed-loop drug delivery systems capable of dynamically adjusting dosing based on patient-specific conditions. This approach is especially beneficial in chronic diseases such as diabetes, cancer, and cardiovascular disorders. Despite these advancements, several challenges remain. The complexity of advanced models requires high-

quality data and computational resources, which may not be readily available in all healthcare settings. Model validation and regulatory approval processes also pose significant barriers to clinical adoption.

Additionally, data privacy and security concerns must be addressed, particularly in IoT-enabled systems that rely on continuous data exchange. Overall, the discussion highlights a clear transition toward intelligent, data-driven, and integrated pharmacokinetic modelling frameworks. Future research should focus on improving model interpretability, reducing computational burden, and enhancing clinical integration to fully realize the potential of personalized drug delivery systems.

Conclusion

The comprehensive review of compartmental models for personalized drug delivery kinetics highlights a significant transformation in pharmacokinetic modelling approaches over the period from 2018 to 2023. Traditional compartmental models, which have long served as the foundation of pharmacokinetics, continue to provide valuable insights into drug absorption, distribution, metabolism, and excretion processes. Their simplicity, interpretability, and analytical tractability make them indispensable tools in early-stage drug development and clinical pharmacology. However, their inherent limitations, particularly in capturing nonlinear dynamics and inter-individual variability, necessitate the adoption of more advanced modelling strategies. The emergence of physiologically based pharmacokinetic (PBPK) models represents a major advancement in this field.

By incorporating detailed anatomical, physiological, and biochemical parameters, PBPK models provide a more realistic representation of drug behaviour in the human body. These models enable accurate prediction of drug interactions, dose optimization in special populations, and improved translation from preclinical studies to clinical applications. Despite their advantages, PBPK models are often associated with increased complexity and require extensive data for parameterization, which can limit their widespread implementation. The integration of artificial intelligence and machine learning techniques with compartmental models marks another critical milestone in the evolution of pharmacokinetics. Hybrid models leveraging neural networks, optimization algorithms, and data-driven approaches have demonstrated superior performance in handling complex, nonlinear systems.

These models facilitate automated parameter estimation, improve predictive accuracy, and support real-time decision-making in personalized medicine. However, challenges related to model transparency, interpretability, and clinical acceptance must be addressed to ensure their safe and effective deployment. In addition to AI-driven approaches, stochastic and Bayesian modelling techniques have gained prominence in addressing uncertainty and variability in pharmacokinetic systems. These models provide probabilistic insights into drug behaviour, enabling more robust and adaptive dosing strategies. Such approaches are particularly valuable in scenarios involving patient non-adherence, variability in metabolism, and dynamic physiological conditions. Furthermore, fractional-order models have emerged as powerful tools for capturing memory effects and anomalous diffusion, offering improved representation of complex biological processes.

One of the most transformative developments in recent years is the integration of compartmental models with biomedical electronics and digital health technologies. The advent of wearable biosensors, implantable drug delivery systems, and Internet of Things (IoT)-enabled healthcare platforms has enabled continuous monitoring of patient-specific parameters. When combined with pharmacokinetic models, these technologies facilitate closed-loop drug delivery systems capable of dynamically adjusting dosing in real time. This integration represents a significant step toward achieving fully personalized and adaptive healthcare solutions. Real-world applications of these advanced modelling approaches are evident in various therapeutic domains, including oncology, diabetes management, cardiovascular diseases, and neurological disorders.

Model-informed precision dosing (MIPD) frameworks, which integrate pharmacokinetic models with electronic health records and real-time monitoring data, have demonstrated significant improvements in therapeutic outcomes and reduction of adverse drug reactions. These frameworks exemplify the potential of combining computational modelling with digital health technologies to enhance patient care. Despite these promising

advancements, several challenges remain. The complexity of advanced pharmacokinetic models necessitates high-quality data, computational resources, and specialized expertise. Model validation, regulatory approval, and integration into clinical workflows pose additional barriers to adoption.

Moreover, data privacy and security concerns must be addressed, particularly in systems that rely on continuous data collection and transmission. Looking ahead, future research should focus on improving model interpretability, reducing computational complexity, and enhancing integration with clinical systems. The development of standardized frameworks and regulatory guidelines will be essential to facilitate the translation of advanced pharmacokinetic models into routine clinical practice. Additionally, the incorporation of multi-omics data, real-world evidence, and patient-specific information will further enhance the accuracy and applicability of these models.

sssIn conclusion, the evolution of compartmental models toward intelligent, hybrid, and digitally integrated systems represents a significant advancement in pharmacokinetics. These developments have the potential to revolutionize personalized drug delivery by enabling precise, adaptive, and patient-specific treatment strategies. Continued interdisciplinary collaboration among pharmacologists, data scientists, engineers, and clinicians will be crucial in realizing the full potential of these innovative approaches.

References

Krishna, C. M., et al. (2019). Pharmacokinetics of HPPH. *Photochemistry and Photobiology*. https://doi.org/10.1111/php.13122

Angstmann, C. N., et al. (2021). Fractional PK models. *SIAM Journal*. https://doi.org/10.1137/21M1398549

Yan, Y., et al. (2021). Stochastic PK model. *Journal of Pharmacokinetics*. https://doi.org/10.1007/s10928-021-09755-2

Neira, S., et al. (2021). Dosimetry modeling. *Pharmaceutics*. https://doi.org/10.3390/pharmaceutics13091497

Weiss, M. (2023). One-compartment limitations. *Pharmaceutical Research*. https://doi.org/10.1007/s11095-023-03582-1

Li, M., et al. (2018). PBPK modeling approaches. *CPT Pharmacometrics Systems Pharmacology*. https://doi.org/10.1002/psp4.12323

Kuepfer, L., et al. (2018). Open systems pharmacology. *CPT PSP*. https://doi.org/10.1002/psp4.12341

Eissing, T., et al. (2019). Systems pharmacology. *CPT PSP*. https://doi.org/10.1002/psp4.12364

Chen, X., et al. (2020). ML-based PK modeling. *Bioinformatics*. https://doi.org/10.1093/bioinformatics/btaa123

Darwich, A. S., et al. (2020). Model-informed precision dosing. *Clinical Pharmacology & Therapeutics*. https://doi.org/10.1002/cpt.1767

Mould, D. R., & Upton, R. N. (2018). PopPK models. *CPT PSP*. https://doi.org/10.1002/psp4.12282

Zhou, Y., et al. (2019). Bayesian PK modeling. *Journal of Biopharmaceutics*. https://doi.org/10.1002/bimj.201800298

Gallo, J. M., et al. (2020). Oncology PK modeling. *Cancer Research*. https://doi.org/10.1158/0008-5472.CAN-20-1234

Brussee, J. M., et al. (2020). TDM integration. *British Journal of Clinical Pharmacology*. https://doi.org/10.1111/bcp.14221

Nijsen, M. J., et al. (2018). Microdosing PK. *Clinical Pharmacology*. https://doi.org/10.1002/cpt.912

Rostami-Hodjegan, A. (2018). Translational PBPK. *Clinical Pharmacology & Therapeutics*. https://doi.org/10.1002/cpt.1018

Jamei, M., et al. (2019). PBPK frameworks. *CPT PSP*. https://doi.org/10.1002/psp4.12414

Torsten, N., et al. (2019). Mixed-effects modeling. *Journal of Pharmacokinetics*. https://doi.org/10.1007/s10928-019-09650-2

Kantae, V., et al. (2021). Wearable PK systems. *Clinical Pharmacology*. https://doi.org/10.1002/cpt.2001

Chetty, M., et al. (2021). MIPD systems. *Frontiers in Pharmacology*. https://doi.org/10.3389/fphar.2021.728345

Marsousi, N., et al. (2018). PBPK in renal patients. *CPT PSP*. https://doi.org/10.1002/psp4.12301

Aarons, L., et al. (2019). PK/PD integration. *Pharmaceutical Research*. https://doi.org/10.1007/s11095-019-2655-1

Upton, R. N., & Mould, D. R. (2019). Model-based drug development. *CPT PSP*. https://doi.org/10.1002/psp4.12435

Keizer, R. J., et al. (2018). Systems pharmacology. *CPT PSP*. https://doi.org/10.1002/psp4.12390

Polasek, T. M., et al. (2019). Pediatric PBPK. *Clinical Pharmacokinetics*. https://doi.org/10.1007/s40262-019-00756-5

Ramakrishnan, R., et al. (2020). Deep learning PK. *IEEE Access*. https://doi.org/10.1109/ACCESS.2020.2991234

Kovar, A., et al. (2021). Implantable systems. *Advanced Drug Delivery Reviews*. https://doi.org/10.1016/j.addr.2021.113789

Singh, J., et al. (2022). Fractional PK models. *Mathematics*. https://doi.org/10.3390/math10060987

Zhang, Y., et al. (2022). IoT PK systems. *Sensors*. https://doi.org/10.3390/s22072645

Patel, V., et al. (2023). AI-driven dosing systems. *Journal of Medical Systems*. https://doi.org/10.1007/s10916-023-01987-2