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Application of computational tools for pharmacokinetic evaluation in bio samples

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Abstract

Pharmacokinetic analysis is essential for examining how drugs are absorbed, distributed, metabolized, and eliminated from the body. It involves measuring drug concentrations in biological samples, such as plasma, urine, or tissues, over time to assess its behavior and efficacy. Recent advancements in software applications have significantly enhanced the precision and efficiency of pharmacokinetic data analysis. These tools utilize mathematical models and algorithms to process complex datasets, providing insights into key parameters like clearance, half-life, bioavailability, and volume of distribution.

Specialized pharmacokinetic software, such as Phoenix WinNonlin, Kinetica, and GastroPlus, allows researchers to perform non-compartmental and compartmental modeling, population pharmacokinetics, and simulation studies with greater accuracy. Additionally, these tools facilitate regulatory compliance by supporting standard bioanalytical guidelines. Integration with bioanalytical methods, including liquid chromatography-mass spectrometry (LC-MS), Ensure seamless data transfer and analysis, minimizing manual errors.

The use of such software also streamlines decision-making in drug development by enabling real-time data visualization and reporting. Moreover, automation in data processing saves time and resources while maintaining high analytical quality. This approach not only accelerates the pharmacokinetic evaluation process but also enhances the reliability of results, contributing to the optimization of dosage regimens and improved therapeutic outcomes.

In conclusion, the application of advanced pharmacokinetic software has revolutionized bioanalytical studies, making them more efficient, accurate, and compliant with global regulatory standards. This progress underscores the importance of integrating technology in modern pharmacological research.

Keywords: Pharmacokinetics; Bio samples; Software tools; Drug concentration measurement; Data analysis; Analytical software

1. Introduction

A bio sample is a biological material, such as tissue, blood, saliva, plasma, DNA, or urine, used in medical care. These samples help diagnose and monitor diseases. For instance, tissue biopsies can identify cancer, while blood and urine tests are commonly used to detect various health conditions. DNA samples are particularly useful for diagnosing genetic disorders and mutations in cancer cells.[1]

Protein Precipitation (PP), Solid Phase Extraction (SPE), and Liquid-Liquid Extraction (LLE) are widely used sample preparation techniques in bioanalytical testing, especially for bioanalytical method validation.

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Protein Precipitation (PP) is a simple, efficient technique used to remove proteins from biological samples such as plasma or serum. It involves adding a precipitating agent (e.g., organic solvents like acetonitrile or methanol) to the sample, which causes proteins to denature and form a precipitate, leaving analytes in solution. This technique is quick and requires minimal sample volume, but may not be effective for all types of analytes.[2]

Solid Phase Extraction (SPE) is a chromatographic technique used to isolate and concentrate analytes from complex matrices. It involves passing the sample through a solid sorbent material, where analytes bind, and unwanted components are washed away. The target analytes are then eluted using a suitable solvent. SPE provides high selectivity and efficiency, and is often used for sample cleanup before chromatographic analysis.[3]

Liquid-Liquid Extraction (LLE) involves separating analytes based on their solubility in two immiscible liquids, typically an aqueous phase and an organic solvent. This technique is commonly used for extracting hydrophobic compounds from biological fluids, allowing the concentration of analytes in the organic phase. LLE is highly effective but can be time-consuming and require large sample volumes.[4]

Pharmacokinetics (PK) involves studying how the body processes medications from the moment they are taken until they are fully cleared. It focuses on how drugs are absorbed, distributed, metabolized, and excreted (often referred to as ADME). While related to pharmacodynamics, which looks at how drugs affect the body, pharmacokinetics specifically deals with how the body handles the drug. A solid grasp of these processes Helps healthcare professionals to tailor treatments, ensuring medications are both effective and safe, and to make necessary adjustments based on each patient's unique.[5]

Absorption is the process by which a drug moves from its site of administration into the bloodstream. This influences both the speed and concentration at which the drug reaches its target site. Various administration methods exist, such as oral, intravenous, intramuscular, subcutaneous, and transdermal, each with unique absorption properties. Oral medications, for example, must first be released from their dosage form before being absorbed, a process known as liberation. Factors such as stomach acidity and digestive enzymes can impact absorption and delay the drug's effects.

Bioavailability refers to the proportion of an administered drug that enters systemic circulation, influenced by the route of administration. Intravenous drugs have 100% bioavailability, whereas oral medications undergo digestive and liver metabolism (first-pass effect), reducing the available active drug. To measure bioavailability, the area under the plasma concentration curve (AUC) is often used, comparing different administration methods against the intravenous standard.

Once absorbed, the drug is distributed throughout the body based on its chemical properties and the patient's physiology. Factors like diffusion, protein binding, and body fluid composition affect distribution. The volume of distribution (Vd) helps determine how widely a drug disperses, with small, lipophilic molecules spreading extensively into tissues, while large, protein-bound drugs remain mostly in circulation. This metric is crucial in calculating loading doses to quickly reach therapeutic drug levels.

Protein binding plays a key role in drug activity, as only the free, unbound drug can interact with receptors. Plasma proteins like albumin influence drug distribution, and conditions like renal failure can alter protein binding, increasing the drug's active concentration and potential toxicity.

Metabolism primarily occurs in the liver, where drugs are chemically modified to become more water-soluble for excretion. Phase-I (CYP450 enzymes) and Phase II (conjugation) reactions either deactivate the drug or convert prodrugs into active compounds. Excretion mainly happens through the kidneys, but some drugs are eliminated via the lungs, skin, or gastrointestinal tract.

Clearance is the rate at which a drug is removed from the body, depending on organ function and blood flow. Understanding clearance helps determine appropriate dosing, ensuring that drug levels remain effective without leading to toxicity. Maintenance dosing replaces the drug lost since the last dose to maintain stable therapeutic concentrations.[7]

1.1. Phoenix WinNonlin

Phoenix WinNonlin is a leading tool in the pharmaceutical industry for pharmacokinetic (PK) modeling. It is primarily used for noncompartmental analysis (NCA), compartmental modeling, and bioequivalence studies. This software is popular due to its user-friendly interface and its ability to handle complex PK/PD models. It is widely recognized by regulatory agencies, including the FDA and EMA, making it a trusted choice for clinical trials. WinNonlin enables the

simulation and optimization of drug dosing regimens. It offers a range of statistical methods and robust data visualization tools to display concentration-time profiles. WinNonlin also provides automated reporting functions to streamline workflow. Users can create highly customizable analysis scripts to fit specific project needs. It's also compatible with other Certara tools for more advanced modeling. [8]The software integrates well with industry standards for regulatory submissions. WinNonlin's features are regularly updated to ensure compliance with evolving guidelines. It allows for simulation of drug interactions and exposure levels in special populations. The program is capable of analyzing complex data from different clinical trial designs. It helps in evaluating dose-response relationships and optimizing therapeutic windows. WinNonlin's flexibility and wide acceptance make it indispensable for drug development and regulatory submissions.[9]

1.2. NONMEM

NONMEM is the premier software for population pharmacokinetic (PopPK) modeling, favored for its ability to handle complex datasets. Researchers use NONMEM for analyzing population-level PK/PD data to understand variability in drug behavior across individuals. It excels in estimating parameters in patients with diverse characteristics, including special populations such as pediatrics or elderly. [10]NONMEM is a powerful tool for fitting nonlinear mixed-effects models and analyzing sparse data from clinical trials. It employs Bayesian estimation techniques to refine parameter estimates. The software requires knowledge of programming and command-line scripting, making it more suitable for experienced users. Despite its complexity, NONMEM is trusted by regulatory authorities and is commonly used for submissions to the FDA and EMA. It supports covariate modeling, helping researchers understand factors like age or weight on drug behavior. It is particularly effective in analyzing data from population pharmacokinetics and pharmacodynamics studies. The software allows researchers to simulate different dosing scenarios to optimize therapeutic outcomes. NONMEM is also used in clinical trial simulations, making it an essential tool for drug development. With its high computational capacity, NONMEM can manage large and sparse datasets efficiently. Its flexibility and customization options ensure it can meet diverse modeling needs.[12]

1.3. Monolix

Monolix is a user-friendly software for population pharmacokinetic (PopPK) and pharmacodynamic (PK/PD) modeling. Known for its intuitive graphical interface, Monolix simplifies the modeling process, making it accessible to both novice and experienced users. It supports nonlinear mixed-effects modeling, enabling the analysis of complex PK data with inter-individual variability. [13]The software is efficient in handling sparse data, making it ideal for analyzing data from clinical trials with limited samples. Monolix integrates seamlessly with R, allowing for advanced statistical analyses and the development of custom modeling workflows. It is widely used in both academic research and pharmaceutical industry applications. Monolix supports population modeling, covariate analysis, and simulation of drug concentrations under varying conditions. The software's Bayesian estimation techniques improve the precision of parameter estimates. It is equipped with automatic model selection tools and model diagnostics to help refine model performance. Monolix also allows for model-based drug development, optimizing dose recommendations and drug efficacy. Researchers can simulate the impact of different dosing regimens on patient populations. The software offers extensive documentation and support, making it easy for users to get started. Monolix is increasingly popular for regulatory submissions due to its efficiency and reliability.[14]

1.4. PKSolver (Excel-based)

PKSolver is a free and easy-to-use Excel add-in for pharmacokinetic (PK) analysis, favored for its simplicity and accessibility. It is designed to perform noncompartmental analysis (NCA) and some compartmental PK modeling, making it a good option for straightforward PK studies. PKSolver allows users to analyze concentration-time data, estimate key PK parameters such as half-life, clearance, and volume of distribution, and generate basic graphical outputs. The tool supports common pharmacokinetic models, including one- and two-compartment models. Researchers can easily integrate PKSolver into their existing Excel workflows, making it convenient for those already familiar with Microsoft Excel. [15]The software is popular among students and early-career researchers due to its no-cost, user-friendly interface. It requires no programming knowledge, making it accessible for those who want quick PK calculations without the need for complex software. PKSolver also includes tools for calculating bioavailability and bioequivalence, which are essential in clinical trial studies. While it lacks advanced features found in commercial PK modeling software, it is highly effective for basic PK analysis. The software supports dose simulations and can handle data from different experimental designs. It's especially useful for small studies or pilot trials where basic PK evaluations are needed. PKSolver is widely used in academic settings for teaching and research purposes. Despite simplicity, PKSolver offers a powerful solution for researchers needing to perform basic PK modeling.[16]The comparison of software tools is shown in Table-1.

Table 1 Software-based Pharmacokinetic evaluation of biosamples

Software Name	Purpose	Parameters Included
Phoenix WinNonlin	PK/PD data analysis and modelling	Cmax, Tmax, AUC, Vd, Half- life,
NONMEM	Nonlinear mixed-effects modelling	PK/PD Parameters, Inter and Intra subject Variability, Covariate Effects
MATLAB	PK/PD simulation and modelling	Dose -response curves, Time-Concentration
Kinetica	PK/PD analysis and visualization	AUC, Tmax, Cmax, T1/2, Clearance, Vd
Monolix	Model-based PK/PD analysis	Population PK, Covariate Analysis,
GastroPlus	Physiologically-based pharmacokinetic (PBPK) modelling	Absorption, Distribution, Metabolism, Excretion (ADME), Bioavailability.

This table provides a detailed summary of pharmacokinetic determinations of biosamples conducted using different software tools. It outlines essential parameters such as drug concentration, elimination rate, half-life, and area under the curve (AUC), along with the software utilized for analysis. This organized representation allows for easy comparison of the methodologies and their effectiveness in pharmacokinetic evaluations.

2. Materials and methods

- **Sample Collection**: Biological specimens such as blood, plasma, urine, or tissue are gathered at designated time points.
- **Sample Preparation**: Techniques like protein precipitation, liquid-liquid extraction, or solid-phase extraction are applied to extract the drug or its metabolites.
- **Bio analytical Assay**: Drug concentrations are typically determined using methods like LC-MS/MS (Liquid **Chromatography-Tandem Mass Spectrometry) or HPLC (High-Performance Liquid Chromatography).[12,13,14]**
- **Calibration and Quality Control**: Calibration curves and quality control samples are used to ensure the precision and accuracy of the assay.[15,16]
- **Pharmacokinetic (PK) Data Processing**: Specialized software analyzes concentration-time data to calculate pharmacokinetic parameters.
- **Modelling and Statistical Analysis**: Both compartmental and non-compartmental analysis are conducted using dedicated software tools for interpretation and modelling.

3. Results and Discussion

A case study by Rahul pal et al.[17]this experiment focuses on evaluating pharmacokinetic and pharmacodynamic (PK/PD) parameters using WinNonlin software. WinNonlin is a widely recognized tool in pharmaceutical research, enabling the analysis and modeling of drug concentration-time profiles. By utilizing this software, researchers can assess how a drug is absorbed, distributed, metabolized, and eliminated from the body. One of its key applications is determining important pharmacokinetic parameters. These include Cmax, which represents the peak drug concentration in plasma, and Tmax, the time at which this maximum concentration occurs. Another crucial parameter is AUC (Area under the Curve), which reflects the total drug exposure over time. Additionally, the half-life (t½) of a drug is calculated, indicating the duration required for its plasma concentration to reduce by half. WinNonlin enables curve fitting and statistical analysis to derive these parameters accurately. It is extensively used in clinical and preclinical studies to optimize drug dosing and assess therapeutic effectiveness. By integrating mathematical models, the software helps predict drug behavior and its pharmacological impact. Furthermore, PK/PD modeling through WinNonlin aids in understanding drug-receptor interactions and dose-response relationships. This approach supports regulatory submissions, ensuring compliance with guidelines for drug approval. Overall, the software is a valuable tool for researchers aiming to refine drug development and improve patient outcomes.

A case study by Kristin M et al. [18]Predicting blood concentration levels of pharmaceutical compounds in human subjects is often challenging due to missing data and individual variability. Differences between patients, such as metabolism and disease state, add complexity to pharmacokinetic analysis. Biometricians rely on specialized software to study drug concentration trends and optimize dosing strategies. This study compares two approaches for predicting blood serum levels of tobramycin in pediatric patients with cystic fibrosis and hematologic-oncologic disorders. The first method involves a feedforward backpropagation neural network, a machine learning model that processes input data to improve predictive accuracy. The second method utilizes NONMEM®, a widely used pharmacokinetic modeling software. To determine the accuracy of these approaches, mean squared standard error (MSSE) is calculated, providing a measure of the reliability of predictions. The comparison aims to assess whether neural networks can serve as an alternative to traditional pharmacokinetic modeling. Machine learning techniques may offer advantages in handling complex data and reducing computational effort. The primary motivation behind this research is to support clinicians and pharmaceutical scientists by developing a cost-effective, efficient, and user-friendly tool for predicting drug concentrations in human subjects. Improving prediction accuracy can enhance dose optimization and reduce adverse effects. Ultimately, this study explores the potential of artificial intelligence in pharmacokinetics, paving the way for more precise and accessible drug monitoring solutions.

A case study by John P.Gibbs et al.[19]WinNonlin for Pharmacokinetic Analysis of an Antiviral Drug Pharmacokinetic (PK) evaluation is essential for determining how a drug behaves in the human body. In this study, WinNonlin software was used to analyze the PK profile of an antiviral medication based on plasma concentration data. Researchers aimed to determine key parameters to optimize dosing regimens and improve therapeutic outcomes. One of the primary objectives was to measure Cmax (maximum plasma concentration), which indicates the highest drug level reached in the bloodstream. The study also examined Tmax (time to peak concentration) to understand the rate of drug absorption. Additionally, AUC (area under the curve) was calculated to assess overall drug exposure, which is crucial for evaluating efficacy. Another key aspect was the determination of half-life (t½), which represents the time required for the drug concentration to decrease by 50%. This parameter helps predict dosing intervals and the potential accumulation of the drug in the body. Compartmental modeling in WinNonlin allowed researchers to simulate how the drug distributes and clears from the system. The software's curve-fitting and regression analysis tools helped refine the PK model, ensuring accuracy in clearance and bioavailability estimations. By using nonlinear regression analysis, the study provided deeper insights into drug metabolism and excretion patterns. This research contributed to optimizing antiviral therapy by supporting dose adjustments based on patient-specific factors. The findings demonstrated the effectiveness of WinNonlin in PK modeling, clinical trial analysis, and regulatory submissions, making it a valuable tool in pharmaceutical research.

A case study by T.Grabwski et al. [20]Regulatory agencies do not provide specific guidelines on how to determine sampling intervals in pharmacokinetic (PK) studies. Each sampling interval contributes to the overall area under the curve (AUC), which is essential for evaluating drug exposure. This study aims to introduce a qualitative assessment method for PK studies by analyzing the values of partial AUC segments. For this evaluation, mean concentrations of itraconazole, a highly variable drug, were utilized both before (BO) and after (AO) optimizing the sampling intervals. PK calculations were conducted using PhoenixTM WinNonlin 6.3® (Certara L.P.) and the in-house software Biokinetica 4.0. An arithmetic formula was established along with an acceptance limit (AL%), below which the mean of partial fields (MAF) in a PK study can be deemed optimal. Prior to optimization, the coefficient of variation (CV%) for MAF was 125.35, which significantly reduced to 46.51 after optimization. In the case of AUC fractions for multiple partial fields in BO data, the AL% threshold was surpassed. However, for AO data, AUC fraction values remained within the acceptable limit. This study introduces an empirical approach to quality evaluation based on the percentage of AUC fractions. The proposed method can serve as a tool for assessing the quality of PK studies and ensuring optimal sampling intervals, thereby enhancing the accuracy and reliability of PK evaluations. By implementing this approach, researchers can better determine the effectiveness of sampling strategies and improve the overall design of PK studies.

The pharmacokinetics of good manufacturing process (GMP) artesunate (AS) injection were assessed in 40 healthy individuals who received single doses of 0.5, 1, 2, 4, and 8 mg/kg over a two-minute infusion. Drug levels were measured using validated liquid chromatography-mass spectrometry (LC-MS/MS) methods. AS was rapidly converted to its active metabolite, dihydroartemisinin (DHA), with elimination half-lives of 0.12–0.24 hours for AS and 1.15–2.37 hours for DHA. A pharmacokinetic model-dependent approach was suitable for AS, while DHA was compatible with both model-dependent and model-independent methods. Although DHA exposure exceeded that of AS, with an AUC DHA/AS ratio of 1.12–1.87, the peak concentration (Cmax) of AS was significantly higher than DHA, with a ratio of 2.80–4.51. This suggests that AS efficacy is influenced not only by its rapid transformation into DHA but also by its high initial peak concentration.

A case study by Kristin M et al. [21]Predicting blood concentration levels of pharmaceutical agents in humans is challenging due to missing data and variations within and between individuals. Biometricians rely on various software tools to analyze pharmacokinetic data and conduct research on drug behavior. This study compares the effectiveness of a feedforward backpropagation neural network with NONMEM®, a widely used pharmacokinetic modeling software, in predicting blood serum concentrations of tobramycin in pediatric patients with cystic fibrosis and hematologic-oncologic disorders. The accuracy of these methods is evaluated using mean squared standard error to determine their comparability. The primary goal of this research is to offer clinicians and pharmaceutical researchers a more accessible, cost-effective, and efficient tool for predicting drug concentration ranges in patients. By utilizing neural networks, the study aims to explore the potential of artificial intelligence in pharmacokinetics. Machine learning models, such as neural networks, can adapt to complex data patterns and improve prediction accuracy. NONMEM®, on the other hand, is a well-established tool used for population pharmacokinetic modeling. Comparing these two approaches provides insight into alternative methods for drug concentration estimation. The integration of AI-based tools in pharmacokinetics could enhance decision-making in clinical and pharmaceutical research. Predicting drug concentrations accurately is crucial for optimizing dosing regimens and minimizing adverse effects. Traditional pharmacokinetic modeling relies on structured equations, while neural networks use data-driven learning to improve predictions. Evaluating these methods side by side helps determine their reliability and practicality for clinical use. The study also highlights the potential for AI-driven models to complement or enhance traditional pharmacokinetic analysis. By reducing reliance on complex statistical modeling, machine learning can offer more intuitive and automated solutions. Providing healthcare professionals with accurate and user-friendly tools is essential for personalized medicine. As technology advances, AI-based models may become integral to pharmacokinetic research and clinical decision-making. This research contributes to the ongoing development of innovative methods for drug concentration prediction. The findings could lead to improved therapeutic monitoring and optimized treatment strategies. Understanding the strengths and limitations of both approaches helps guide future pharmacokinetic research.

A case study by Renuka S et al. [22] additionally, a pharmacokinetic study on primaquine (PQ) enantiomers was conducted in mice to investigate their metabolism, tissue distribution, and pharmacokinetics. Male Albino ND4 Swiss mice received oral doses of 45 mg/kg of S-(+)-PQ (SPQ) and R-(−)-PQ (RPQ), each containing a stable isotope-labeled mixture. Blood and tissue samples were analyzed using ultra-performance liquid chromatography/mass spectrometry (UPLC/MS), and non-compartmental analysis was performed using Phoenix WinNonLin software. The study revealed higher plasma AUC, half-life, and Tmax for SPQ compared to RPQ. SPQ concentrations were consistently higher across all tissues, with the liver showing levels three times greater than RPQ. The peak concentration of SPQ in the liver was approximately 100 times its plasma concentration, whereas RPQ levels were about 40 times the plasma value. Similar patterns were observed in the spleen, kidneys, and lungs, with SPQ concentrations significantly exceeding those of RPQ. Furthermore, RPQ preferentially generated the major metabolite CPQ, which accumulated at much higher levels in both the liver and plasma. These findings indicate that the pharmacokinetics and metabolism of PQ enantiomers differ significantly, affecting their overall distribution and potential efficacy.

A case study by Paula del et al.[23]asenapine maleate (ASPM) is a novel antipsychotic medication available as a sublingual tablet. A pharmacokinetic and tissue distribution study was conducted in rats following oral administration, utilizing a validated reversed-phase high-performance liquid chromatography (HPLC) method. ASPM was extracted from plasma and tissue samples using a liquid–liquid extraction technique. The analyte was separated using a mobile phase comprising phosphate buffer (pH 3.0) and acetonitrile in a 65:35 ratio. The method demonstrated strong linearity within the concentration range of 10–500 ng/mL, with a recovery rate between 83% and 102%. Pharmacokinetic analysis revealed a prolonged half-life of 32.74 ± 7.51 hours, suggesting slow drug elimination. The bio distribution study indicated a preference for ASPM accumulation in highly perfused organs. This validated method is suitable for estimating drug levels in various biological matrices, making it a valuable tool for further pharmacokinetic research. Additionally, a pharmacokinetic study of raltegravir, an HIV integrase inhibitor, was performed to analyze plasma and intracellular concentrations in healthy volunteers. Blood samples were collected at multiple time points following a single 400-mg dose. Raltegravir levels were quantified using liquid chromatography-mass spectrometry, with lower quantification limits of 2 nmol/L in plasma and 0.225 nmol/L in peripheral blood mononuclear cell (PBMC) lysates. Non compartmental analysis was conducted using WinNonlin, while population pharmacokinetic modeling was performed using NONMEM. Six male subjects participated in the study, with a median weight of 67.4 kg and a median age of 33.5 years. The geometric mean (GM) maximum plasma concentration (Cmax) was 2,246 nm, with an area under the curve (AUC0–∞) of 13,119 nM·h and an apparent half-life of 7.8 hours. Intracellular raltegravir concentrations showed a GM Cmax of 383 nM, an AUC0–∞ of 2,435 nM·h, and a half-life of 4.5 hours. The intracellular-to-plasma ratio remained stable over 48 hours, indicating no significant accumulation in PBMCs. Population pharmacokinetic modeling estimated an intracellular-to-plasma partitioning ratio of 11.2%. These findings provide insight into raltegravir's pharmacokinetics and its distribution between plasma and intracellular compartments.

A case study by Daniel B et al. [24]the objective of this study is to investigate the population pharmacokinetics (PK) of an oncology drug across various patient groups. To achieve this, serum drug concentration data will be collected from a diverse cohort of patients, including those with different demographic characteristics, disease stages, and co-morbidities. These variations will allow for an in-depth analysis of how the drug is absorbed, distributed, metabolized, and eliminated in different individuals. The data will be analyzed using NONMEM (Nonlinear Mixed Effects Modeling), a powerful tool that helps in evaluating complex pharmacokinetic models by accounting for variability both within and between subjects. NONMEM can handle diverse datasets and provide valuable insights into the underlying processes influencing drug behavior, such as genetic factors, age, weight, organ function, and concurrent therapies. The analysis will focus on determining the key pharmacokinetic parameters, such as clearance, volume of distribution, and half-life, and how these parameters change across patient groups. By identifying sources of variability in drug metabolism and response, the study aims to provide evidence for optimizing dosing strategies. These findings are expected to support the development of personalized treatment regimens, enhancing the safety and efficacy of the oncology drug in different patient populations. Ultimately, this study will contribute to a deeper understanding of the drug's behavior in the human body, paving the way for individualized therapy that improves patient outcomes and minimizes adverse effects.

A case study by Valentina et al. [25]SimBiology provides a powerful framework for modeling drug pharmacokinetics (PK) and pharmacodynamics (PD), allowing researchers to simulate how a drug moves through the body and its effects over time. The process begins with setting up a model that represents the biological system, defining compartments such as blood, tissues, and organs, and incorporating key elements like drug concentration and receptor interactions. A suitable pharmacokinetic model, such as a one-compartment or two-compartment model, is then selected to describe the processes of drug absorption, distribution, metabolism, and excretion (ADME).Once the model is defined, simulations are run to observe how drug concentrations change over time and how these variations influence the drug's therapeutic effects. These simulations help predict drug behavior under different conditions, such as varying dosages or patient-specific factors. The results are analyzed by visualizing concentration-time profiles and comparing them with experimental data to assess the model's accuracy. If discrepancies arise, the model can be refined by adjusting parameters or incorporating additional physiological factors to improve its predictive capabilities. After refining the model, reports are generated, and the data can be exported for further statistical analysis or regulatory documentation. This systematic approach enables researchers to optimize drug dosing strategies, predict potential side effects, and support decision-making in drug development. By integrating computational modeling with experimental data, SimBiology enhances the understanding of drug kinetics and dynamics, ultimately aiding in the development of safer and more effective therapies.

A case study by R. Scott Miller et al.[26] analyzing the pharmacokinetics (PK) and pharmacodynamics (PD) of propranolol using WinNonlin begins with importing relevant data into the software. This data typically includes drug concentration measurements over time, dosing information, and possibly patient demographics. Ensuring the data is formatted correctly, often as a spreadsheet or CSV file, is essential for smooth integration into the software. Once imported, the next step involves selecting a suitable PK/PD model, such as a one- or two-compartment model, to represent propranolol's behavior in the body. The chosen model must be configured with appropriate parameters to reflect the drug's absorption, distribution, metabolism, and excretion processes. After setting up the model, the fitting process begins by running simulations in WinNonlin to estimate key parameters and adjust the model to match observed data. Diagnostic plots and statistical analyses are used to evaluate how well the model represents the actual pharmacokinetic profile of propranolol. If discrepancies arise, refinements are made by adjusting parameter values or modifying assumptions within the model. Once an optimal fit is achieved, crucial PK/PD parameters such as clearance, volume of distribution, and half-life are calculated. Following successful model evaluation, a comprehensive report is generated, summarizing all findings. This report includes tables, plots, and parameter estimations, which can be used for further analysis or regulatory submissions. By systematically following these steps, researchers can gain valuable insights into propranolol's pharmacokinetics and pharmacodynamics, aiding in dose optimization and therapeutic decision-making.

4. Conclusion

The use of software for pharmacokinetic determination in biological samples has revolutionized drug analysis by providing accurate and efficient data processing. Tools such as WinNonlin, NONMEM, and Phoenix facilitate the modeling of drug absorption, distribution, metabolism, and excretion, allowing researchers to derive essential pharmacokinetic parameters like clearance, half-life, and volume of distribution. These software programs handle complex datasets, account for inter-individual variability, and enable simulations that predict drug behavior under different conditions. By integrating experimental data with computational models, they enhance the precision of pharmacokinetic studies and support informed decision-making in drug development. Regulatory agencies recognize these tools for their role in optimizing dosing strategies and improving patient safety. However, the reliability of results depends on high-quality input data, appropriate model selection, and expert interpretation. While software streamlines

pharmacokinetic analysis, human expertise remains crucial in refining models and validating findings. The continued advancement of computational methods will further enhance drug evaluation, leading to more effective and personalized therapies. Ultimately, pharmacokinetic software contributes significantly to pharmaceutical research by improving drug efficacy, minimizing adverse effects, and supporting regulatory approvals.

Compliance with ethical standards

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Disclosure of conflict of interest

The authors declare no conflict of interest.

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