World Journal of Pharmaceutical Science and Research
www.wjpsronline.com
Short Communication
ISSN: 2583-6579
SJIF Impact Factor: 5.111
Year - 2024
Volume: 3; Issue: 5
Page: 365-370

OPTIMISING DRUG DEVELOPMENT- A DYNAMIC APPROACH WITH MODEL AND SIMULATION STRATEGIES

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Article Received: 04 August 2024 | | ***Article Revised: 23 September 2024*** | | ***Article Accepted: 15 October 2024***

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DOI: https://doi.org/10.5281/zenodo.14025213

How to cite this Article: Dr. Yuvraj Kaushal and Dr. Pranav Goyal. (2024). OPTIMISING DRUG DEVELOPMENT- A DYNAMIC APPROACH WITH MODEL AND SIMULATION STRATEGIES. World Journal of Pharmaceutical Science and Research, 3(5), 365-370. https://doi.org/10.5281/zenodo.14025213

ABSTRACT

In 2021, the Food and Drug Administration recognized the potential of modeling and simulation (M&S) tools in enhancing drug policy development, postmarket product evaluation, and premarket analysis. While mathematical modeling isn't new to drug research, pharmacokinetic/pharmacodynamic (PK/PD) modeling uniquely examines the interactions between drug kinetics and dynamics in the body. PK modeling quantifies drug absorption and distribution, whereas PD modeling assesses the biological response over time. M&S techniques support various FDA centers, such as CDER, CDRH, and NCTR, in product evaluation and safety assessments, particularly through physiologically based pharmacokinetic (PBPK) modeling. These models help predict drug bioequivalence, optimize dosing, and assess risks associated with new substances, as seen in the FDA's PHASE initiative for synthetic opioids. Recent collaborations have further advanced the use of mechanistic-based PBPK modeling for toxicology testing and impurity evaluation, reducing the need for extensive experimental studies. Despite the benefits, limitations exist, such as the simplification of complex biological systems and the challenge of modeling drug-drug interactions. Nevertheless, continuous advancements in computational techniques and clinical validations are essential to refine these models for better predictive accuracy and regulatory decision-making. The use of M&S in drug development and regulatory processes is expanding, with significant implications for improving drug safety, efficacy, and personalized medicine strategies.

KEYWORDS: Pharmacokinetics, Pharmacodynamics, Drug Development, Computer Simulation, Models.

Comment

In 2021, the Food and Drug Administration gained knowledge on the virtues of M&S tools in policy creation and execution, postmarket product evaluation, premarket product analysis, and the use of M&S tools. Although

mathematical models are not new for drug research and development, PK/PD modeling is distinct in its analysis of systemic pharmacokinetics (PK), pharmacodynamics (PD), and their interactions.[2,3] PD modeling studies assess the time response of pharmacological action in the body's biological system, which also includes rate-limiting conditions and mechanisms of action. In contrast, PK modeling comprehensively quantifies drug absorption and distribution in the body.[4] Drug-specific-related factors such as clearance and receptor-binding ability, the delivery system-specific-related factors including the clearance rate, release rate, and the internalization rate of the carrier are also related to the site-of-action factors such as blood flow, cell-life span, their expression of enzymes and transporters, and pathological system-specific parameters and all these factors can be measured in relation.

Along with CDER and CDRH at the FDA, numerical and computational modeling and simulation (M&S) techniques play a role in premarket and postmarket product applications. The NCTR, advised by population-based modeling methodologies, implements pre-admission approval and works with product-focused centers to obtain M for post-market assessment.[7]

The authors of global reports have underlined the model utilization features that can be used in new drug development at different stages of the life cycle. CDER introduced PHASE, a multicomponent computational structure evaluation method. This was a noteworthy project. According to the Process for the Assessment of Synthetic Opioids (PHASE), the authority wants to identify the risk that novel synthetic opioids carry to public safety, while medical data about the substance are absent or scarce. PHASE aids emergency hindsight for possible drugs of abuse and enables the improvement of primary scheduling by the high resource demand of experimental investigations on all conceivable fentanyl analogs. Moreover, with the assistance of comprehensive mechanistic-based PBPK modeling, BPA, and metabolite testing, NTP and NCTR have recently come together to carry out toxicology testing and pharmacokinetic studies can now be done. One of the important investments made by the FDA in the past two decades has been the creation and development of chemical structure tissue data banks that were used to resolve toxic impurities in medicines. Since 2014, [(Q)SAR models have been able to predict] the probability of mutagenicity in impurities. They work with high throughput, thus eliminating the need for a normal time-consuming toxicity test. Furthermore, both these sites, the Office of Food Additive Safety (OFAS) by the Center for Food Safety and Applied Nutrition (CFSAN), and the Office of Applied Research and Science Assessment (OARSA) by the Center for Food Safety and Applied Nutrition (CFSAN), have set in motion the process of creating the methods needed to support both pre- and post-market safety assessments.[8-10]

In addition to testing it as a measure of efficacy, S&M has been implemented to test for bioequivalence (BE), newly known as "Virtual Bioequivalence" (VBE). M&S operates both instead of and together with clinical studies to display the VBE concept. The FDA acknowledges that to simplify the regulatory decisions regarding both new and generic molecules, both the posology and route of administration can be established clinically without reference to human volunteer studies by using physiologically based pharmacokinetic modeling (PBPK). To elicit the bioequivalence of 6-MP, Bhavatharini Arun et al. established their models using PCastic, particularly the Non-Compartment Model of Phoenix WinNonlin® version 8.2. Simcyp also utilizes the MPML approach to develop the MechDermATM model, which is designed for Mechanistic Dermal Absorption. This just-in-time model of flex-time with increased automation was accepted by the FDA in 2019, which incorporated an accelerated new drug submission protocol.

The very purpose of this study by Bhavatharini Arun et al.[1] was to help doctors regarding the determination of the 20% lesser dose of 6-Mercaptopurine Powder for Oral Suspensions (PFS) which was more helpful than the traditional tablets in the treatment of acute lymphoblastic leukemia. The researchers defined an appropriate dose of PFOS by simulating several PFOS exposure levels using a population pharmacokinetic (PopPK) model. The main aim of this study was to determine the pharmacokinetic and clinical similarities or discrepancies between the reference formulation (tablet) and the test formula (oral solution). The physicochemical, in vitro, and clinical pharmacokinetics of the soil were investigated.

Modeling and simulation (M&S) is a computational adjunct that is in line with the traditional techniques of data processing for the substances/items governed by the FDA and is also a useful adjunct for influencing FDA policy. The role of the FDA's support of M&S in many areas of its preclinical and clinical drug development processes broadens, allowing the FDA to explore various approaches to research design, data analysis, and forecasting of study outcomes to narrow the gap between the discovery of new treatments and finding those that are both safe and effective during preclinical trials up to commercialization. To project long-term outcomes, improve clinical trial designs, ensure products are effective, target population groups, and assess safety, it is imperative to check the models and simulations by the FDA. In-silico clinical trials are sometimes substituted for human trials especially when the drug-drug interactions are the beginning point in analysis.[13]

The utilization of M&S by European regulatory agencies is largely led by the support for effective clinical development of anti-infective as well as pediatric-focused medicines with the patients as that is their primary concern. The regulatory process is heavily focused on the clinical phases of medicine development, emphasizing the methodology and supporting it instead of simply verifying the final product. It is estimated that M&S will have a greater impact on this domain. The ICH Topic E4 recommended guideline, which is also internationally accepted, has advised developers and regulators to be open to different methods that may include the use of different statistical techniques and pharmacometrics for ease of interpretation and extraction of the data, especially in identifying dose-response relationships or concentration-response relationships.[14] While there are no particular European guidelines on Model and Simulation (M&S) applications, the last regulatory strategy considers the adoption of M&S utilization to help formulate adequate dosages. For example, this case may be mentioned in guidelines for children[16–18] and subjects with organ failure.[19–20]

Researchers are promoting the application of exposure-response models in line with drug development, which is moving towards modeling and simulation (M&S). This will help to establish an optimal and less toxic dosage, followed by a series of simulations to educate both audiences. However, this methodology generates money in addition to labor cost savings, which ultimately directly affects the drug's developmental cost. Concerning drug distribution, the M&S assists patients and scientific staff. Inspiring evidence of developing stations is when the successful PFOS 6-mp (this is the first drug formulation produced in India using a model and strategy) was developed. The drug system can check and offer the required ongoing targets more effectively and help both shareholders reach their markets, the concerned physicians to undertake healing, and better and more accurate treatment availability for the patient.

Limitations

PK modeling usually applies the assumption and simplification of linear pharmacokinetics and homogenous compartments. Thus, there is the possibility that they lack the real picture of the complex biological systems. This

veracity is only as respectable as the reliability and precision of the information that is fed into the system. An abstruse parameterization can cause huge incorrect prediction errors, for example, the use of Back-calculating in vitro intrinsic clearance from in vivo data as a method including enzyme fractional contributions in the simulation of pharmacokinetics with varied enzyme activity or abundance. Its accuracy is contingent on precise information about the enzyme contributions, systemic clearance (if available), and bioavailability (as well). This information might be uncertain.[21] Moreover, the ability to manipulate the 3D body in real-time is a major part, the fact is that both the models and people have different factors including age, weight, genetics, and health factors that may not be similar.[22] However, other limitations include the lack of suitable tools for the modeling of drug-drug interactions involving several pathways or mechanisms of action.[6] The inventory can have no end if we move on by scratching the surface. As such, the hurdles can be overcome by utilizing progressing measurements, advanced calculations, and continuous clinical validation to improve the ability of models to predict pharmacokinetics.

DECLARATIONS

a) Ethics Statement: NA

b) Informed Consent: NA

c) Acknowledgment: NA

d) Funding: No funding received.

e) Conflict of Interest Statement: The authors declare no conflict of interest.

f) Availability of data and materials: NA

g) Authors' contributions: Credit authorship contribution statement.

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