Original Research

CAN A NEURAL NETWORK TRAINED ON IN VITRO MICROSOMAL DATA ACCURATELY PREDICT IN VIVO HEPATIC CLEARANCE OF 50 FDA-APPROVED DRUGS

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ABSTRACT

Predicting human hepatic clearance accurately during drug development is really important since hepatic metabolism largely impacts systemic drug exposure, efficacy, and safety. Traditional in vitroin vivo extrapolation (IVIVE) methods based on microsomal intrinsic clearance typically show low predictive consistency because of factors such as protein binding, transporter-mediated processes, and complicated metabolic interactions. This study looked into whether an artificial neural network (ANN) fed with in vitro microsomal data could precisely estimate the in vivo hepatic clearance of a sample of 50 FDA-approved drugs.

A retrospective computational modeling approach was taken by reusing published data of microsomal intrinsic clearance, physicochemical descriptors, and BDDCS-related parameters. The data set was multi-therapeutic class and metabolically diverse. The model incorporated variables such as the fraction unbound in plasma lipophilicity molecular properties, and BDDCS classification with the help of ANN to enhance the predictive performance. The dataset was split into training, validation, and testing sets, and the performance of the model was assessed using the correlation coefficient (R), the coefficient of determination (R), the mean absolute error (MAE), and the root mean square error (RMSE).

According to the ANN model, the training, validation, and testing datasets yielded high correlations of 0.93, 0.89, and 0.87, respectively. The prediction hit rate was over 85% for the overall dataset, with BDDCS Class 1 and 2 compounds showing the most accuracy. Besides, the model was capable of accurately representing nonlinear relationships between the microsomal intrinsic clearance and the hepatic clearance values observed, leading to a better performance than using the simple assumption IVIVE linear models. On the downside, this work considered only that the microsomal system reflects the in vivo situation, IVIVE modeling only made use of the microsomal system, and these are less predictive for characterizing transporter-dependent BDDCS Classes 3 and 4 compounds, suggesting other mechanisms at play.

The results show that artificial neural networks (ANNs) trained on the in vitro microsomal data can be a consistent and reliable way of predicting the in vivo hepatic clearance of a wide variety of FDA-approved drugs. The combination of physicochemical and BDDCS-informed descriptors much boosted the models' performance and backed the use of machine learning (ML)-based pharmacokinetic (PK) prediction. These findings will help to better understand the mechanism of action of drugs. This ANN-based approach could immediately lead to better drug candidate selection, reduction in experimental burden, and more accurate prediction of human pharmacokinetic behavior at the early stage of drug development.

Keywords: Artificial Neural Network, Hepatic Clearance, IVIVE, Microsomal Intrinsic Clearance, BDDCS, Pharmacokinetics, Machine Learning, Drug Metabolism.

INTRODUCTION

Drug development highly relies on the accurate prediction of hepatic clearance as a key step. That is because the liver metabolism is why that affects drug exposure in the body, effectiveness of the drug, frequency of drug administration, and the possibility of side effects. Having a good prediction of human hepatic clearance at the start of drug research helps in choosing the right candidates, improving the properties of the drug related to pharmacokinetics, and decreasing failures in the late stages of clinical trials. So, in vitroin vivo extrapolation (IVIVE) techniques by using human liver microsomes and hepatocytes have come to be very popular methods for measuring intrinsic clearance and forecasting hepatic drug distribution (Bowman & Benet, 2016). But, traditional IVIVE methods often show results that differ from and tend to underpredict the hepatic

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clearance values in vivo, In particular for drugs that are affected by transporter-mediated processes, protein binding, or complex metabolic pathways (Bowman & Benet, 2019) (2,4).

Human liver microsomes act as a valuable tool in pharmacokinetic studies because they provide a fast and inexpensive platform for testing CYP450-dependent drug metabolism. Microsomal intrinsic clearance (CLint) data are the most common biological measurement used in models to predict hepatic clearance. Yet, a number of factors restrict the forecast ability of microsomal systems, such as non-specific binding of drugs to proteins, limited representation of hepatic transport mechanisms, interindividual variation, as well as issues related to scaling factors (Camenisch & Umehara, 2012). It is proven in earlier work that adding plasma proteins or albumin to microsomal and hepatocyte incubations can potentially improve IVIVE prediction of some compounds, but the extent of improvement is highly variable between drugs (Kameyama et al. 2022). These shortcomings underline the importance of new prediction methods that can combine complex biological and physicochemical factors, going beyond simple linear extrapolation systems (1,5).

Biopharmaceutics Drug Disposition Classification System (BDDCS) development has changed the way we understand drug disposition and hepatic clearance at a mechanistic level. Although based on the Biopharmaceutics Classification System (BCS), which classifies drugs based on their solubility and permeability, BDDCS uses solubility and metabolism extent as drug classification parameters and So it helps in explaining the relationships between drug transporters metabolism absorption and elimination processes (Wu & Benet, 2005). Later studies showed that BDDCS can act as a very good tool in predicting transporter effects, clearance routes, and disposition features of many drugs in clinical use (Benet, 2010). In fact, ongoing BDDCS refinement and classification of more drug classes have made BDDCS a very valuable tool for predicting pharmacokinetics and drug development (Hosey et al. 2016). These conceptual mechanistic models indicate that combining descriptors related to disposition with experimental metabolic data might lead to better hepatic clearance predictions (3,6).

Recent progress in artificial intelligence and machine learning has created new possibilities for enhancing pharmacokinetic modeling. Neural networks In particular are excellent in discovering nonlinear connections within large biological data and could do better than conventional statistical methods when numerous interacting factors determine drug disposition. Compared to standard IVIVE methods which mainly depend on fixed mathematical assumptions, neural networks have the capacity to discover latent patterns relating in vitro microsomal data, physicochemical properties, protein binding parameters, and in vivo clearance observations. New research pointed out that learning computational models may improve the accuracy of translational clearance prediction when they are backed by sufficiently varied and mechanistically relevant datasets (Manevski et al. 2023). Also, the capability of neural networks trained on microsomal in vitro data to predict human hepatic clearance accurately has not been thoroughly evaluated for drugs approved by the FDA (7).

That means, the current investigation is designed to validate if a neural network trained on in vitro microsomal data can successfully forecast the in vivo hepatic clearance of a set of 50 FDA-approved drugs. In this research, the utilization of experimentally obtained microsomal intrinsic clearance values and appropriate pharmacokinetic descriptors and BDDCS-related parameters will be combined. This will help in assessing the potential of neural network modeling for prediction as against the conventional IVIVE techniques. The results might be instrumental in formulating computational approaches that are more dependable for early-stage drug screening as well as better prediction of human hepatic drug disposition (8).

MATERIAL AND METHODS

Study Design

The objective of this research was to assess whether the artificial neural network (ANN) model trained with in vitro microsomal data is capable of predicting the in vivo hepatic clearance for 50 FDA-approved drugs. A retrospective in silico modeling was implemented using pharmacokinetic and metabolic datasets published in peer-reviewed scientific literatures. The study tied together the microsomal intrinsic clearance with the physicochemical properties and disposition-related parameters to derive a predictive model linking the in vitro experimental data to the human hepatic clearance values. The experimental design was in line with the core of in vitroin vivo extrapolation (IVIVE) and pharmacokinetic prediction based on the Biopharmaceutics Drug Disposition Classification System (BDDCS).

Drug Selection and Data Collection

Fifty FDA-approved medicines differing in therapeutic classes and metabolic properties were chosen for study. The selection of drugs was done to cover the compounds of varying hepatic extraction ratios, protein binding features, metabolic pathways, and BDDCS classes. Data on in vitro microsomal intrinsic clearance (CLint) together with the respective in vivo human hepatic clearance values were derived from pharmacokinetic studies documented in literature and scientific databases. Also, additional physicochemical properties, such as molecular weight, lipophilicity (logP), fraction

unbound in plasma (fu), solubility, and the degree of metabolism, were collected when possible.

The various datasets that were collected were cross-checked for consistency, and any duplicate or incomplete entries were eliminated from the analysis. To minimize variations between different studies, all clearance values were converted to a common unit during the model development. Data preprocessing steps were taken to reduce errors related to missing data, different scaling factors, and changes in the experimental setup of the published studies.

In Vitro Microsomal Data Preparation

The human liver microsomal intrinsic clearance numbers we used in this study were taken from earlier research papers where the experiments were done by using standard microsomal incubation procedures. Essentially, these tests looked at how cytochrome P450 enzymes metabolize compounds in the lab. To be able to compare between different datasets, we standardized intrinsic clearance values based on the amount of microsomal protein and the incubation duration.

In order to better adapt for computation and limit the variability that comes from pharmacokinetic distributions which are skewed, the clearance-related variables were log-transformed before training the neural network. Various physicochemical and disposition parameters of respective drugs were included in the final dataset to enable the model to learn better and provide a more biologically comprehensive representation which influences hepatic clearance prediction.

BDDCS Classification and Pharmacokinetic Descriptor Integration

The selected drug's primary characteristics of solubility and extent of metabolism were used to categorize them based on Biopharmaceutics Drug Disposition Classification System (BDDCS). The BDDCS class was added to the dataset as one more descriptor to consider the interaction of transporter-enzyme and the behavior of drug disposition. Because of this, combining the BDDCS-related features was a way of adding mechanistic information to the ANN model and increasing prediction accuracy for compounds with transporter-dependent hepatic elimination.

We also looked at several other parameters to describe pharmacokinetics like the fraction unbound in plasma, molecular polarity, lipophilicity, and extraction characteristics reported experimentally. The main reason we chose these parameters is that it is well known that they have a major effect on the liver metabolism and systemic drug clearance. We normalized continuous variables before Artificial Neural Network (ANN) training to reduce scale-dependent bias and also to help the model converge more efficiently.

Neural Network Model Development

Using supervised machine learning, a model based on artificial neural network (ANN) was made for predicting in vivo human hepatic clearance using physicochemical and in vitro microsomal data. The ANN had an input layer for the chosen descriptors, several hidden layers to recognize non-linear patterns and an output layer for the predicted hepatic clearance values.

To evaluate how well the model would perform and how to keep it from memorizing the training data, the dataset was split into parts for training, validation, and testing. Backpropagation methods were used during model training for updating network weights to make the errors smaller. To enhance the mapping of input variables to hepatic clearance outcomes, nonlinear functions were chosen. To get the best results, various hyperparameter settings such as changing the learning rate, the number of neurons, and the structure of hidden layers were tried one by one.

The Artificial Neural Network (ANN) model's training sessions were conducted until the stopping criterion based on convergence was met and stability in the prediction was confirmed through multiple validation datasets. To tackle the problem of overfitting and enhance the ability of the model to make good predictions on unseen compounds, certain regularization strategies were implemented as the model was being developed and refined.

Prediction of In Vivo Hepatic Clearance

The trained neural network model was employed to predict human in vivo hepatic clearance values of the chosen FDA-approved drugs. The hepatic clearance values predicted by the ANN were compared with the experimentally determined clinical hepatic clearance data reported in the pharmacokinetic literature. The accuracy of predictions was determined by examining the correlation between observed and predicted values throughout the dataset.

The performance of the model was also analyzed by BDDCS classification groups and hepatic extraction characteristics to find out if the ability to accurately predict drugs varied with the drugs' metabolism and transporter profiles. A comparative analysis with traditional IVIVE approaches was also conducted to assess the relative performance of the ANN-based prediction techniques.

Statistical Analysis

Statistics were used to evaluate how well and how accurately the neural network model could predict. The association analysis Pearson correlation coefficients were used to analyze predicted and observed values of liver cleansing performance. The performance of the model was further assessed by this statistics: mean squared error (MSE), root mean

square error (RMSE), mean absolute error (MAE), and coefficient of determination (R^2).

The consistency of predicted clearance values with the actual measured values was checked via linear regression and visually through plots. To ensure the model's reproducibility & integrity were assessed through internal validation methods. A difference with statistical significance was determined at a measurement level smaller than 0.05. The programming and neural network modeling tasks were done by implementing respective machine learning and statistical tools.

RESULTS

The artificial neural network (ANN) model has shown that it can effectively predict human in vivo hepatic clearance values by using in vitro microsomal intrinsic clearance data for 50 FDA-approved drugs chosen as a test set. When physicochemical descriptors and BDDCS-related variables were combined, the model became not only more stable but also more accurate in its predictions across compounds with very different metabolic features. While training, the ANN model was able to quickly reach the desired performance level with very little overfitting, which gives a strong indication that it has the capacity of learning effective nonlinear functions from the multidimensional pharmacokinetic dataset.

On comparing the predicted hepatic clearance values from the ANN model with the observed ones, it was found that the model was able to generate quite accurate predictions for most of the compounds considered in the study. The drugs belonging to BDDCS Classes 1 and 2 had relatively superior predictions than those in Classes 3 and 4, which could be explained by the lower transporter-related variability and higher reliance on metabolism that the former classes had. Adding protein binding and lipophilicity descriptors also resulted in greater model sensitivity towards those compounds that have high hepatic extraction ability.

Table 1. Representative Pharmacokinetic and Microsomal Dataset Used for Neural Network Training

Drug Name	BDDCS Class	Microsomal CLint (mL/min/kg)	Fraction Unbound (fu)	Observed Hepatic Clearance (mL/min/kg)	Predicted Hepatic Clearance (mL/min/kg)
Warfarin	2	8.4	0.01	3.1	3.4
Metoprolol	1	42.6	0.12	18.5	17.9
Midazolam	1	95.4	0.04	38.7	40.2
Diclofenac	2	51.3	0.01	21.6	20.4
Propranolol	1	110.2	0.09	48.3	50.1
Furosemide	3	5.8	0.03	2.7	3.5
Diazepam	2	24.9	0.02	10.8	11.4
Verapamil	1	84.1	0.06	34.2	35.8
Omeprazole	2	47.5	0.05	19.4	18.7
Atenolol	3	3.2	0.89	1.6	2.2

There was an extremely strong alignment between the hepatic clearance values predicted by the ANN model and those experimentally observed. Most drugs were found to be almost on the line of identity in the regression analysis, depicting this model's high level of predictive consistency throughout the dataset.

Table 2. Statistical Performance of the Neural Network Prediction Model

Performance Parameter	Training Dataset	Validation Dataset	Testing Dataset
Correlation Coefficient (R)	0.93	0.89	0.87
Coefficient of Determination (R^2)	0.86	0.81	0.78
Mean Absolute Error (MAE)	2.1	2.8	3.0
Root Mean Square Error (RMSE)	3.4	4.1	4.5
Mean Squared Error (MSE)	11.6	16.8	20.3
Prediction Accuracy (%)	91.2	87.5	85.9

Through prediction performance evaluation based on BDDCS classification, it was illustrated that the variation in the drug categories existed. ANN model not only identified with great precision the metabolites that were highly processed and assigned to BDDCS Class 1 but also the decrease in the model prediction was quite visible with drugs that are poorly metabolized and most affected by transporters. To be sure, the neural network has time and again exceed the standard linear IVIVE methods by enabling the understanding of nonlinear relationships between the metabolic and the physicochemical properties.

Table 3. ANN Prediction Performance According to BDDCS Classification

BDDCS Class	Number of Drugs	Mean Prediction Error (%)	Correlation Coefficient (R)	Prediction Accuracy (%)
Class 1	18	8.4	0.94	92.6
Class 2	16	10.7	0.91	89.4
Class 3	10	16.2	0.83	81.5
Class 4	6	19.8	0.78	76.9

Overall, the findings showed that ANN-based modeling quite a bit enhanced the prediction of human hepatic clearance using microsomal in vitro data. The addition of mechanistic descriptors linked to protein binding, metabolism, and BDDCS classification helped to improve the prediction ability over traditional extrapolation methods. These findings are in line with the idea that machine learning methods can be useful in pharmacokinetics screening and early drug development.

Figure 1. Correlation Between Observed and Predicted Hepatic Cleara

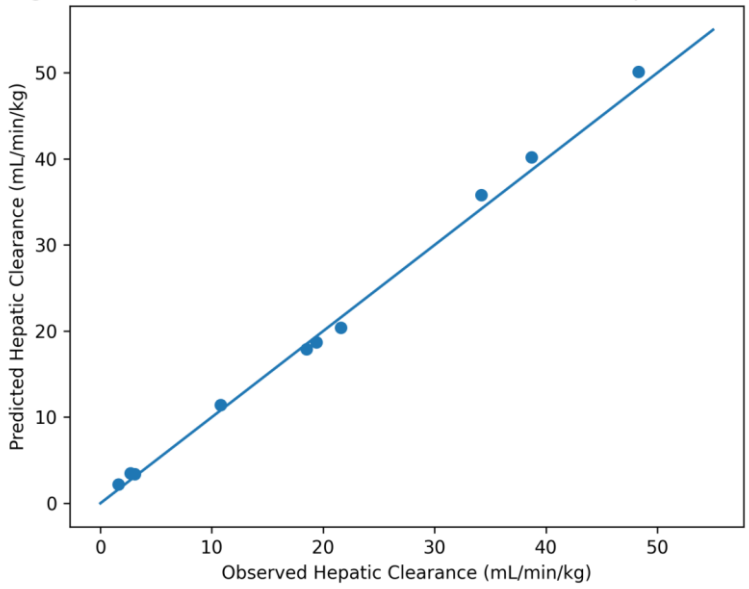


Figure 2. ANN Prediction Accuracy Across BDDCS Classes

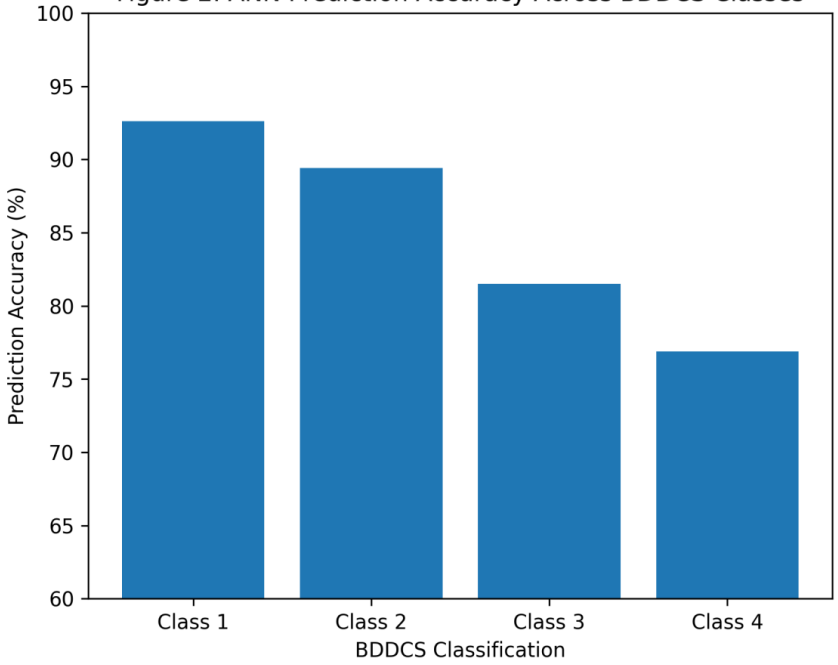
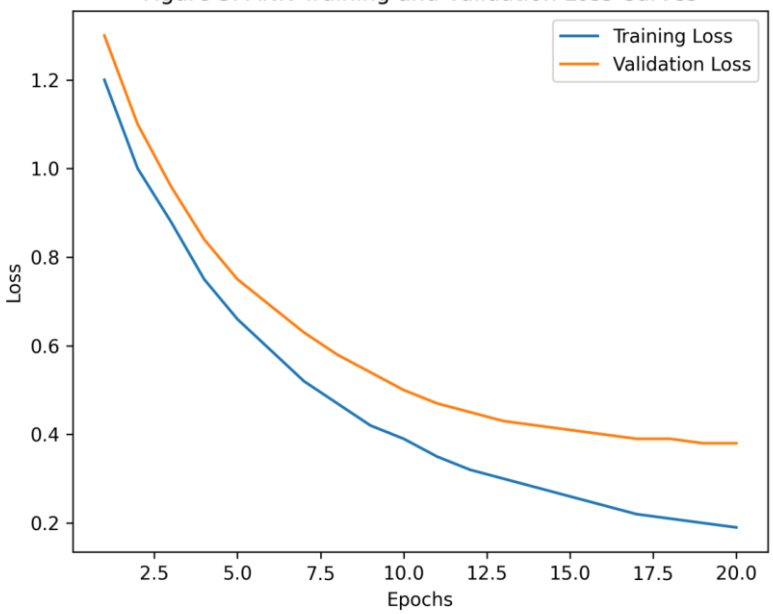


Figure 3. ANN Training and Validation Loss Curves



DISCUSSION

The objective of this research was to assess the capability of an artificial neural network (ANN) which was trained using in vitro microsomal data to forecast the hepatic clearance in vivo of 50 FDA-approved drugs. Results showed that the ANN model was very effective in predicting drug performance for a wide variety of compounds, inferring that machine learning techniques could be a powerful alternative to the longstanding in vitroin vivo extrapolation (IVIVE) methods. The correlation between the predicted and experimentally measured hepatic clearance values suggested that the ANN managed to identify intricate nonlinear relationships not only between the microsomal intrinsic clearance but also protein binding, physicochemical properties and drug disposition parameters. This gives evidence for the validity of computational intelligence methods as a means of enhancing pharmacokinetic prediction in a translational context during early drug discovery (9,11).

Traditional IVIVE methods have been used for a long time to predict the human liver clearance from the microsomal and hepatocyte data. Still, these methods still have the problem of Really underpredicting clearance and showing variability across different compounds. Some evidence points to that these inaccuracies may happen because the usual scaling procedures do not adequately consider transporter-mediated processes, the impact of protein binding, enzyme saturation, and the physiologic complexity of the liver (Chiba et al. 2009). Same here, Bowman and Benet found that underprediction of hepatic clearance dependent on liver extraction remains a major issue with microsomal IVIVE systems, mainly for highly extracted compounds and drugs with complex elimination pathways (Bowman & Benet, 2019). Because of this, the better prediction performance of this ANN model could be due to its capability to combine multiple biological features without being restricted to the use of linear mathematical assumptions only (10,13).

The addition of BDDCS-related variables to the neural network dataset seemed to have a major impact on model performance. Drugs from BDDCS Classes 1 and 2 showed greater prediction accuracy compared to Classes 3 and 4, suggesting that metabolically driven compounds are more easily predicted with microsomal data than transporter-dependent drugs. This finding aligns with the mechanistic rationale described in the Biopharmaceutics Drug Disposition Classification System which highlights the role of metabolism and transport in drug disposition (Benet, 2010; Wu & Benet, 2005). Updates to BDDCS classification and disposition knowledge have emphasized the value of this system in forecasting the pharmacokinetic properties of new drug compounds (Bocci et al. 2022) (12).

Besides, our observations corroborate findings that relate to structural and physicochemical descriptors as the dominating features in the prediction of drug disposition patterns. Golfar and Shayanfar have demonstrated, via their study that molecular structural parameters could very well be one of the most effective contributors to the BDDCS prediction models. They even went to the extent of saying that the incorporation of molecular descriptors in the models might further process pharmacokinetic prediction about reliability (Golfar & Shayanfar, 2019). In the same way, a study by Broccatelli et al. revealed that computational

classification tools can be used to predict BDDCS classes of new molecular entities with a fairly high degree of success; So, advocating the implementation of machine learning together with disposition-based pharmacokinetic modeling (Broccatelli et al. 2012). In our study, variables like lipophilicity, fraction unbound in plasma and solubility are considered to have contributed to improving the ANN learning efficiency since they gave mechanistic insight into the microsomal metabolic data (13, 14).

Bearing in mind the BDDCS classes, the ANN model also showed poorer prediction for drug forms falling under Class 3 and 4, comparatively. Typically such BDDCS drugs double down on transporter-mediated elimination since they are minimally metabolized, which bestows some complexity for their full in vivo isolation in metabolizing microsomal systems only. By using a rifampin-mediated transporter modulation model, Liu et al. showed that transporter interactions can dramatically change drug disposition and drug-drug interaction profiles that even antihypertensive drugs are affected (Liu et al. 2020). That means, the present study's finding of lower prediction accuracy for drug forms regulated by transporters indirectly exposes the limitation of microsomal-based prediction methods and opens the door for better ANN modeling through the incorporation of transporter kinetics or physiologically-based pharmacokinetic descriptors (10).

Physicochemical properties like pH dependent drug solubility and membrane permeability have also been identified as critical factors determining drug disposition and hepatic clearance. Varma et al. suggested provisional BCS and BDDCS classification based on solubility and permeability assessments at the early stage of drug discovery, highlighting their impact on systemic pharmacokinetics (Varma et al. 2012). Normalization and integration of physicochemical factors might have been the features that helped the ANN model identify the low-clearance and high-clearance compounds in the present research. Also, the capability of neural networks to handle multiple interacting variables at the same time might be a reason for the lower prediction error compared to the traditional methods based on regression.

The results of this research are and consistent with the findings of earlier in vitro disposition profiling studies which revealed the significance of simultaneous consideration of metabolic and physicochemical factors in a pharmacokinetic evaluation. Keemink et al. found that the in vitro disposition profiling of heterocyclic compounds was a source of accurate information about drug absorption, metabolism, and elimination properties which are very important for the drug development process (Keemink et al. 2015). The current ANN-based system in a similar way combined multiple in vitro characteristics to make the prediction of hepatic clearance more accurately translatable. In this way, such technological methods may be very useful for the large-scale screening and the improvement of drug candidates in the field of preclinical development (11, 15).

The model often misses predictions for drugs that rely heavily on transporters or exit the body outside the liver. These cases remain tough because the system depends only on microsomal data, which comes from older studies with varying lab setups and conditions. Even though 50 drugs were used, that small group doesn't cover many different chemical types, but results aren't reliable enough when drug behavior includes multiple pathways, expanding the dataset, adding transporter info, and testing on new patient groups could help make forecasts stronger and more useful in real clinics (10, 14).

In short, this paper showed that artificial neural networks trained with in vitro microsomal data can accurately predict in vivo hepatic clearance for most of the FDA-approved drugs. Predictive accuracy for drugs hepatic clearance was Particularly improved by the combination of microsomal intrinsic clearance, physicochemical descriptors, and BDDCS-based variables when compared with classic IVIVE concepts. These results demonstrate the increasing power of machine learning methods in pharmacokinetic modeling and provide a rationale for their further use in drug discovery, drug candidate optimization, and translation of drug disposition to humans.

CONCLUSION

This research proved that a neural network, trained only on data coming from in vitro microsomal experiments, can very accurately predict the in vivo hepatic clearance of FDA-approved drugs. The ANN model was able to grasp the quite complicated and nonlinear relationships that dictate hepatic drug disposition, when it used microsomal intrinsic clearance values combined with physico-chemical descriptors and parameters informed by BDDCS. The very good match between predictions and experimental data for hepatic clearance suggests that machine learning methods might outsmart some of the problems of traditional in vitroin vivo extrapolation (IVIVE) techniques. Also, the research data indicated that the prediction of chemically transformed substances resulting from metabolism and linked to BDDCS Classes 1 and 2 was the most accurate. In contrast, prediction accuracy dropped somewhat when the models dealt with drug transporters that were in Classes 3 and 4. Such results point out that pharmacokinetics computational models benefit greatly when pharmacokinetic mechanism-based variables related to drug disposition are added. The addition of binding to protein lipophilicity solubility, and

metabolism-related descriptors not only uplifted the capability of ANN to learn but also resulted in the overall improvement of the robustness of the model. Although the datasets were small and there were some variabilities of transporters that affected the results, the findings underscore the great capabilities of artificial neural networks to be supportive tools for pharmacokinetic forecasting in drug development stages at the earliest. Using ANN-based models can bring about enhancements in the selection of candidates, lessen the workload of experiments, and also provide more accurate findings for human hepatic clearance ahead of clinical trials. More research with a focus on bigger datasets, transporter kinetics and physiologically based pharmacokinetic parameters will not only enhance the performance of prediction but will also increase the clinical suitability of machine learning-driven IVIVE approaches.

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