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Prediction of Skin Penetration using Artificial Neural Network

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Abstract

The artificial neural networks (ANN) technologies provide on-line capability to analyze many inputs and provide information to multiple outputs, and have the capability to learn or adapt to changing conditions. No doubt that the determination of Skin permeability is a time consuming process; which involves a quite tedious work. **Material and method:** Software Neurodimension was used for this study. A data set was taken from literature and used to train the network. A set of 20 compounds were used to construct the ANN models for training and 10 compounds used for prediction of skin penetration (n=30, molecular weight>500 da). Skin permeability expressed in log Kp (cm/h). Abraham descriptors of R_2 (excess molar refraction), $\pi 2$ H (dipolarity/polarizability), $\Sigma\alpha_2$ H, $\Sigma\beta_2$ H (the overall or effective hydrogen-bond acidity and basicity), and Vx (the McGowan characteristic volume) were obtained. **Result:** The correlation between the skin permeability coefficient and the Abraham descriptors were obtained from the trained neural network. The regression coefficient was 0.856 for training subset and MSE was 0.04. In addition, the predictability of the neural network model was compared to the experimental data. This paper uses artificial neural network for prediction of Skin permeability study.

Keywords: Artificial Neural Network, Mean Square Error, Correlation Coefficient, Abraham Parameters.

1. Introduction Transdermal therapeutic systems require drugs to penetrate the stratum corneum into the systemic circulation in sufficient concentrations for the desired therapeutic effect. To achieve this, an absorption enhancer is usually needed. Many studies have discussed percutaneous absorption enhancers and mechanisms of their enhancing activity [1-3]. Skin permeability is of relevance to a number of applications including the design of skin cream products, risk assessment of hazardous chemicals, and in particular, transdermal delivery of drugs. Knowledge of the skin permeability is of critical importance for the understanding of their mode of action in skin. This is partly due to ethical difficulties with respect to human and animal experiments and partly due to economic considerations and increasing legislation in the risk assessment of industrial chemicals. Previous studies on predicting skin permeability can be categorized into mechanistic and empirical models [4, 5]. QSAR (Quantitative Structure Activity Relationship) has been used to predict the optimum molecular structure and to provide a means of understanding their mechanism of action and an important part of modern drug discovery. Hansch used physicochemical properties and correlated with biological activity using regression analysis [6]. QSAR methods, stretching back over a century, had been applied in many fields [7, 8]. In the last years, QSAR methods had been developed to relate penetration properties of a range of chemical compounds to their physicochemical parameters. Compared with the mechanism model, the QSAR model for skin permeability does not consider the dynamic process of skin permeation. Main problem with the QSAR models is that, it cannot be extrapolated. Various QSAR models for skin permeability have been reported. A comprehensive review was given on different QSAR models for skin permeability. An early study relates the skin permeability of the analyzed compounds to their octanol-water partition property and molecular weight [9, 10]. They proposed the empirical equation of skin permeability as log Kp=0.71 log Kow -0.0061MW-6.3, where log Kp is skin permeability is given in cm/s, log Kow is solute partition coefficient in octanol/water, MW is molecular weight. Other researchers using other structural molecular parameters such as the number of hydrogen bonds and molecular volume 11 also proposed equations. QSAR models for skin permeability employed the multiple linear regression (MLR) method and the main drawback of the MLR approach is that it assumes linearity between the descriptors and skin permeability. Neural networks are increasingly being seen as an addition to the statistics toolkit which should be considered alongside both classical and modern statistical methods. The artificial neural network (ANN) is similar to the MLR approach, but is more suitable for extracting the effects of chosen descriptors on skin

permeability. Recently ANN model is used to predict skin permeability [12, 13]. Abraham *et al* [14] argued that log *Kow* was an empirical variable and did not give the actual structural features of the chemical compounds that influence skin permeability. Therefore, some researchers have related skin permeability to Abraham descriptors, which they believe, can better describe the actual features of molecules and improve the precision of the model[15, 16]. The utility of ANN in pharmaceutics was demonstrated by successful construction of a number of QSPkR[17, 18]. They have been shown to be fast and reliable method for the prediction of human pharmacokinetic parameters. In number of diverse fields, there has been an increasing use of Artificial Neural Networks (ANN) as black-box simplified models. This is mainly justified by their ability to model complex non-linear patterns; in addition, they can self-adjust and produce a consistent response when 'trained' using observed outputs. Neural networks and generic algorithms are two branches of artificial intelligence that can provide many benefits in engineering and medical applications. The artificial neural networks (ANN) technologies provide on-line capability to analyze many inputs and provide information to multiple outputs, and have the capability to learn or adapt to changing conditions. No doubt that the determination of Skin permeability is a time consuming process; which involves a quite tedious work. This paper uses this artificial neural network in Skin permeability study. The results are almost as compared to experimental value of skin penetration.

2. Material and Method

Abraham descriptors were used for predicting skin permeability. A database of skin permeability containing 20 data points was compiled from literature[19]. These parameters were used to train the artificial neural network. The correlation between the skin permeability coefficient and the Abraham descriptors were obtained from the trained neural network. In addition, the predictability of the neural network model was compared to the experimental data.

2.1 Data set

A set of 20 compounds were used to construct the ANN models (n=20 molecular weight>500 da) used for prediction from literature. Skin permeability expressed in log Kp (cm/h). Abraham descriptors of R_2 (excess molar refraction), $\pi 2$ H (the dipolarity/polarizability), $\Sigma\alpha_2$ H, $\Sigma\beta_2$ H (the overall or effective hydrogen-bond acidity and basicity), and *V*x (the McGowan characteristic volume) were obtained using Abraham Solvation Parameters (ABSOLV) program (Pharma Algorithms Software, Toronto, Canada). The program was written to read molecular structures as Simplified Molecular Input Line Entry System (SMILES) strings, which were obtained from software Molecular Modelling Pro given in table 1.

Compound no.	Molecular Formula	SMILES Notation
QD-1	C27H19N3O	c1(=O)n(N=C(c2=cc=cc=c2)c3=cc=cc=c3)c(c4=cc=cc=c4)=nc(c=cc=c5)=c15
QD-2	C22H17N3O	c1(=O)n(N=C(C)c2=cc=cc=c2)c(c3=cc=cc=c3)=nc(c=cc=c4)=c14
QD-3	C22H17N3O2	c1(=O)n(N=C(C)c2=cc=c(O)c=c2)c(c3=cc=cc=c3)=nc(c=cc=c4)=c14
QD-4	C22H16N4O3	c1(=O)n(N=C(C)c2=cc=cc(N(=O)=O)=c2)c(c3=cc=cc=c3)=nc(c=cc=c4)=c14
QD-5	C22H18N4O	c1(=O)n(N=C(C)c2=cc=cc(N)=c2)c(c3=cc=cc=c3)=nc(c=cc=c4)=c14
QD-6	C27H17N 3OF 2	c1(=O)n(N=C(c2=cc=c(F)c=c2)c3=cc=c(F)c=c3)c(c4=cc=cc=c4)=nc(c=cc=c5)=c15
QD-7	C27H18N3OCl	c1(=O)n(N=C(c2=cc=cc=c2)c3=cc=c(Cl)c=c3)c(c4=cc=cc=c4)=nc(c=cc=c5)=c15
QD-8	C23H19N3O2	c1(=O)n(N=C(C)c2=cc=c(OC)c=c2)c(c3=cc=cc=c3)=nc(c=cc=c4)=c14
QD-9	C22H18N4O	c1(=O)n(N=C(C)c2=cc=c(N)c=c2)c(c3=cc=cc=c3)=nc(c=cc=c4)=c14
Qd-10	$C_{39}H_{42}FN_3O_5S$	O=S(=O)(OOCCCCCCCCCCCCC)c1ccc(cc1)C(=N/N3C(=Nc2ccccc2C3=O)c4ccccc4)/c5ccc(F)cc5

Table 1 showing SMILES notation for synthesized compounds

The data were divided into 2 subset; one was training data set, which has skin permeability according to literature (table 2). Other was prediction subset, which contain list of synthesized compounds (table 3). The Neural Network Expert of Neurosolution (Neurodimension 5, Gainesville, FL 32606) was used to construct the ANN model. Back propagation networks have been employed in this study. There are some empirical rules about constructing artificial

neural networks, for example, 2 hidden layers are sufficient for generality [20]. The number of units of the hidden layer normally is not more than twice the input. In our example, there were 5 inputs corresponding to the 5 Abraham descriptors and 1 output for skin permeability. To determine the ANN architecture, all network structures with the maximum allowed numbers of hidden layers and hidden units limited to 5 and 10, respectively, had been investigated and results of training given in (table 4) network was trained by 3-folding cross validation and almost 1000-5000 epochs were used to train the network. For the training of each network, the mean square errors (MSE) between the model prediction and experimental data were obtained. The ANN architecture with the smallest average value of MSE was chosen. The MSE is log *Kp,* obs is the experimental value minus log *Kp*, cal is the predicted value divided by *N* is the number of data points in the training dataset.

Name	**R_2**	**αH_2**	**βH_2**	**π_2**	**Vx**	**Logkp (cm/hr) (experimental)**	**Logkp (cm/hr) (ANN)**
4-Cresol	0.8100	0.8500	0.5000	0.3900	0.9160	-1.7600	-1.7446
4-Cyanophenol	0.9600	1.3900	0.6700	0.5300	0.9298	-1.9830	-2.6994
4-Ethylphenol	0.8000	0.9000	0.5500	0.3600	1.0569	-1.4600	-1.4498 3
4-Methyl-2-pentanol	0.2200	0.4300	0.3100	0.3700	1.0127	-2.3300	-1.5902
Amylobarbital	0.9800	1.3500	0.5200	1.2400	1.7966	-2.6440	-2.6831
Aniline	0.8600	1.0800	0.2300	0.4300	0.8162	-2.6500	-2.5977
Anisole	0.6200	0.7900	0.0000	0.3300	0.9160	-1.6000	-1.9517
Benzene	0.6100	0.5200	0.0000	0.1400	0.7164	-0.9547	-1.5637
Benzyl alcohol	0.8030	0.8700	0.3900	0.5600	0.9160	-2.2200	-2.0727
Butobarbital	0.9800	1.3600	0.5200	1.2100	1.6557	-3.7144	-3.1058
Caffeine	1.9400	1.8100	0.0000	1.4700	1.3600	-4.0000	-4.2814
Catechol	0.9700	1.2300	0.5900	0.7400	0.8925	-2.7700	-3.403
Chlorocresol	0.9600	0.9600	0.6700	0.3800	1.0384	-1.2600	-1.4581
Chloroxylenol	0.9800	0.9000	0.6700	0.3800	1.1793	-1.2774	-1.3089
Chlorpheniramine	1.5200	1.4900	0.0000	1.0200	2.2098	-2.6600	-2.2046
Codeine	2.0200	1.7800	0.2600	1.7500	2.2100	-4.3098	-4.1422
Corticosterone	1.8600	3.4300	0.4000	1.6300	2.7389	-3.5229	-3.8399
Diclofenac	1.9700	1.8800	0.7800	0.8700	2.0300	-1.7399	-2.0849
Ethanol	0.2460	0.4200	0.3700	0.4800	0.4491	-3.0000	-3.178
Salicylic acid	0.9100	1.1000	0.7000	0.4000	0.9904	-1.9031	-1.9239

Table 2 Names R_2, αH_2, βH_2, π_2, Vx of the compounds used in the study

Name	R_2	αH_2	βH_2	π_2	Vx
QD-1	3.20	0	1.28	2.69	3.083
QD-2	2.63	0	1.19	2.23	2.616
QD-3	2.86	0.50	1.46	2.44	2.674
QD-4	2.90	0	1.29	2.80	2.790
QD-5	2.93	0.23	1.51	2.61	2.715
QD-6	3.04	0	1.28	2.62	3.118
QD-7	3.35	0	1.27	2.77	3.054
QD-8	2.69	0	1.40	2.32	2.8157
QD-9	2.93	0.23	1.51	2.61	2.715
QD-10	3.29	0.0	2.23	3.83	5.187

Table 3 showing Abraham parameters of synthesized compounds

Model	No. of hidden layers	Training set *N*	R^2	MSE
ANN	5	20	0.856	0.040

Table 4 architecture of ANN

3. Result

The ANN model was used to analyze the influence of each Abraham descriptor. Skin permeability was calculated using the ANN model by varying Abraham descriptor each time while keeping the rest of the descriptors constant mean value of each range. The results are shown in Figure 1. The ANN model on the same training dataset produced results with R^2=0.856 and MSE=0.04, respectively. There was very less error in prediction. This was trained network used for prediction of log kp value for other compounds. The ANN model can better predict skin permeability from Abraham descriptors (Table 5).

Name	Logkp (cm/hr) (ANN)
QD-1	-3.1854
QD-2	-2.3805
QD-3	-2.7468
QD-4	-2.8405
QD-5	-3.0943
QD-6	-2.8646
QD-7	-2.3908
QD-8	-2.3908
QD-9	-2.0727
QD-10	-3.2058

Table 5 Skin penetration from artificial Neural Network

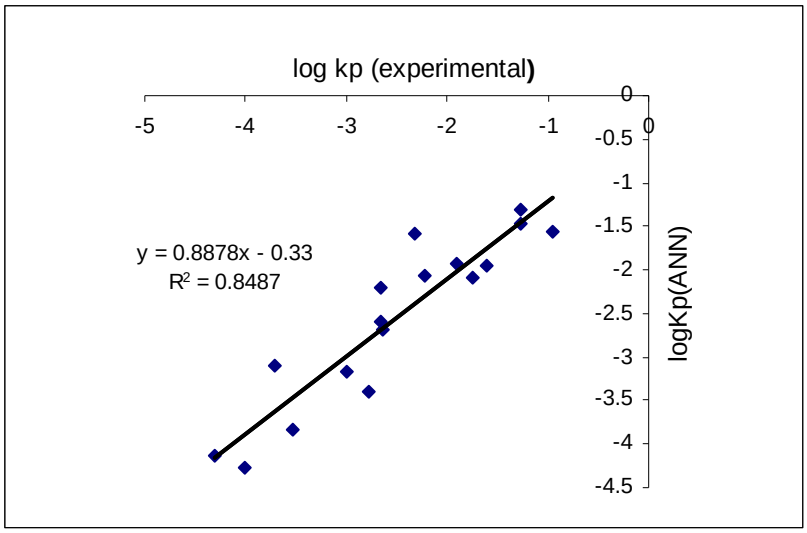

Figure 1 showing comparison of predicted and experimental value

4. Discussion

Generally, log *Kp* has inversely depended on π^2H, the solute polarity. The stratum corneum (SC) lipid phase is mainly composed of hydrocarbon substance. It is well known that solute partition into the lipid phase decreases in the hydrocarbon solvents with increasing solute polarity. The relationship between skin permeability and the partition coefficient can be expressed by the following equation: where *Km* is the skin-water partition coefficient of the solute, *D* is its diffusivity through the skin, and δ is the diffusion path length. $\Sigma\alpha^2$H and $\Sigma\beta^2$H reflect solute hydrogen bonding activity. Predicted skin permeability increased with the decrease in π^2H value because an inverse relationship between hydrogen bonding and skin permeability. This was also observed in this study. The reason is similar as that of π^2H; the increasing solute hydrogen bond acceptor and donor activity resulted in decreased partitioning into the organic phase due to the free energy cost associated with the disruption of hydrogen bonds.

5. Conclusion

ANN is valuable and robust tool for development and drug discovery. ANNs have the potential to aid in drug discovery and development by providing a tool to complement existing screening techniques. It is not proposed that ANN will replace current in vitro and in vivo screen tools. Rather if they are appropriately incorporated into overall drug design and development process they provide considerable savings in resources and allow more rapid progression of potential drug candidates to the markets The results demonstrate that ANN provide a valuable modeling tool that may be useful in drug discovery and development.

6. References:

[1] Scheuplein, RJ, "Mechanism of percutaneous absorption I. Routes of penetration and the influence of solubility" *J Invest Dermatol* 1965 45: 334–346.
[2] Scheuplein, RJ, "Mechanism of percutaneous absorption. II. Transient diffusion and the relative importance of various routes of skin penetration" *J Invest Dermatol*. 1967; 48: 79–88.
[3] Scheuplein, RJ, Blank IH, "Permeability of the skin". *Physiol Rev*. 1971; 51: 702–747
[4] Scheuplein, RJ, Blank, IH**, "**Mechanism of percutaneous absorption. IV. Penetration of nonelectrolytes (alcohols) from aqueous solutions and from pure liquids" *J Invest Dermatol,* 1973; 60(5)**:**286-296.
[5] Guy, RH, Hadgraft, J, "A theoretical description relating skin penetration to the thickness of the applied medicament" *Int J Pharm.* 1980; 6: 321–32.
[6] Moss, GP, Dearden, JC, Patel, H, "Quantitative structure-permeability relationships (QSPRs) for percutaneous absorption" *Toxicology In vitro* 2002; 16: 299–317.
[7] Ma, XL, Chen, C, Yang, J, "Predictive model of blood-brain barrier penetration of organic compounds" *Acta Pharmacol Sin* 2005; 26: 500–12.
[8] Chen, C, Yang, J, "MI-QSAR models for prediction of corneal permeability of organic compounds" *Acta Pharmacol Sin* 2006; 27: 193–204.
[9] Potts, RO, Guy, RH, "Predicting skin permeability" *Pharm Res.* 1992; 9: 663–9.

[10] Lien, EJ, Gao, H, "QSAR analysis of skin permeability of various drugs in man as compared to *in vivo* and *in vitro* studies in rodents" *Pharm Res.* 1995; 4: 583–7.
[11] Pugh, WJ, Degim, T, Hadgraft, J, "Epidermal permeability-penetrant structure relationships: QSAR of permeant diffusion across human stratum corneum in terms of molecular weight, H-bonding and electronic charge" *Int J Pharm.* 2000; 197: 203–11.
[12] Degim, T, Hadgraft, J, Ilbasmis, S, Ozkan, Y, "Prediction of skin penetration using artificial neural network (ANN) modeling" *J Pharm Sci.* 2003; 92: 656–64.
[13] Degim, T, "Understanding skin penetration: computer aided modelling and data interpretation" *Current Computer-Aided Drug design* 2005; 1: 11–9.
[14] Abraham, MH, Martins, F, Mitchell, RC, "Algorithms for skin permeability using hydrogen bond descriptors: the problem of steroids" *J Pharm Pharmacol*. 1997; 49: 858–65.
[15] Potts, RO, Guy, RH, "A predictive algorithm for skin permeability-the effects of molecular-size and hydrogen-bond activity" Pharm *Res*. 1995; 12: 1628–33.
[16] Johnson, ME, Blankschtein, D, Langer, R, "Evaluation of solute permeation through the stratum corneum: Lateral bilayer diffusion as the primary transport mechanism" *J Pharm Sci.*1997; 86: 1162–72.
[17] Saini, S, and Singh, S.K., "Quantitative structure pharmacokinetic relationship (QSPkR) of cox-2 inhibitors using artificial neural network" *Acta Pharmaceutica Sciencia*, 2009; 51: 313- 321.
[18] Singh, S. K., Saini, S., Verma, B., Mishra, D. N. "Quantitative Structure Pharmacokinetic Relationship Using Artificial Neural Network: A Review". *International Journal of Pharmaceutical Sciences and Drug Research*. 2009; 1(3): 144-153.
[19] Chen, L, Lian, G, Han, L. "Prediction of human skin permeability using artificial neural network (ANN) modeling." *Acta Pharmacol Sin.* 2007; 28 (4): 591–600.
[20] Sontag, ED. Feedback stabilization using two-hidden-layer nets. *IEEE Transactions on Neural Networks.*1992; 3: 981–90.