Prediction of Drug Penetration Coefficients for Transdermal Drug Delivery using Artificial Neural Networks

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Abstract: The penetration of drug molecules into the skin is a crucial stage in the transdermal drug delivery process. Traditional direct measuring techniques have a number of flaws. The creation of a transdermal penetration model that predicts a drug's penetration coefficient might be a viable answer to these issues. Combined with the analysis of the quantitative structure-activity relationship, a new statistical method, artificial neural network, is introduced. Establish a BP neural network, take the molecular weight of the drug molecule, the n-octanol/water partition coefficient, the number of hydrogen bond donors and acceptors as the input values of the artificial neural network, and the drug transdermal permeability coefficient as the output of the neural network value. Train and optimize the built network model and predict the transdermal permeability coefficients of 10 drugs. The correlation coefficient between the predicted value and the measured value is R2=0.9953, and there is no significant difference within the 99% confidence interval. It shows that the model has a high prediction accuracy and a wide prediction range, which can provide reliable data reference help for the actual drug design stage.

1 INTRODUCTION

Oral administration is currently the most common route of administration, and most small molecule medications are given this way (Yu, Yang, Wu, Fan, 2021). Portability, consistent dose, and patient self-administration are all advantages of the oral route (Brambilla, Luciani, Leroux, 2014; Ita, 2014). However, due to variables such as quick breakdown and restricted transport in the stomach and small intestine, most protein-based medicines are not supplied by the oral route (McCrudden, Singh, Migalska, Donnelly, 2013). As a result, injection is the most common method of administering big molecule medications. Injectable medication delivery still has significant drawbacks because it causes tissue damage, discomfort, and the risk of infection (Schoellhammer, Blankschtein, Langer, 2014).

Transdermal drug delivery is a painless way of systemically distributing medications by putting the drug formulation to healthy skin that is intact (Han, Das, 2015). Transdermal drug delivery has several advantages over other traditional modes of administration, including a more consistent pharmacokinetic profile with fewer peaks, which reduces the likelihood of harmful side effects. Pre-systemic metabolism is avoided with transdermal medication administration, which improves bioavailability (Arora, Prausnitz, Mitragotri, 2008). The mobility of the drug through the skin barrier is crucial to the effectiveness of transdermal drug delivery.

Although the skin serves as the primary vehicle for transdermal medication delivery, the stratum corneum acts as a significant barrier to drug penetration (Dhote, 2012; Grice et al., 2017), limiting both local and transdermal bioavailability (Subramony, 2013). The medication's penetration is thus crucial in transdermal drug development.

To facilitate later operations in the research and development of transdermal medications, it is vital to understand the features of the relevant drug percutaneous penetration in advance. The old method of directly measuring the drug's permeability coefficient in vitro or on the skin has several flaws. The experimental conditions, for example, are demanding, requiring a particular level of skin activity and medication concentration to be maintained. Individual differences influence measurement results, so they are not universally applicable. It leads to drug misuse and waste, and the

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squandering of some expensive pharmaceuticals raises development expenses. The experiment will take some time to complete (Terzić et al., 2017). It is necessary to establish a drug transdermal penetration model to predict drug penetration characteristics in the process of drug development, which can effectively avoid the above-mentioned problems.

2 LITERATURE REVIEW

2.1 Drug Penetration Influencing Factors

2.1.1 Hydrogen Bonding

Hydrogen bonding is an important type of interaction because it plays a key role in structural stability, enzyme catalysis and drug distribution and permeability (Coimbra, Feghali, Ribeiro, Ramos, Fernandes, 2021). The presence of functional groups capable of establishing hydrogen bonds in the structure of a drug molecule boosts its solubility and capacity to make critical interactions with its biomolecular targets, resulting in successful binding and selectivity. Excess hydrogen bonding donors/acceptors can have a negative impact on the drug's membrane partitioning and permeability (Coimbra, Feghali, Ribeiro, Ramos, Fernandes, 2021). These polar groups reduce the affinity for hydrophobic membrane regions and increase water desolvation losses during drug permeation.

2.1.2 Oil-Water Partition Coefficients

Because medications must have good pharmacokinetics as well as the required biological activity, a good balance of lipophilicity and hydrophilicity is critical. The partition coefficient can be assessed in terms of a chemical substance's hydrophilicity or hydrophobicity (Ding, 1998), and it can also be used to estimate drug distribution in vivo. Hydrophobic medicines with high octanol-water partition coefficients are primarily found in hydrophobic cell areas like the lipid bilayer. Hydrophilic medicines with low octanol/water partition coefficients, on the other hand, are usually found in watery environments. Transdermally given medicines must be hydrophobic enough to partition into the phospholipid bilayer to be delivered successfully.

2.2 Artificial Neural Networks

Artificial neural networks (ANN) are the product of simulating human brain intelligence (Saxén, Pettersson, 2005). It is a parallel distributed processor with powerful connections. It acquires knowledge and the ability to solve problems through continuous learning. The distribution of knowledge is stored in the weight of the connection. According to the system point of view, an artificial neural network is an adaptive nonlinear dynamic system composed of many neurons through rich and perfect connections (Lv et al., 2018).

Among many types, Rinehart and McClelland et al. proposed the Back Propagation (BP)-learning algorithm of multi-layer feed forward network in 1986 (Ma, Hu, Xu, 2017). BP network uses nonlinear differentiable functions to train the network. The learning algorithm has strong plasticity and a simple structure, so it has been widely used in many fields. BP learning algorithm, also known as BP network, is a supervised learning algorithm. The principle is to select suitable samples from each sample as the input of the network and test them. This is to make a judgment basis for the modification of network weights and thresholds (Moraga, 2007). Through network learning, the total error between the actual output and the expected output of the sample is continuously reduced, to fit the correspondence between the input and output data.

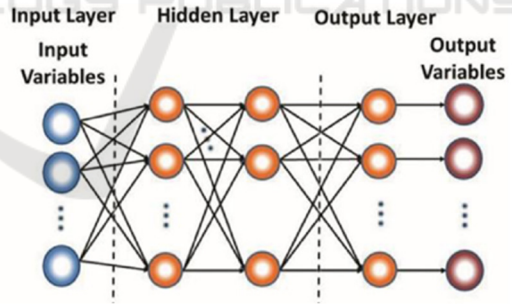

Figure 1: Structure of BP neural network.

The structure of the BP neural network is shown in Figure 1. BP neural network is a kind of multi-layer feed forward neural network, the signal is transmitted forward, and the error is propagated backward, there is no signal feedback process. A typical BP neural network consists of three parts: input layer, hidden layer, and output layer. The number of neurons contained in each layer is arbitrary, and it may also contain a hidden layer structure of 0 to n layers. And there is no interconnection between neurons in the same layer, but the upper and lower layers are fully

connected, and the output of each node is used as the input of the next neural node, and the signal is forwarded in this way.

The entire network is constructed through the forward propagation of the signal and the backward propagation of the error.

3 METHODOLOGY

The quantitative structure-activity connection is a mathematical and statistical tool for analyzing the physicochemical attributes and biological activities of diverse substances using molecular structural data. Other physical and chemical features of substances, biological activity, toxicity, and various metabolic parameters of medications are among the research objects. Drug design, analytical chemistry, environmental chemistry, food science, and material science are among the research fields.

The qualities of drug penetration through the skin are inextricably linked to certain structural factors of drug molecules, such as molecular weight and volume (Matsson, Kihlberg, 2017), molecular polarity (Coimbra, Feghali, Ribeiro, Ramos, Fernandes, 2021), and molecular acidity and alkalinity (Bartlett, van der Voort Maarschalk, 2012). However, because there are complex nonlinearities between the parameters, the created model must have good nonlinear relationship processing capabilities.

3.1 Data Selection

The artificial neural network model is mainly used to predict the permeability coefficient of chemical substances. According to the experimental data obtained from the literature review, the data shows the structure parameters and permeability coefficients of 50 chemical substances. Use this data to construct a neural network to predict the permeability coefficient of chemical substances. Structural parameters, hydrogen bonds and oil-water balance coefficients will all affect the permeability. Table 1 shows the experimental data needed to build the neural network. Table 2 shows another set of experimental data, which will be used to verify the neural network.

Table 1: Model training dataset

Drug	MW	P	HBD	HBA	LogKp	Reference	Drug	MW	P	HBD	HBA	LogKp	Reference
Fentanyl	336.50	4.37	0.00	3.00	-5.56		Levonorgestrel	312.4	2.12	1.00	2.00	-13.60	
Heptanol	116.20	2.72	1.00	1.00	-5.06		Lidocaine	234.3	3.33	1.00	3.00	-8.00	
Hexanol	102.20	2.03	1.00	1.00	-5.45		Methylphenidate	233.3	2.44	1.00	3.00	-9.40	(Maciel Tabosa, Hoppel, Bunge, Guy, & Delgado-Charro, 2020)
Isoquinoline	129.20	2.03	0.00	1.00	-5.34		Nicotine	162.2	2.33	0.00	2.00	-3.20	
Pethidine	247.30	2.72	0.00	3.00	-5.99		Norelgestromin	327.5	1.17	2.00	3.00	-11.30	
Methanol	32.00	-0.77	1.00	1.00	-6.86		Oxybutynin	357.5	4.34	1.00	4.00	-8.20	
morphine	285.30	0.62	2.00	6.00	-8.59		Rivastigmine	250.3	3.72	0.00	4.00	-8.60	
2-naphthol	144.20	2.84	1.00	1.00	-5.11		Rotigotine	315.5	3.96	3.00	1.00	-8.80	
Naproxen	230.30	3.18	1.00	3.00	-6.96		Scopolamine	303.1	2.24	1.00	5.00	-8.00	
Chloroxylenol	156.60	3.39	1.00	1.00	-4.84	(Qin & Xu, 2010)	Selegiline	187.3	4.79	0.00	1.00	-7.50	
cocaine	299.40	0.89	1.00	4.00	-7.87		nicotine	158.20	1.17	0.00	2.00	-5.27	
Ether	74.10	0.83	0.00	1.00	-5.36		Nitroglycerin	227.10	2.00	3.00	9.00	-5.52	
Ephedrine	165.20	1.03	2.00	2.00	-5.78		3-nitrophenol	139.10	2.00	1.00	4.00	-5.81	
Ethylbenzene	106.20	3.15	0.00	0.00	-3.84		4-nitrophenol	139.10	1.96	1.00	4.00	-5.81	
Aldosterone	360.40	1.08	0.00	4.00	-7.79		Amyl alcohol	88.10	1.56	1.00	1.00	-5.78	
4-bromophenol	173.00	2.49	1.00	1.00	-5.00		Phenobarbital	232.20	1.47	2.00	5.00	-6.90	(Coderch, Collini, Carrer, Barba, & Alonso, 2021)
Butyric acid	88.10	0.79	1.00	2.00	-6.56		Pregnenolone	316.50	3.13	1.00	2.00	-6.38	
Butanol	74.00	0.88	1.00	1.00	-6.16		Progesterone	314.50	3.77	0.00	2.00	-4.92	
2-chlorophenol	128.60	2.15	1.00	1.00	-5.04		Salicylic acid	138.10	2.26	2.00	3.00	-5.76	
Buprenorphine	467.6	4.98	2.00	5.00	-8.3		water	18.00	-1.38	2.00	1.00	-6.86	
Clonidine	230.1	1.59	2.00	3.00	8.00		Thymol	150.20	3.34	1.00	1.00	-4.81	
Estradiol	272.4	4.01	2.00	2.00	-10.30		Toluene	92.10	2.75	0.00	0.00	-3.56	
Ethinyl estradiol	296.4	3.67	2.00	2.00	-10.30		4-chlorophenol	128.60	2.39	1.00	1.00	-5.00	
Fentanyl	336.5	4.05	0.00	3.00	-9.00		Resorcinol	110.10	0.80	1.00	2.00	-7.18	
Granisetron	312.4	1.62	1.00	5.00	-10.50		4-ethylphenol	122.20	2.40	1.00	1.00	-5.02	

MW is molecular weight, P is the octanol-water partition coefficient, HBD is the number of hydrogen bond donors and HBA is the number of hydrogen bond acceptors.

Table 2: Model validation dataset.

Drug	MW	P	HBD	HBA	LogKp	Reference
Isopentobarbital	226.30	1.96	2.00	5.00	--6.20	(Sobansk a & Brzezińsk a, 2020)
Barbital	184.20	0.65	2.00	5.00	--7.51	
Benzyl	108.10	1.10	1.00	1.00	--5.78	
Chlorocresol	142.60	3.10	1.00	1.00	--4.82	
Cortisone	360.40	1.42	2.00	5.00	--8.56	
Decanol	158.30	4.00	1.00	1.00	--4.66	
Ethanol	46.10	--0.31	1.00	1.00	--6.66	
bitter	144.20	3.00	1.00	2.00	--5.16	
Octanol	130.20	2.97	1.00	1.00	--4.84	
Valeric acid	102.10	1.30	1.00	2.00	--6.26	

3.2 The Training Process of BP Neural Network

The working process of the artificial neural network model is mainly divided into 4 parts. First, the data is preprocessed, and then the data is divided into a training group, a verification group and a test group. Then the artificial neural network is constructed, and the artificial neural network is trained using the training data. Use the trained artificial neural network to predict the result (Saxén, Pettersson, 2006).

Artificial neural networks need to select appropriate data from the database as input and output values. The permeability coefficient of the drug is selected as the output value of the neural network. The choice of input value has a significant impact on the construction and prediction ability of the artificial neural network model and will affect the accuracy of the prediction result to a large extent. The relative molecular weight, the number of hydrogen bond donors and acceptors, and the oil-water balance coefficient are used as input values. Use Equation 3.1 to normalize the input data.

$$S_{ik} = \frac{X_{ik} - \min(X_{i1,2\ldots,\ldots n})}{\max(X_{i1,2,\ldots\ldots,n}) - \min(X_{i1,2,\ldots\ldots,n})} \quad \text{(Eq. 3.1)}$$

Among them, Sik represents the parameter after normalization, Xik represents the parameter before normalization, i is the number of types of input parameters, and k is the number of groups of data (Lv et al., 2018). After the input value and output value are selected, the data is divided into a training group, verification group and test group. The more and more extensive the data used for training, the better the learning effect of the neural network. Data were randomly split into 70%: 15%: 15% to construct an artificial neural network.

3.3 Optimization of Neural Networks

It was shown that an artificial neural network with a single hidden layer could be sufficient for the accurate prediction of drug permeability, so a three-layer artificial neural network was created. The range of the number of hidden neurons is determined by the following empirical formula (Lv et al., 2018).

1. $n = \sqrt{N + M} + (1\sim10)$, N is input neurons, M is output neurons
2. $n = \log_2 N$
3. $\sum_{j=0}^{N} C_j^L > R$, R is number of sample

After completing the training, the number of hidden neurons with the lowest error is selected as the final choice to complete the construction of the artificial neural network.

By inputting the verification data into the optimized artificial neural network model, the permeability coefficient is predicted through the model. Compare the predicted permeability coefficient with the experimental value to judge the applicability of the artificial neural network.

4 RESULT AND DISCUSSION

4.1 Optimization Results of the Neural Network

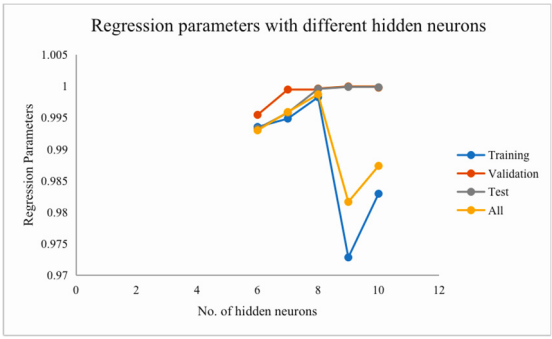

Figure 2: The relationship between regression parameters and the number of hidden neurons.

The optimized training of the network needs to set the corresponding training parameters, where the maximum number of training times is 500, and the number of displayed training iterations is 50. It can be seen from Figure 2 that under the same accuracy requirements, the number of neurons in the hidden layer is in the range of 6-10, and the regression parameters have significant changes. In the case of 8 hidden neurons, the regression parameter is closest to 1. According to the "razor" principle: If a smaller neural network can meet the requirements, then a larger network is not used. Because the more hidden nodes and the more hidden layers, the phenomenon of "over-fitting" tends to occur, which in turn leads to a decrease in the generalization ability of the neural network. At the same time, in order to ensure the computational efficiency of the artificial neural network, a smaller number of neurons is selected.

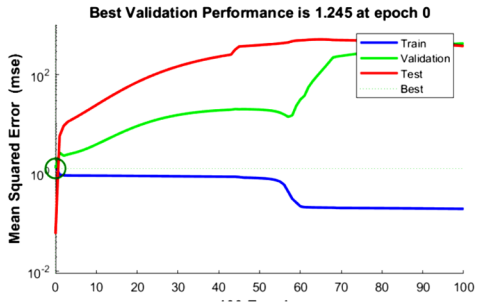

Figure 3: Performance of forwarding model for permeability coefficient.

The calculation result of the neural network is shown in Figure 3. The best performance is obtained after 75 trainings at epoch 0, and the minimum verification is 1.245. The artificial neural network requires that the error between the predicted value and the experimental value is small. The smaller the mean square error, the more accurate the prediction result. As shown in the figure, because the test curve does not increase significantly before the verification curve increases, there is no over-fitting phenomenon.

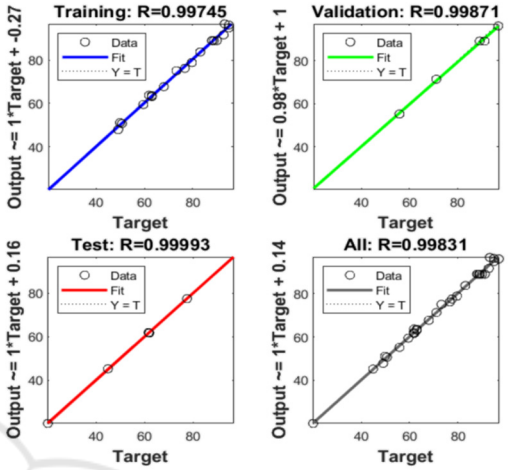

Figure 4: Regression parameters of the forward model for permeability coefficient.

Figure 4 shows that the regression parameters for training, validation, testing, and overall are 0.99745, 0.99871, 0.99993, and 0.99831, respectively. The values of the four regression parameters are all close to 1. Data analysis based on the mean square error and regression parameters show that the artificial neural network can accurately predict the output parameter, that is, the permeability coefficient of the compound.

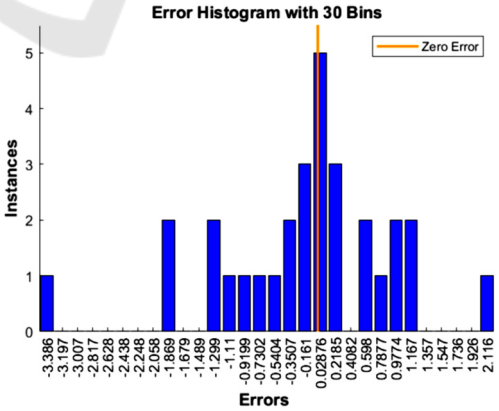

Figure 5: Error histogram of forwarding model for permeability coefficient.

The error histogram can also be used to verify and evaluate the performance of artificial neural networks.

As shown in Figure 5, the error range is divided into 30 bins. Most errors are in the range of -1.299 to 1.167. There are some errors, such as -3.386, -1.869, and 2.116. The error value of abnormal data is also very small. In general, the error between the experimental value and the output value is small, and the obtained artificial neural network can give more accurate predictions.

According to the analysis of the prediction results of the above artificial neural network, the successful construction of the model is indicated, which can be used for further verification and analysis.

4.2 Verification of the Artificial Neural Network Model

Input the experimental data set used to verify the accuracy of the model into the optimized artificial neural network model. After model prediction and calculation, the final prediction results of penetration parameters are obtained. By comparing the predicted value with the experimental value, according to the results of t-test, it is found that based on the 99% credit rating, it is found that the predicted value of the artificial neural network constructed using the experimental data is similar to the actual experimental data, and there is no significant difference. It shows that the network model can effectively and reasonably predict the permeability coefficient.

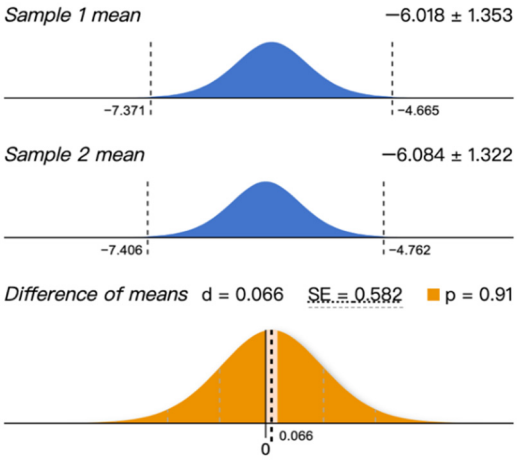

Figure 6: The result of t-test.

According to the regression linear equation of the predicted value and the experimental value, the regression parameter of the equation is 0.9953, which is very close to 1.

Table 3: Predicted values and errors.

LogKp	Predict value	Deviation
-6.20	-6.25	-0.05
-7.51	-7.63	-0.12
-5.78	-5.83	-0.05
-4.82	-4.92	-0.1
-8.56	-8.53	0.03
-4.66	-4.63	0.03
-6.66	-6.87	-0.21
-5.16	-5.15	0.01
-4.84	-4.79	0.05
-6.26	-6.18	0.08

Table 3 shows the errors between the experimental values and the predicted values derived from the artificial neural network model. Therefore, the experimental value and the predicted value conform to a linear relationship, and the error between the two is very small. The artificial neural network has a good predictive ability for infiltration parameters.

Since the data used to build the artificial neural network model and verify the model contains a variety of chemical substances, the results of the model prediction show that the model has a good ability to predict penetration parameters. Therefore, the model is universal in prediction and can be widely used to predict the permeability coefficient of various drugs.

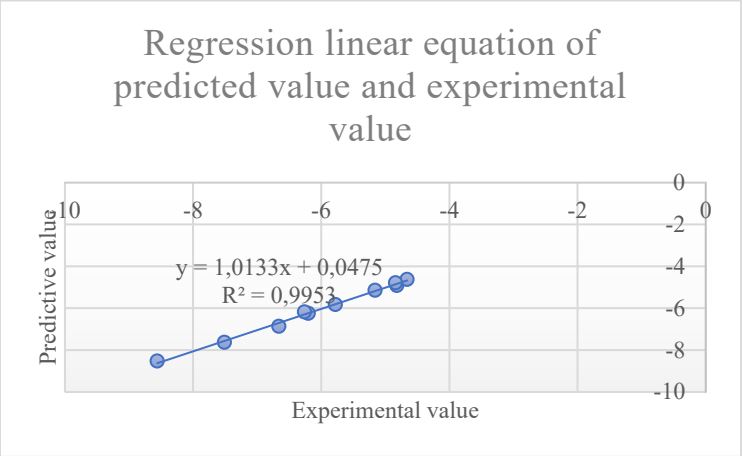

Figure 7: Linear equation of experimental value and predicted value.

5 CONCLUSION

Based on quantitative constitutive relationships, new statistical methods, such as artificial neural networks, were introduced to extend the range of data structures that can be modeled by two-dimensional quantitative constitutive relationships. A three-layer BP neural network was constructed using the molecular weight of the drug, the oil-water partition coefficient and the number of hydrogen bond donors and acceptors as the input values for the artificial neural network, which was trained and optimized. The results of comparing the predicted values of the network with the experimental values show that the prediction accuracy and confidence of the model are high. Moreover, the network model has predictive generality and can be used for the prediction of permeation coefficients for a wide range of drugs. It can provide a more accurate data reference in the drug development phase of transdermal drug delivery, avoiding unnecessary time and financial consumption. The model has only been shown to predict the permeation rate of a single drug but has not been shown to predict the state of a mixture of multiple drugs. Therefore, more sophisticated models could be developed to achieve permeation prediction for mixed drugs. Interactions between drugs could be included in the range of variables, while more accurate genetic algorithms could be introduced to improve the accuracy of the artificial neural network model.

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