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Application of mathematical methods in pharmacology

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Abstract

The application of mathematical methods in pharmacology is relevant for the development of accurate models of drug action and optimisation of their dosing, which

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increases the effectiveness of treatment and reduces the risks of side effects, and accelerates and cheapens the process of developing new drugs. The purpose of this research is to explore the application of mathematical methods in pharmacology to optimise drug development and improve drug efficacy. The methods used include analytical method, classification method, functional method, statistical method, synthesis method. This research covers the main aspects of using mathematical modelling in pharmacology, covering a variety of issues that arise at different stages of drug development. Specific examples of using mathematical modelling to solve these problems are presented. Various approaches to modelling the pharmacokinetics (PK) of drugs, and the analysis of their absorption, distribution and excretion are reviewed. Mathematical methods for analysing efficacy and safety and approaches to determining the therapeutic window of a drug are discussed. The research into the application of mathematical methods in pharmacology is of practical significance as it contributes to the development of more accurate PK and pharmacodynamic (PD) models, optimisation of drug dosing and improved predictive accuracy, leading to the development of more effective and safer drugs.

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1. Introduction

Exploring the application of mathematical methods in pharmacology is inevitable as it offers significant benefits to improve the drug development process. Using mathematical models and methods, allows for more accurate estimation of drug dosage, investigating and predicting their pharmacokinetics (PK) and pharmacodynamics (PD), and predicting their efficacy and safety. It, in turn, leads to a reduction in the time and cost required for research, accelerates the process of finding new drugs and increases the likelihood of successful development of innovative drugs. Thus, using mathematical methods in pharmacology is of great practical significance and contributes to progress in the field of drug development and improvement. Research into the application of mathematical methods in pharmacology faces several challenges, such as the difficulty of integrating mathematical models with biological systems, the need to consider multiple factors of drug-drug interactions and the lack of reliable data for model construction and verification. In addition, there is an essential problem of transferability of research results to real-world conditions and practices, requiring consideration of individual patient and pharmacological drug characteristics. The solution to these problems would be essential for more effective and safer development of pharmacology.

In their research, I.M. Chamseddine and K.A. Rejniak [1] emphasise that mathematical methods can more accurately determine the optimal dosage of a drug, considering various factors such as patient characteristics and interactions with other drugs. It helps to improve treatment efficacy and reduce the risk of unwanted side effects. Following N. Aliyev and S. Muhammadjonov [2], the research on the application of mathematical methods in pharmacology is a relevant and important area of scientific research. Using mathematical models can improve the prediction of the effect of drugs on the body, which reduces the need for long-term clinical trials and contributes to the faster development of new drugs. According to research by P. Dogra et al. [3], the application of mathematical methods in pharmacology helps to optimise the drug development process. Modelling of PK and PD allows a more accurate assessment of the pharmacological properties of a drug and prediction of its behaviour in the body, which reduces the need for a large number of experiments.

F.R. Pinu et al. [4] indicate the challenges associated with the integration of mathematical models with biological systems. One of the challenges is to consider complex physiological processes and the multifactor interaction of drugs with the body. Thus, it depends on various factors such as age, gender, genetic features of the patient, and comorbidities and intake of other drugs [5, 6]. Considering all these factors in mathematical models is a complex task, but is necessary to achieve accuracy and reliability of modelling results in pharmacology. K.N. Alam et al. [7] note that for the successful application of mathematical methods in pharmacology it is necessary to have reliable data for the construction and verification of models. A lack of qualitative information can limit the effectiveness and applicability of mathematical approaches. R. Hamamoto et al. [8] believe that the application of mathematical methods in pharmacology has great potential and contributes significantly to the development of science. They emphasise the importance of continuing research in this area to overcome the current problems and discover all the advantages of the mathematical approach in pharmacology.

The purpose of this research is to analyse the potential of using mathematical methods in pharmacology to optimise drug development and increase drug efficiency.

2. Materials and Methods

The analytical method helped to overcome the problems of integrating mathematical models with biological systems. This method allowed

analysing and exploring complex physiological processes, their interaction with drugs and considering the multifactorial nature of the interaction. Using mathematical algorithms, the analytical approach has allowed the development of models that reflect biological reality as accurately as possible and can predict the effects of drugs on the body. It helps to optimise treatment, predict dosages and reduce the risk of unwanted side effects. The statistical method was used to process large amounts of data related to pharmacological studies. This method allowed the identification of relationships and patterns between different variables such as drug dosage, FC and PD parameters, their effects on the body and treatment outcomes. In addition, statistical processing enabled comparative studies, evaluation of drug effectiveness and prediction of long-term effects.

By applying the functional method, the dynamics and changes in pharmacological processes and effects of drugs on the body were analysed. This method allowed describing and modelling functional dependencies between input and output variables such as drug concentration, time of action, and treatment efficacy. In addition, the functional approach has also enabled the optimisation of drug dosage, considering the variability and individual patient characteristics. In addition, it facilitates the development of individualised treatment approaches and consideration of personalised factors such as the patient's genetic profile to achieve the best results. The structure-function method has helped in exploring the relationships between the structure of drugs and their functional properties in the context of pharmacology. This method allowed the exploration of the chemical structure of drugs and the determination of their interactions with biological targets, PD processes and PK characteristics. The investigation of structure-function relationships allowed predicting the effects of drugs on the organism, identifying potential purposes for new drug developments and optimising their action.

The method of deduction helped in drawing logical conclusions and generalisations based on existing facts and data in pharmacology. This method allowed hypotheses to be developed based on existing theory and empirical observations and then tested through experimentation and study of the results. By applying logical reasoning and rational thinking, the method of deduction allowed establishing cause and effect relationships and understanding the principles of drug action. This contributes to the theoretical foundation of pharmacology and provides a foundation for further progress in the development of new drugs and optimisation of existing therapeutic approaches. In this research, there was a formula that illustrates using a mathematical approach in determining the overall

efficacy of a drug product by calculating the mean of individual trial results:

$$E = \sum_{i=1}^{n} \left(\frac{1}{n} * D_i \right), \quad (1)$$

and the equation that is used to describe dose-effect relationships in pharmacology:

$$E = \frac{E_{\max} * C^{\gamma}}{C^{\gamma}_{50} + C^{\gamma}}. \quad (2)$$

By applying the synthesis method, new drugs were developed, and optimal combinations of existing components were designed to maximise the therapeutic effect. This method has allowed the combination of knowledge from different fields of pharmacology, chemistry and biology to establish innovative and effective drugs. By synthesising new compounds or modifying existing ones, desired pharmacological properties such as increased activity, better selectivity and reduced toxicity can be achieved. In addition, the synthesis method allows the establishment of drug combinations with synergistic effects, which can lead to improved treatment outcomes and reduced risk of resistance development.

3. Results

The introduction of a drug into the body triggers complex interactions between the drug and the biological system (3). The organism influences the drug, while the drug itself influences the organism or a particular system in the organism [9-13]. This interaction can be described using PK and PD. PK studies how the body affects the drug product. It involves the processes of absorption, distribution, metabolism and excretion of the drug from the body. The PK characteristics of a drug determine how the drug moves through the body, how long it stays in the body, and how quickly it is metabolised and excreted from the body. The study of PK allows evaluation of how the body processes and affects the drug. On the other hand, pharmacodynamics studies the expected effects of a drug on an organism or system. It involves assessing how the drug interacts with targets in the body and what pharmacological effects it causes. Pharmacodynamic studies provide an understanding of how a drug affects physiological processes, biological receptors or molecular targets in the body [14]. In addition to exploring the effects of the drug, it is essential to evaluate the safety of the drug. For this purpose, a safety profile is

prepared, which includes analysing the unwanted effects occurring in subjects after administration of the drug. It allows evaluation of which adverse events may occur during the use of the drug and to what extent they may be dangerous or unacceptable for patients.

$$E = \sum_{i=1}^{n} \left(\frac{1}{n} * D_i \right), \tag{3}$$

where: E – drug efficacy; n – number of trials; D_i – individual efficacy of each trial.

This formula demonstrates the application of a mathematical approach to calculate the overall efficacy of a drug product based on the average of individual trial results. To optimise the effect of a drug on a biological system, its PK is mathematically analysed. The main processes considered in PK are absorption, distribution, metabolism and excretion (ADME). The application of mathematical modelling in the process of drug absorption allows consideration of different ways of drug administration, specific features of drug liberation and absorption for complex forms of drugs, mating their bioavailability and considering the influence of food intake. Distribution analysis studies the ability of the drug to reach target organs, penetrate the blood-brain barrier to the central nervous system and through the placental barrier to the foetus. Evaluation of metabolism and excretion allows analysis of the pathways and rate of excretion of the drug from the body [15]. In addition, it is necessary to consider possible drug interactions when multiple drugs are administered concomitantly. The wide range of research challenges in the field of PK is reflected by the variety of mathematical methods of analysis. For example, simple empirical analysis of non-compartmentalised data (NCA) allows estimation of the main characteristics of PK, such as maximum concentration (C_{max}), time to reach maximum concentration (T_{max}), half-life (t1/2) and area under the concentration-time curve (AUC0-t), which reflects drug exposure. Population-based PK models are now widely used in drug development to optimise decision-making and consider individual patient characteristics. Physiologically based modelling (PBPK) methods are used to achieve a mechanistic description of the physiology of processes in PK.

The medicine leaves the body's bloodstream through excretion with urine or other excretory fluids such as bile, saliva or breast milk. In addition, the drug may be metabolised in the body's tissues or plasma. The final elimination of the drug from the body usually occurs through irreversible elimination processes, which include various routes of

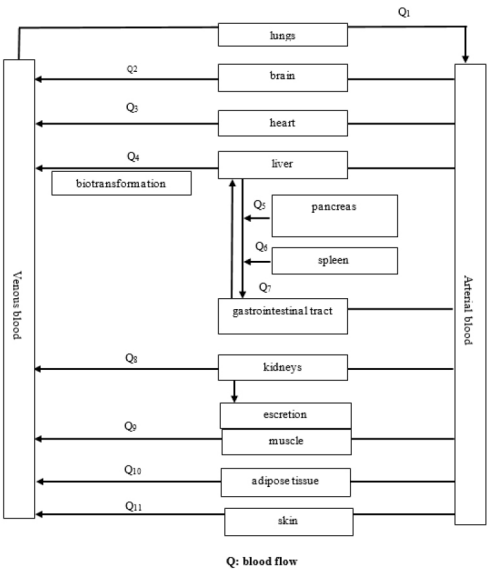

Figure 1

Blood circulation pattern

excretion and metabolic inactivation such as excretion through the kidneys, lungs, bile, faeces, skin and biotransformation. Since the penetration of a drug into a particular tissue depends on its blood supply, drugs are generally considered to have relatively good access to blood, interstitial fluid and highly vascularised tissues such as the heart, brain, lung, liver, kidney and internal secretion glands. The remaining tissues are generally less accessible for drug penetration [16] (Figure 1).

For solving problems related to clinical PK, using mathematical modelling is both appropriate and necessary. Frequently, it is the correct choice of an appropriate model, a suitable algorithm and accurate identification of its parameters based on available measurements of drug concentration and blood sampling time during the monitoring procedure that determines the accuracy of prediction of treatment efficacy and safety, and sometimes even the possibility of such prediction. Drug PD allows the investigation of the effect of a drug on a biological system. Drugs, by binding to the target, can activate or inhibit biological processes, manifested in the form of agonistic or antagonistic effects, which may be complete or partial, reversible or irreversible [17]. It is crucial to consider that most processes in biological systems are nonlinear in time. A saturating effect is frequently observed, in which a further increase in the dose (and, therefore,

concentration) of the drug does not cause an increase in the positive pharmacological effect. Mathematically, such an effect can be described using Michaelis-Menten or Hill-type equations [18]. As the dose increases, the safety profile of the drug increases. Achieving a balance between drug efficacy and safety, as well as defining the "therapeutic window", represents one of the important challenges for drug developers. Among the approaches to modelling PD, direct and indirect response models should be distinguished. Direct response models are used when the system rapidly reaches equilibrium, and they directly relate the dose or concentration of a drug to the effect on a measurable biomarker or surrogate indicator of clinical response. A general formula for this type of response can be summarised as follows:

$$E = \frac{E_{\max} * C^{\gamma}}{C_{50}^{\gamma} + C^{\gamma}}, \tag{4}$$

where: E and E_{max} – effect and achievement of maximum effect; C and C_{50} – drug concentration level and concentration at which 50% of the maximum effect is achieved; γ – coefficient that reflects the rate of change of the concentration-effect curve in the region of values C_{50}.

Indirect response models allow the description of drug effects that are mediated or delayed. Indirect response models consider the significance of matching the rate of the processes responsible for the generation of an effect or biomarker and the rate of its elimination. To evaluate the effect of the therapy examined, mathematical models of PD can consider deviations from baseline levels, and the biomarkers examined, and separately consider the influence of placebo and circadian rhythms, which affect different biological processes [19]. Safety assessment is an essential step in pharmacology research and is the analysis of data on undesirable side effects that may occur during drug administration. Side effects are classified according to their severity, frequency and direct effects on the body to describe their characteristics more thoroughly. The medical dictionary for regulatory activities (MedDRA) is used to systematise and classify such effects [20]. In addition, safety assessment requires consideration of the possibility of delayed adverse effects. Some side effects, such as carcinogenic, mutagenic and teratogenic effects, may become apparent only after prolonged use of a drug. They may have long-term health effects, especially on the reproductive system. In addition, when discontinuing some medications, withdrawal syndrome may occur when undesirable effects become noticeable or intensify. It can be due to

physiological dependence on the drug or changes that occur in the body after discontinuation. A crucial aspect of safety assessment is the collection and analysis of data on adverse effects in clinical trials and post-marketing surveillance. It allows new or rare side effects to be identified, their frequency assessed and their association with a particular drug's application. In addition, it is essential to consider the context of using the drug, such as patient population, comorbidities and co-administration of other medicines, to better understand the factors affecting safety.

Among the mathematical modelling methods that are used to assess the safety of drug compounds or compare the efficacy of different therapies, it is significant to mention meta-analyses, including Bayesian meta-analyses [21]. These methods allow the calculation of posterior distributions of parameters of PK and PD systems, and probabilities of occurrence of specific events. In early-phase clinical trials, linear mixed-effects models are widely used to estimate the dose-dependent relationship of interval prolongation with drug dose associated with the risk of life-threatening atrial fibrillation. In addition, there are more complex mechanistic models of PK and PD, such as a model of the development of neutropenia during antineoplastic drug administration. Mathematical modelling is a powerful tool for data analysis and can significantly improve the efficiency of drug development. This approach maximises the extraction of useful information from the available data and, if the objectives are set correctly, facilitates informed decision-making at all stages of drug development.

4. Discussion

The application of mathematical methods in pharmacology is essential for assessing the safety of medicines. Modelling of undesirable side effects and assessment of safety profile allows anticipating possible risks and taking measures to minimise them. However, notably, the application of mathematical methods in pharmacology requires accurate calibration of models and validation against experimental data.

According to the results of recent studies by E.L. Bradshaw et al. [20], the application of quantitative systems pharmacology (QSP) in model-based drug development is an innovative approach that improves the understanding of drug interactions with biological systems and optimises the process of new drug development. QSP is based on mathematical modelling and computational simulation, which allows the establishment of quantitative models that consider the PK and PD characteristics of

drugs, their interactions with target molecules and the responses of the biological system to the drugs. Such models allow conducting virtual experiments, predicting the efficacy and safety of drugs, and optimising their dosage and regimens. The benefits of using QSP in drug development include the ability to reduce the time and cost of research that is typically required to develop new drugs. QSP allows researchers to conduct a large number of virtual experiments, analyse different scenarios and predict outcomes without the need for physical experiments. It helps to accelerate the decision-making process in the pharmaceutical industry and reduce the risks of research failures. Notably, QSP is still a relatively new approach and further development and validation of models for different types of drugs and biological systems is required [22]. In addition, it is necessary to consider the diversity of patients and their response to medicines to ensure that the models developed are sufficiently representative and have broad applicability.

Referring to the definition of V. Vakil and W. Trappe [21], drug combinations are a strategy in which two or more drugs are used together to achieve a synergistic effect or improve the therapeutic outcome. The application of mathematical modelling and network methods in the research of drug combinations provides new opportunities for optimising and predicting the outcomes of such combinations. The combination of mathematical modelling and network methods allows the complexity of interactions between drugs and the biological system to be considered at the system level. It can help researchers identify the most effective drug combinations, predict their effects and optimal dosages, and identify new purposes for developing combination therapies. However, notably, the application of mathematical modelling and network methods to explore drug combinations is challenging. It requires accurate calibration of models and analysis of large amounts of data, and consideration of various factors such as PK, PD, dosage and patient characteristics.

Researchers K. Azer et al. [23] determined that the disciplines of quantitative systems pharmacological modelling play an essential role in drug development and application. These disciplines combine mathematical modelling, computational modelling, and systems approach to analyse and optimise drug interactions with biological systems. One of the key disciplines of quantitative systems pharmacological modelling is PK modelling. It explores how drugs interact with the body, including their absorption, distribution, metabolism and excretion. PK models can predict drug concentrations in different tissues and organs of the body over time, which helps to optimise dosing and administration regimens.

Another important discipline is PD modelling. It explores how drugs affect biological processes and molecular targets in the body. PD models help predict the pharmacological effects of drugs, their dose-effect relationships and interactions with other drugs. In addition to these disciplines, important aspects of quantitative systems pharmacological modelling include statistical modelling, including data analysis and predictive model building, and using network methods to explore complex interactions between molecules, cells and organs.

G. Koch et al. [24] identified that pharmacometrics and machine learning play a significant role in improving clinical data analysis in the field of pharmacology. Pharmacometrics is a discipline that uses mathematical and statistical methods to explore the interactions between drugs and biological systems. Machine learning, on the other hand, is a subset of artificial intelligence that allows computer systems to learn on their own and make predictions or decisions based on data. However, the implementation of pharmacometrics and machine learning in clinical data analysis faces some challenges. It is crucial to have reliable and high-quality data to train the models, and to consider their limitations and caveats. Incorrect use or interpretation of machine learning results can lead to incorrect conclusions or poor decision-making in clinical practice.

L. Hutchinson et al. [25] demonstrated that deep learning is a branch of machine learning based on using artificial neural networks with multiple layers to extract and process complex data structures. In recent years, deep learning has attracted a lot of attention in various fields, including clinical pharmacology. This pioneering field offers many opportunities to improve the understanding and prediction of drug effects. One of the major advantages of deep learning in clinical pharmacology is its ability to analyse and process large amounts of diverse data, including medical records, genetic data, and images. Neural networks can learn complex drug-patient interactions, considering factors such as genetic predispositions, metabolic pathways, and the body's responses to therapy. It can more accurately predict drug effects and optimise their use in individual cases. However, the implementation of deep learning in clinical pharmacology comes with some challenges. One of them is the need for high-quality and reliable data for training neural networks. Ethical and legal aspects related to using sensitive patient medical data are required.

As noted by J. Malinzi [26], mathematical analysis of the chemovirotherapy model can be a useful tool to explore and evaluate the impact of different drug infusion methods on treatment outcomes.

Chemovirotherapy is a combination therapeutic strategy that combines the application of chemotherapy and viral therapy to combat tumour disease. A mathematical model of chemovirotherapy can consider factors such as drug distribution in body tissues, infusion regimens and drug concentrations, tumour growth rate, virus and drug interactions with tumour and healthy cells and other parameters. Analysis of this model can help to determine the optimal drug infusion parameters that can maximise treatment efficacy and minimise side effects. One important aspect that can be explored using mathematical analysis is determining the optimal duration and frequency of drug infusion. Modelling can demonstrate how changes in infusion duration and frequency affect the concentration of the drug in the tissue and its effect on the tumour. It allows treatment regimens to be optimised to achieve the best possible results.

5. Conclusions

In conclusion, notably, mathematical modelling is a powerful tool for data analysis and plays an important role in drug development. The application of mathematical methods in pharmacology is an integral part of drug development and optimisation. As a result of the research on this subject, the following conclusions can be drawn. Using mathematical modelling allows establishing accurate models of drug action, analysing their PK and PD, and optimising dosing. It helps to improve treatment efficacy, reduce the risks of side effects and accelerate the process of new drug development. Mathematical modelling helps to extract the most useful information from the available data, which facilitates informed decision-making at various stages of drug development. It helps in determining the optimal model structure, training it, validating it and performing further analyses based on the predictions obtained. Mathematical modelling addresses a wide range of issues that arise at different phases of drug development. It covers the modelling of drug PK, absorption, distribution and elimination analyses, and efficacy and safety analyses. In addition, approaches to defining the therapeutic window of a drug are explored.

The research on the application of mathematical methods in pharmacology is of practical significance. It contributes to the development of more accurate models of PK and PD, optimising drug dosing and improving prognostic accuracy. It results in the development of more effective and safer drugs, which, in turn, contributes to improving the quality of patient care. Thus, the application of mathematical methods in

pharmacology is a necessary and promising area of research. Further research should be devoted to the investigation of drug interactions with other medicines, and the consideration of possible side effects in the combined use of drugs. It will allow disclosing more fully the potential of mathematical modelling in pharmacology and improve the efficiency of drug development.

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