International Journal of Unique and New Updates (IJUNU)
Volume 4, Issue 1, January-June, 2022, Available online at: www.ijunu.com

# Optimizing Drug Dosage Regimens Using Pharmacokinetic/Pharmacodynamic Modeling

**Dr. Christine Kooper**

Dept. of Pharmaceutical Sciences, University of Toronto, Canada

**Article history:** Received: 18 December 2021, Accepted: 9 January 2022, Published online: 15 January 2022

## ABSTRACT

**In the field of pharmacology, optimizing drug dosage regimens is essential for achieving therapeutic efficacy while minimizing adverse effects. Pharmacokinetic/pharmacodynamic (PK/PD) modeling has emerged as a powerful tool to guide dosage regimen optimization by integrating data on drug concentration-time profiles (pharmacokinetics) and drug effects (pharmacodynamics). This abstract provides an overview of the principles and applications of PK/PD modeling in drug dosage regimen optimization. First, the basic concepts of pharmacokinetics and pharmacodynamics are outlined, emphasizing their interplay in determining drug concentrations at the site of action and subsequent pharmacological effects. PK/PD modeling involves mathematical representation of these processes, enabling quantitative prediction of drug concentrations and responses over time. The utility of PK/PD modeling in optimizing drug dosage regimens is exemplified across various therapeutic areas, including infectious diseases, oncology, and anesthesia. By characterizing the relationship between drug exposure and response, PK/PD models facilitate the identification of optimal dosing strategies to achieve desired therapeutic outcomes while avoiding toxicity or therapeutic failure. Moreover, PK/PD modeling allows for personalized dosing regimens by accounting for interindividual variability in pharmacokinetics and pharmacodynamics. Furthermore, PK/PD modeling plays a crucial role in drug development, informing decisions regarding dose selection, regimen design, and the evaluation of drug-drug interactions. Integration of PK/PD modeling into clinical practice enhances the precision and efficiency of therapeutic interventions, leading to improved patient outcomes and reduced healthcare costs. In conclusion, pharmacokinetic/pharmacodynamic modeling represents a valuable approach for optimizing drug dosage regimens, offering insights into the relationship between drug exposure and response. Its application spans from drug development to clinical practice, contributing to personalized medicine and therapeutic optimization across diverse medical conditions.**

**Keywords: Pharmacokinetics, Pharmacodynamics, Drug dosage optimization, PK/PD modeling, Therapeutic efficacy.**

## INTRODUCTION

Optimizing drug dosage regimens is a fundamental aspect of pharmacotherapy aimed at achieving maximal therapeutic benefits while minimizing adverse effects. The discipline of pharmacokinetics (PK) focuses on understanding the time course of drug absorption, distribution, metabolism, and excretion within the body, while pharmacodynamics (PD) elucidates the relationship between drug concentrations and pharmacological effects. The integration of PK and PD principles through pharmacokinetic/pharmacodynamic (PK/PD) modeling provides a systematic framework for quantitatively assessing the relationship between drug exposure and response.

The importance of optimizing drug dosage regimens cannot be overstated, as suboptimal dosing may lead to treatment failure, development of drug resistance, or unwanted toxicity. Traditional dosing approaches often rely on empirical strategies or population averages, which may not adequately account for individual variability in drug response. In contrast, PK/PD modeling offers a tailored approach to dosing optimization by leveraging mathematical modeling techniques to predict drug concentrations at the site of action and subsequent pharmacological effects. This introduction sets the stage for exploring the principles and applications of PK/PD modeling in optimizing drug dosage regimens across various therapeutic areas. By elucidating the intricate interplay between drug exposure and response, PK/PD modeling holds promise for enhancing therapeutic outcomes, advancing personalized medicine, and optimizing drug development processes.

## LITERATURE REVIEW

Pharmacokinetic/pharmacodynamic (PK/PD) modeling has gained widespread recognition as a valuable tool for optimizing drug dosage regimens across diverse therapeutic areas. The literature on PK/PD modeling encompasses a broad spectrum of applications, ranging from drug development to clinical practice, and highlights its pivotal role in advancing pharmacotherapy. One of the key strengths of PK/PD modeling lies in its ability to characterize the complex relationship between drug exposure and response. Numerous studies have demonstrated the utility of PK/PD modeling in elucidating the pharmacokinetic-pharmacodynamic profiles of various drugs, including antibiotics, anticancer agents, and analgesics. By quantitatively linking drug concentrations to pharmacological effects, PK/PD models facilitate the identification of optimal dosing regimens that maximize efficacy while minimizing toxicity.

In infectious diseases, PK/PD modeling has emerged as a valuable tool for optimizing antibiotic therapy. Studies have utilized PK/PD modeling to determine the pharmacokinetic parameters associated with bacterial killing and to establish dosing regimens that achieve optimal antimicrobial activity. Similarly, in oncology, PK/PD modeling plays a critical role in guiding chemotherapy dosing, with the aim of maximizing tumor response while minimizing systemic toxicity.
The application of PK/PD modeling extends beyond traditional therapeutic areas to include niche fields such as anesthesia and critical care medicine. In these settings, PK/PD modeling is used to tailor drug dosing to individual patient characteristics and clinical scenarios, thereby optimizing anesthesia induction, sedation, and pain management.
Moreover, PK/PD modeling contributes significantly to drug development by informing dose selection, regimen design, and the evaluation of drug-drug interactions. By integrating preclinical and clinical data, PK/PD models provide valuable insights into drug exposure-response relationships, facilitating rational decision-making throughout the drug development process.

Despite its numerous advantages, challenges remain in the widespread adoption of PK/PD modeling in clinical practice. These include the need for robust pharmacokinetic and pharmacodynamic data, as well as the complexity of model development and validation. Nevertheless, ongoing advancements in modeling techniques and computational tools are poised to overcome these challenges, further enhancing the utility of PK/PD modeling in optimizing drug dosage regimens.

In summary, the literature underscores the pivotal role of PK/PD modeling in optimizing drug dosage regimens across various therapeutic areas. By providing a quantitative framework for understanding drug exposure-response relationships, PK/PD modeling holds promise for advancing personalized medicine, improving therapeutic outcomes, and optimizing drug development processes.

## RECENT METHODS

**Mechanism-Based Modeling**: Mechanism-based PK/PD modeling integrates detailed mechanistic insights into drug action, including molecular interactions, signaling pathways, and physiological processes. By capturing the underlying biological mechanisms driving drug response, these models offer a more comprehensive understanding of drug effects and enable the prediction of outcomes under diverse physiological conditions.

**Population Pharmacokinetics**: Population pharmacokinetic modeling leverages data from large patient cohorts to characterize interindividual variability in drug pharmacokinetics. Recent advances in this field include the use of nonlinear mixed-effects modeling and Bayesian approaches to account for covariates such as age, weight, genetics, and disease status. Population pharmacokinetic models enable the estimation of population-wide pharmacokinetic parameters and facilitate personalized dosing recommendations based on individual patient characteristics.

**Quantitative Systems Pharmacology (QSP)**: Quantitative systems pharmacology integrates computational modeling with experimental data to elucidate the complex interactions between drugs, biological systems, and disease processes. QSP models capture the dynamics of drug distribution, target engagement, and downstream effects at multiple scales, from molecular pathways to physiological systems. By simulating the effects of drug interventions in silico, QSP facilitates hypothesis generation, drug discovery, and the optimization of therapeutic strategies.

**Model-Informed Precision Dosing (MIPD)**: Model-informed precision dosing combines pharmacokinetic modeling with individual patient data to optimize drug dosing regimens on a personalized basis. Recent developments in this area include the integration of patient-specific covariates, such as genetic polymorphisms and biomarker measurements, to tailor dosing recommendations to individual patient profiles. MIPD approaches enable the optimization of drug therapy based on factors such as age, renal function, hepatic function, and concomitant medications, thereby maximizing therapeutic efficacy while minimizing the risk of adverse events.

**Machine Learning and Artificial Intelligence**: Machine learning and artificial intelligence techniques are increasingly being applied to PK/PD modeling to handle large datasets, identify complex patterns, and predict drug response. Recent advances include the use of deep learning algorithms for drug discovery, virtual screening, and the prediction of pharmacokinetic properties. Machine learning approaches enhance the predictive accuracy of PK/PD models and enable the identification of novel drug targets, biomarkers, and therapeutic strategies.

In conclusion, recent methods in PK/PD modeling are driving innovation in dosage regimen optimization by leveraging mechanistic insights, population data, systems biology approaches, precision medicine principles, and computational techniques. These advancements hold promise for improving therapeutic outcomes, accelerating drug development, and advancing personalized medicine across a wide range of therapeutic areas.

## PROPOSED METHODOLOGY

The proposed methodology for optimizing drug dosage regimens using pharmacokinetic/pharmacodynamic (PK/PD) modeling involves a systematic approach that integrates data collection, model development, validation, and application in clinical practice. The following steps outline the proposed methodology:

**Data Collection and Preprocessing**:

[1]. Gather pharmacokinetic and pharmacodynamic data from preclinical studies, clinical trials, or real-world patient data.
[2]. Ensure data quality by addressing issues such as missing values, outliers, and measurement errors.
[3]. Collect additional patient-specific covariates, such as age, weight, genetics, and disease status, if applicable.

**Model Selection and Development**:

[1]. Choose an appropriate PK/PD model structure based on the drug's pharmacokinetic and pharmacodynamic properties.
[2]. Develop mechanistic PK/PD models that incorporate physiological processes, drug-receptor interactions, and downstream effects.
[3]. Utilize population pharmacokinetic modeling techniques to account for interindividual variability and covariate effects.
[4]. Employ machine learning algorithms for data-driven modeling approaches, if warranted by the complexity of the data.

**Parameter Estimation and Model Fitting**:

[1]. Estimate model parameters using nonlinear regression techniques, maximum likelihood estimation, or Bayesian inference methods.
[2]. Validate the model using goodness-of-fit criteria, such as visual inspection, residual analysis, and diagnostic plots.
[3]. Perform sensitivity analysis to assess the robustness of model predictions to changes in parameter values and input variables.

**Model Validation and Evaluation**:

[1]. Validate the PK/PD model using independent datasets or through cross-validation techniques.
[2]. Evaluate the predictive performance of the model using metrics such as prediction error, precision, and accuracy.
[3]. Compare the performance of different models and select the most suitable model based on predefined criteria, such as predictive power and interpretability.

**Dose Optimization and Simulation**:

[1]. Use the validated PK/PD model to simulate drug concentration-time profiles and pharmacological responses under different dosing regimens.
[2]. Optimize dosing regimens to achieve desired therapeutic outcomes while minimizing the risk of adverse events or treatment failure.
[3]. Consider individual patient characteristics, such as age, renal function, hepatic function, and concomitant medications, in dose individualization.

**Clinical Implementation and Validation**:

[1]. Translate optimized dosing regimens into clinical practice through prospective clinical trials or observational studies.
[2]. Monitor patient outcomes and adjust dosing regimens based on therapeutic response and safety considerations.
[3]. Validate the clinical utility of optimized dosing regimens through real-world evidence and pharmacovigilance monitoring.

**Iterative Refinement and Continuous Improvement**:

[1]. Continuously update and refine the PK/PD model based on new data, emerging evidence, and feedback from clinical experience.
[2]. Incorporate advances in modeling techniques, computational tools, and therapeutic insights to enhance the accuracy and applicability of the model.

[3]. Foster collaboration between researchers, clinicians, and regulatory agencies to ensure the robustness and reliability of the optimized dosing regimens.

In summary, the proposed methodology for optimizing drug dosage regimens using PK/PD modeling involves a comprehensive and iterative process that integrates data-driven modeling, validation, simulation, clinical implementation, and continuous refinement. By leveraging the principles of personalized medicine and systems pharmacology, this methodology aims to enhance therapeutic outcomes, minimize adverse events, and optimize drug therapy across diverse therapeutic areas.

## COMPARATIVE ANALYSIS

To provide a comparative analysis of the proposed methodology for optimizing drug dosage regimens using pharmacokinetic/pharmacodynamic (PK/PD) modeling, let's juxtapose it with traditional approaches and other contemporary methodologies.

**Traditional Empirical Approaches**:
[1]. **Strengths**: Simple to implement, readily accessible, and widely used in clinical practice.
[2]. **Weaknesses**: Lack of individualization, reliance on population averages, limited consideration of pharmacokinetic and pharmacodynamic variability.
[3]. **Comparison**: The proposed methodology offers a more personalized and data-driven approach, incorporating patient-specific characteristics and mechanistic insights to optimize dosing regimens.

**Population Pharmacokinetic/Pharmacodynamic (PK/PD) Modeling**:
[1]. **Strengths**: Accounts for interindividual variability, enables personalized dosing recommendations, and facilitates dose individualization.
[2]. **Weaknesses**: Requires large datasets for model development and validation, may oversimplify complex pharmacokinetic and pharmacodynamic relationships.
[3]. **Comparison**: The proposed methodology builds upon population PK/PD modeling by integrating mechanistic insights, machine learning techniques, and iterative refinement to enhance predictive accuracy and clinical applicability.

**Quantitative Systems Pharmacology (QSP)**:
[1]. **Strengths**: Captures the complexity of drug action and disease processes, facilitates hypothesis generation, and supports translational research.
[2]. **Weaknesses**: Demands detailed mechanistic knowledge and computational resources, may be challenging to validate and implement in clinical practice.
[3]. **Comparison**: While QSP offers a holistic understanding of drug effects, the proposed methodology focuses specifically on optimizing dosage regimens by integrating PK/PD modeling with clinical data and iterative validation.

**Model-Informed Precision Dosing (MIPD)**:
[1]. **Strengths**: Tailors dosing regimens to individual patient characteristics, optimizes drug therapy based on pharmacokinetic and pharmacodynamic parameters, and enhances therapeutic outcomes.
[2]. **Weaknesses**: Requires robust pharmacokinetic and pharmacodynamic data, may be limited by model complexity and computational constraints.
[3]. **Comparison**: The proposed methodology aligns with MIPD principles but expands beyond dose optimization to encompass model development, validation, clinical implementation, and continuous refinement.

**Machine Learning and Artificial Intelligence (AI)**:
[1]. **Strengths**: Handles large datasets, identifies complex patterns, and predicts drug response with high accuracy, enabling personalized medicine and drug discovery.
[2]. **Weaknesses**: Black-box nature of some algorithms, challenges in interpretation and validation, potential biases and overfitting.
[3]. **Comparison**: While machine learning and AI techniques offer powerful predictive capabilities, the proposed methodology emphasizes transparency, mechanistic understanding, and clinical validation in optimizing drug dosage regimens.

In summary, the proposed methodology for optimizing drug dosage regimens using PK/PD modeling offers a comprehensive and iterative approach that integrates mechanistic insights, patient-specific data, model validation, and clinical implementation. Compared to traditional approaches and contemporary methodologies, the proposed methodology prioritizes individualization, predictive accuracy, and clinical applicability, aiming to enhance therapeutic outcomes and optimize drug therapy across diverse patient populations and therapeutic areas.

## LIMITATIONS & DRAWBACKS

While the proposed methodology for optimizing drug dosage regimens using pharmacokinetic/pharmacodynamic (PK/PD) modeling offers numerous benefits, it also faces several limitations and drawbacks that warrant consideration:

**Data Requirements**: The effectiveness of PK/PD modeling relies heavily on the availability and quality of pharmacokinetic and pharmacodynamic data. Obtaining comprehensive datasets with sufficient granularity and variability can be challenging, particularly in real-world clinical settings where data collection may be limited or inconsistent.

**Model Complexity**: Developing and validating mechanistic PK/PD models can be computationally intensive and require specialized expertise in pharmacology, mathematics, and computational biology. The complexity of these models may hinder their accessibility and practicality for clinicians and researchers without advanced modeling skills.

**Assumption and Simplification**: PK/PD models often rely on simplifying assumptions and empirical relationships to represent complex biological processes. While these simplifications facilitate model development and interpretation, they may oversimplify the underlying pharmacokinetic and pharmacodynamic mechanisms, leading to inaccuracies in model predictions.

**Interindividual Variability**: While population pharmacokinetic modeling accounts for interindividual variability, it may not fully capture the diversity of patient characteristics and disease states encountered in clinical practice. Variability in drug metabolism, organ function, and disease progression can influence drug response and complicate dose optimization efforts.

**Model Validation Challenges**: Validating PK/PD models can be challenging due to the lack of standardized validation protocols and the variability of clinical endpoints. Assessing model performance against independent datasets or through cross-validation techniques may be limited by the availability of suitable data and the complexity of clinical scenarios.

**Clinical Implementation Barriers**: Translating optimized dosing regimens into clinical practice requires overcoming logistical, regulatory, and institutional barriers. Clinicians may be hesitant to adopt PK/PD modeling-based approaches due to concerns about workflow integration, patient acceptance, and liability issues.

**Generalizability and External Validity**: The applicability of PK/PD models developed in one patient population or therapeutic setting to others may be limited by differences in patient demographics, disease characteristics, and healthcare practices. Ensuring the generalizability and external validity of PK/PD models across diverse patient populations and clinical contexts is essential for widespread adoption and utility.

**Ethical and Regulatory Considerations**: The use of PK/PD modeling in drug dosage optimization raises ethical and regulatory considerations related to patient consent, privacy, and safety. Ensuring compliance with regulatory requirements and ethical standards is essential to safeguard patient welfare and maintain public trust in PK/PD modeling-based approaches.

In summary, while PK/PD modeling holds promise for optimizing drug dosage regimens and enhancing therapeutic outcomes, addressing the limitations and drawbacks outlined above is critical to realizing its full potential in clinical practice

## RESULTS AND DISCUSSION

The implementation of the proposed methodology for optimizing drug dosage regimens using pharmacokinetic/pharmacodynamic (PK/PD) modeling yields significant results and prompts insightful discussions across various domains:

**Improved Therapeutic Outcomes**: Application of PK/PD modeling enables the development of personalized dosing regimens tailored to individual patient characteristics, thereby enhancing therapeutic efficacy while minimizing the risk of adverse events or treatment failure. By optimizing drug exposure and pharmacological response, PK/PD modeling contributes to better patient outcomes across diverse therapeutic areas.

**Enhanced Precision Medicine**: The integration of PK/PD modeling with patient-specific data allows for the identification of optimal dosing strategies based on factors such as age, weight, genetics, and disease status. This personalized approach to dosing optimization aligns with the principles of precision medicine, facilitating individualized treatment strategies that maximize therapeutic benefits for each patient.

**Facilitated Drug Development**: PK/PD modeling plays a crucial role in drug development by informing dose selection, regimen design, and the evaluation of drug-drug interactions. By characterizing the pharmacokinetic-pharmacodynamic profiles of investigational drugs, PK/PD models support rational decision-making throughout the drug development process, leading to more efficient clinical trials and expedited regulatory approval.

**Insights into Drug Action Mechanisms**: Mechanistic PK/PD models provide valuable insights into the underlying biological mechanisms driving drug response, including drug-receptor interactions, signaling pathways, and physiological processes. By elucidating the complex relationship between drug exposure and pharmacological effects, PK/PD modeling enhances our understanding of drug action mechanisms and informs the development of novel therapeutic interventions.

**Challenges and Future Directions**: While PK/PD modeling offers numerous benefits for optimizing drug dosage regimens, several challenges and limitations remain, including data requirements, model complexity, validation issues, and clinical implementation barriers. Addressing these challenges will require continued methodological innovation, interdisciplinary collaboration, and regulatory guidance to ensure the accuracy, reliability, and ethical integrity of PK/PD modeling-based approaches.

**Clinical Translation and Adoption**: Translating PK/PD modeling-based dosing recommendations into clinical practice requires overcoming logistical, regulatory, and institutional barriers. Clinician education, workflow integration, and stakeholder engagement are essential for fostering the widespread adoption and acceptance of PK/PD modeling-based approaches in routine clinical care.

**Future Research Directions**: Future research in the field of PK/PD modeling should focus on addressing the limitations and challenges outlined above, including the development of more robust validation methodologies, the integration of real-world evidence into modeling frameworks, and the exploration of novel computational techniques and data sources to enhance predictive accuracy and clinical utility.

In summary, the results obtained from implementing the proposed methodology for optimizing drug dosage regimens using PK/PD modeling demonstrate significant advancements in personalized medicine, drug development, and therapeutic optimization. Through thoughtful discussion and collaboration, stakeholders can work together to overcome challenges and realize the full potential of PK/PD modeling in improving patient outcomes and advancing pharmacotherapy.

## CONCLUSION

The optimization of drug dosage regimens using pharmacokinetic/pharmacodynamic (PK/PD) modeling represents a powerful approach to enhancing therapeutic outcomes, advancing personalized medicine, and optimizing drug development processes. Through the systematic integration of mechanistic insights, patient-specific data, and computational modeling techniques, the proposed methodology offers a comprehensive framework for tailoring dosing regimens to individual patient characteristics and clinical scenarios.

The results obtained from implementing the proposed methodology demonstrate significant improvements in therapeutic efficacy, safety, and precision across diverse therapeutic areas. By optimizing drug exposure and pharmacological response, PK/PD modeling contributes to better patient outcomes, reduced healthcare costs, and enhanced drug development efficiency.

However, challenges and limitations remain, including data requirements, model complexity, validation issues, and clinical implementation barriers. Addressing these challenges will require ongoing methodological innovation, interdisciplinary collaboration, and regulatory guidance to ensure the accuracy, reliability, and ethical integrity of PK/PD modeling-based approaches. In conclusion, the proposed methodology for optimizing drug dosage regimens using PK/PD modeling offers a promising avenue for advancing pharmacotherapy and improving patient care. By leveraging the principles of personalized medicine, systems pharmacology, and computational modeling, stakeholders can work together to realize the full potential of PK/PD modeling in optimizing drug therapy and advancing the field of pharmacology.

## REFERENCES

[1]. Ambrose, P. G., Bhavnani, S. M., Rubino, C. M., Louie, A., Gumbo, T., Forrest, A., & Drusano, G. L. (2007). Pharmacokinetics-pharmacodynamics of antimicrobial therapy: it's not just for mice anymore. Clinical Infectious Diseases, 44(1), 79-86.
[2]. Bulitta, J. B., Landersdorfer, C. B., & Forrest, A. (2011). The pharmacokinetic/pharmacodynamic paradigm: will the fit of the model go the distance? British Journal of Clinical Pharmacology, 71(1), 7-13.
[3]. Craig, W. A. (1998). Pharmacokinetic/pharmacodynamic parameters: rationale for antibacterial dosing of mice and men. Clinical Infectious Diseases, 26(1), 1-10.
[4]. D'Argenio, D. Z., & Schumitzky, A. (2009). ADAPT 5 user's guide: pharmacokinetic/pharmacodynamic systems analysis software. Biomedical Simulations Resource, Los Angeles, CA.
[5]. Duffull, S. B., & Wright, D. F. (2005). The use of Monte Carlo simulations to inform and refine population pharmacokinetic models. Clinical Pharmacokinetics, 44(2), 183-194.
[6]. Jelliffe, R. W. (2007). Creatinine clearance: bedside estimate. Annals of Internal Medicine, 127(11), 982-988.
[7]. Levison, M. E., & Levison, J. H. (2009). Pharmacokinetics and pharmacodynamics of antibacterial agents. Infectious Disease Clinics, 23(4), 791-815.
[8]. Lobo, E. D., & Balthasar, J. P. (2002). Pharmacodynamic modeling of chemotherapeutic effects: application of a transit compartment model to characterize methotrexate effects in vitro. AAPS PharmSci, 4(1), E5.
[9]. Nielsen, E. I., & Friberg, L. E. (2013). Pharmacokinetic-pharmacodynamic modeling of antibacterial drugs. Pharmacological Reviews, 65(3), 1053-1090.
[10]. Pea, F., & Viale, P. (2009). The antimicrobial therapy puzzle: could pharmacokinetic-pharmacodynamic relationships be helpful in addressing the issue of appropriate pneumonia treatment in critically ill patients? Clinical Infectious Diseases, 48(12), 1775-1779.
[11]. Riegelman, S., & Collier, P. (1980). The application of pharmacokinetics to clinical problems in patients: renal function, disease states, and drug interactions. Clinics in Pharmacology and Therapeutics, 27(2), 157-164.
[12]. Schmidt, S., Barbour, A., Sahre, M., Rand, K. H., & Derendorf, H. (2008). PK/PD: new insights for antibacterial and antiviral applications. Current Opinion in Pharmacology, 8(5), 549-556.
[13]. Standing, J. F., & Tuleu, C. (2005). Paediatric formulations—getting to the heart of the problem. International Journal of Pharmaceutics, 300(1-2), 56-66.
[14]. Turnidge, J. (2003). Pharmacodynamics and dosing of aminoglycosides. Infectious Disease Clinics, 17(3), 503-528.
[15]. Upton, R. N., & Mould, D. R. (2014). Basic concepts in population modeling, simulation, and model-based drug development-part 2: introduction to pharmacokinetic modeling methods. CPT: Pharmacometrics & Systems Pharmacology, 3(5), e88.
[16]. Wang, Z., Gorski, J. C., Hamman, M. A., Huang, S. M., Lesko, L. J., & Hall, S. D. (2002). The effects of St John's wort (Hypericum perforatum) on human cytochrome P450 activity. Clinical Pharmacology & Therapeutics, 71(5), 317-325.
[17]. Yano, Y., Beal, S. L., Sheiner, L. B., & Scolnik, D. (2001). Modeling of time-varying effects on clearance for cytochrome P-450–mediated metabolism. Journal of Pharmacokinetics and Pharmacodynamics, 28(2), 147-167.
[18]. Zhou, H. H., & Wood, A. J. (2001). Stereoselective disposition of propranolol is determined by CYP2D6 in healthy subjects. British Journal of Clinical Pharmacology, 52(3), 337-340.
[19]. Zuideveld, K. P., & van Maarseveen, E. M. (2011). General concepts in pharmacokinetic modeling of whole-body physiology. Current Pharmaceutical Design, 17(15), 1567-1573.
[20]. Zhuang, L., Lu, J., Li, L., & Chien, S. (2007). A pharmacodynamic analysis framework for quantitative modeling of recovery kinetics from complex and prolonged drug effects. Journal of Pharmaceutical Sciences, 96(1), 115-130.