ORIGINAL ARTICLE

Application of artificial neural network model in predicting physicochemical characteristics of pharmaceutically developed wafers of loratadine

Chakraborty Prithviraj, Parcha Versha[1], Chakraborty D. Debarupa, Ghosh Amitava

Departments of Pharmaceutics, Bengal College of Pharmaceutical Sciences and Research, West Bengal University of Technology, B.R.B. Sarani, Durgapur, West Bengal, [1]Chemistry, S. Bhagwan Singh PG Institute of Biomedical Sciences and Research, Balawala, Dehradun, Uttarakhand, India

This study aimed to apply the simultaneous optimization method incorporating artificial neural network (ANN) using multi-layer perceptron (MLP) model to develop buccoadhesive pharmaceutical wafers containing loratadine with an optimized physicochemical property and drug release. The amount of sodium carboxymethyl cellulose and lactose monohydrate at three levels (−1, 0, +1) for each was selected as casual factors. Bioadhesive strength, disintegration time, percent swelling index and $t_{70\%}$ as wafer properties were selected as output variables. Nine buccoadhesive wafers were prepared according to a 3^2 factorial design and their physicochemical property and dissolution tests were performed. Commercially available Statistica Neural Network Software (Stat Soft, Inc., Tulsa, OK, USA) was used throughout the study. The training process of MLP was completed until a satisfactory value of root mean square for the test data was obtained using back propagation, conjugate gradient descent method. This work exemplifies the probability for an ANN with MLP, to support in development of buccoadhesive wafers with enviable characteristics.

Key words: *Artificial neural network, buccoadhesive, loratadine, multilayer perceptron, pharmaceutical wafers*

INTRODUCTION

The pharmaceutical industry now-a-day acquainted with the advantages of adopting the quality-by-design (QbD) principle jointly with process analytical technology in drug development and manufacturing.[1]

Artificial neural networks (ANNs) are computational algorithms implemented by software programs that analyze data in the same way as the human brain functions to learn, generalize and figure out the problems based on experience. Similar to the brain structure, the network comprises of several processing elements or nodes which are competent to extract nonlinear relationships from the data and use this knowledge to interpose the results from desirable conditions. These abilities persuade their implementation in pharmaceutical developments where multivariate systems are generally contributed.[2]

Artificial neural networks are built from nonlinear data processing units (artificial neurons), thus allowing for effective recognition of nonlinear problems, which are sometimes challenging in statistical approaches. Another distinctive feature of ANNs are their abilities to deal effectively with multidimensional problems including several 1000's of features and cases as well.[3] The main lead role of neural networks is their ability to represent complex input/output relationships. They are well-suited for use in data classification, function approximation, and signal processing, among others.[4]

Artificial neural network is utilized for many years in several novel pharmaceutical formulation developments.[5-8] ANNs present superiority over a commonly used multi-linear regression methodology in many complex systems,[2] as well as in particle distribution of fluid bed granules,[9] powder flow

Address for correspondence:
Mr. Chakraborty Prithviraj,
Bengal College of Pharmaceutical Sciences and Research,
West Bengal University of Technology, B.R.B.Sarani,
Durgapur - 713 212, West Bengal, India.
E-mail: prithvirajchakraborty.pc@gmail.com

Access this article online

Quick Response Code:

Website: www.asiapharmaceutics.info

DOI: 10.4103/0973-8398.150036

during mixing,[10] tableting processes,[11] dissolution behavior of poorly soluble drugs,[12] and controlled release matrix tablets.[13]

The present investigation aims to optimize formulations characteristics, through ANNs, the effect of ingredients like concentration of bioadhesive polymer sodium carboxymethyl cellulose (Sod. CMC) and diluent (lactose monohydrate) on the primary properties of pharmaceutically developed wafer formulations containing loratadine, a second-generation tricyclic H1 antihistaminic, as a model drug. The primary properties of wafers were considered as bioadhesion strength, disintegration time, % swelling index, and $t_{70\%}$.

MATERIALS AND METHODS

Chemicals used

Loratadine, hydroxy propyl cellulose (Klucel) and Saccharine sodium was procured from Yarrow Chem Mumbai, India; Sod. CMC, lactose monohydrate, polyethylene glycol 400 was obtained from Merck, India; Sorbitol (liquid 70%) was acquired from Central Drug House, India and glycerol, obtained from Loba chemie, Mumbai, India. All the other chemicals and solvents used were of analytical reagent grade.

Preparation of buccoadhesive wafers

The wafers were prepared[14] employing 3^2 factorial design where the amount of two carrier (s) (factors) were varied at three levels as established in the Table 1. Solvent casting method was employed to prepare the wafers. Different ingredients were mixed and were casted in polypropylene petri plates and dried at 45°C. Wafers of 2.2 cm diameter were cut with in-house fabricated hollow punch and kept in desiccator, maintained at relative humidity of 60% ± 5% until further analysis.

Disintegration study

Disintegration study was performed following the method reported earlier.[14] The wafer size (3.80 cm^2) was placed on a glass petri dish containing 10 ml of distilled water. The time required for wafer to break was noted as *in vitro* disintegration time. Three replicates were done for each formulation.

Table 1: Experimental 3^2 factorial design for wafer formulation

Factors (independent variables)	Level used			Responses (dependent variables)
	−1	0	1	
X_1=Concentration of bioadhesive polymer (%w/v)	0.5	1	1.5	Y_1=Bioadhesive strength Y_2=Disintegration time
X_2=Concentration of lactose monohydrate as hydrophilic matrix former (% w/v)	0	0.5	1	Y_3=% swelling index Y_4=Time taken for 70% drug release ($t_{70\%}$)

Swelling index study

The data set for this study was taken from our previous study.[14] In short the procedure includes recording of initial diameter of the wafers and keeping them on the surface of an agar plate maintained at 37°C. Measurement of the diameter of the swollen patch was done at 1 h. Radial swelling was calculated from the following equation:

$$S_D(\%) = (D_t - D_o)/D_o \times 100$$

Where S_D (%) is the percent swelling obtained by the diameter method, D_t is the diameter of the swollen wafer after time t, D_o is the original wafer diameter at time zero. Three wafers (surface area: 3.80 cm^2) were tested for each formulation.

In vitro measurement of buccoadhesion

The *in vitro* bioadhesion properties of the pharmaceutical wafers were assessed[14,15] with the help of a TAXT2i Texture Analyzer (Stable micro system, Model: TAXT Express Enhanced, Distributed in India by Scientific & Digital Systems, New delhi), (Stable Micro system, USA). In short, preserved, cleaned bovine buccal mucosa was hydrated with simulated saliva solution and was tied to the lower probe of the assembly. The wafer was attached to the upper probe of the assembly using double-sided adhesive. The upper probe was allowed to fall on the lower probe with test speed 0.5 mm/s and posttest speed 1 mm/s. The wafer was allowed to adhere to the bovine buccal mucosa membrane with applied force 150 g, return distance 10 mm. The experiment was carried out at room temperature.

In vitro drug release study from wafers

In vitro drug release study was carried out in a paddle type dissolution apparatus (USP II) in dissolution medium comprised of 250 ml of simulated salivary fluid at pH 6.75. The rotation speed was kept at 50 rpm at 37 ± 0.5°C. At regular interval (30 s) sample aliquots were withdrawn, filtered through a 0.45 μm membrane filter and analyzed by ultraviolet spectrophotometer (Thermo Scientific UV1 Thermo Fisher Scientific, India) at a fixed λ_{max} value of 248 nm.[14,15] The withdrawn amount of dissolution medium was calculated.

RESULT AND DISCUSSION

Model training, validation and optimization

Commercially available STATISTICA Neural Network software (Stat Soft Inc., Tulsa, OK, USA) was used throughout the study. Multi-layer perceptrons (MLP) back propagation (BP) conjugate gradient descent method (CG) was used in modeling and optimization of pharmaceutically developed wafers.

In overview, an MLP is composed of different layers of processing units that are interconnected through weighted connections [Figure 1]. The first layer comprises of the input variables. The last layer comprises of the output variables representing the output class. Intermediate layers called

hidden layer receive the entire input pattern that is tailored by the route through the weighted connections. The hidden layer provides the internal depiction of neural pathways.[16]

Training means a search process for the optimized set of weight values, which can minimize the squared error between the estimated and experimental data of units in the output layer. Training is a long iterative process and ANN often gets stuck in a local minima.[16] The network is popularly trained using different algorithms (BP, CG, Quasi-Newton, Levenberg-Marquardt, quick propagation, delta-bar-delta etc.,).[17]

Importance lies in MLP design include specification of the number of hidden layers and the number of units in these layers.[17] Too few hidden layers may lead to under fitting and too many hidden layers can lead the system towards memorizing the patterns in the data.[16]

In order to validate the ANN model, the model was trained again using nine trial formulations and preserving one formulation. Once the ANN model was trained, the model predicted the four output variables (*Y*1, *Y*2, *Y*3 and *Y*4) for the withhold formulation. All data sets for analysis were taken from our previous work.[14]

Two casual factors corresponding to three levels of Sod. CMC (*X*1) and lactose monohydrate (*X*2) were used as each unit of the input layer in the MLP. Basic wafer characteristics chosen as outputs were *Y*1: Bioadhesive strength, *Y*2: Disintegration time, *Y*3: % swelling index, *Y*4: Time taken for 70% drug release ($t_{70\%}$).

Above mentioned input and output variables were fed into STATISTICA 7 software using MLP with BP, CG method. Optimal ANN MLP structure was determined after several training sessions conducted with different numbers of units (1-10) in the hidden layer.

Selection of the number of units in the hidden layer was done starting with one hidden unit and gradually increasing the number of units. The learning period was assumed to be completed when minimum root mean square (RMS) was reached.

$$RMS = (\sum (y_i^p - y_i^m)^{2/n})^{1/2} \quad (1)$$

Where,

y_i^p is experimental (observed) response, y_i^m is calculated (predicted) response, and n is the number of experiments.

A regression plot constructed for the predicted output variables and observed output variables produced slope and r^2. The slope and r^2 values for all test formulations determined the final optimized model.

The artificial neural network structure for this study

the structured ANN consist of three layers: first layer with two input units, the second layer with 10 hidden units and the third layer with four output units as shown in Figure 2.

Input values for test formulations (v1, v2, v3) were presented to MLP when network was trained to validate the network. The training error (T1) and selection error (S1) of the selected MLP was exhibited in Figure 3.

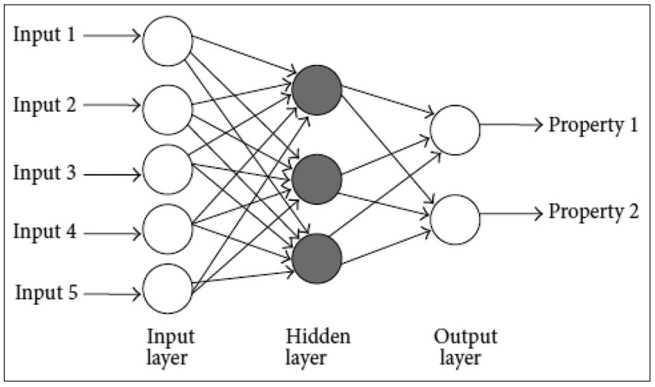

Figure 1: Schematic illustration of multilayer perceptron neural network reproduced from Djuriš J *et al*., 2012[18]

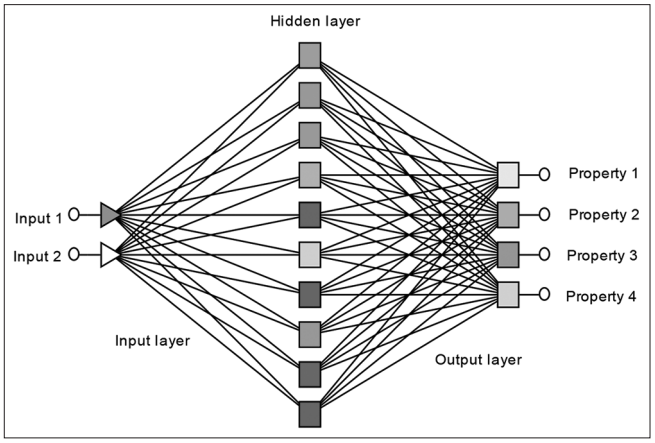

Figure 2: Optimal multilayer perceptron artificial neural network structure for wafer formulation

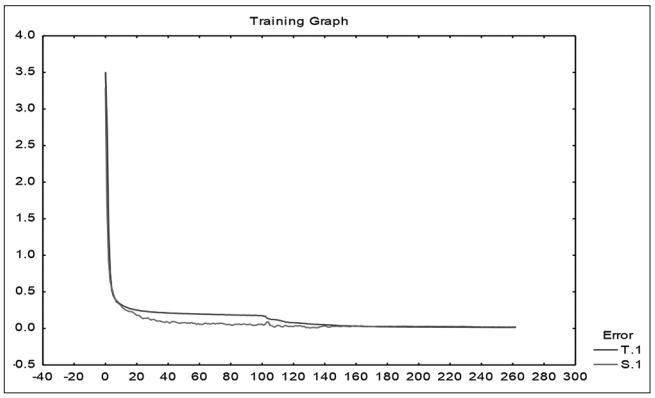

Figure 3: Training graph of the experimental neural structure

Table 2: Experimental (E) and predicted (P) values for chosen outputs (Y_1, Y_2, Y_3, Y_4)

Code	Sod. CMC (X_1)	Lactose (X_2)	Experimental Y_1	Predicted Y_1	Experimental Y_2	Predicted Y_2	Experimental Y_3	Predicted Y_3	Experimental Y_4	Predicted Y
t1	1	0	24.26	29.58	1.23	1.11	63.86	65.20	30.00	57.60
t2	1	0.5	32.90	28.04	1.32	1.27	67.19	66.47	120.00	113.69
t3	1	1	35.90	36.60	1.49	1.65	67.84	67.49	150.00	138.95
t4	1.5	0	38.12	37.19	1.70	1.77	70.93	71.09	180.00	175.95
t5	1.5	0.5	44.80	57.90	2.15	1.92	72.55	71.75	210.00	182.83
t6	1.5	1	81.20	81.39	2.30	2.15	72.60	72.26	150.00	153.41
t7	0.5	0	52.70	50.92	0.50	0.58	59.89	58.65	30.00	15.93
t8	0.5	0.5	42.80	45.69	0.87	0.82	58.74	60.29	90.00	100.16
t9	0.5	1	33.60	33.12	1.19	1.18	60.52	60.69	150.00	157.42
v1	0.5	0.09	51.11	50.72	0.62	0.63	59.01	59.09	30.00	32.51
v2	0.5	0.58	42.98	44.05	0.92	0.86	59.96	60.43	116.97	111.49
v3	0.5	0.12	50.75	50.57	0.64	0.65	59.08	59.22	36.52	37.92

Sod. CMC: Sodium carboxymethyl cellulose

Experimental and predicted values for training formulations (T1–T9) as well as test formulations are presented in Table 2. The ANN predicted values for this study were in close agreement with the observed values for all the test formulations.

Correlation plots were constructed for predicted versus observed values of different outputs for test formulations. The ANN model yielded a regression plot with squared coefficients (r^2) nearer to a value of 1.0, indicative of optimal MLP model was reached.

Response surfaces plots of the effect of concentration of Sod. CMC and Lactose monohydrate on different outputs (*Y*1, *Y*2, *Y*3 and *Y*4), predicted using ANN, were represented in Figures 4a-d.

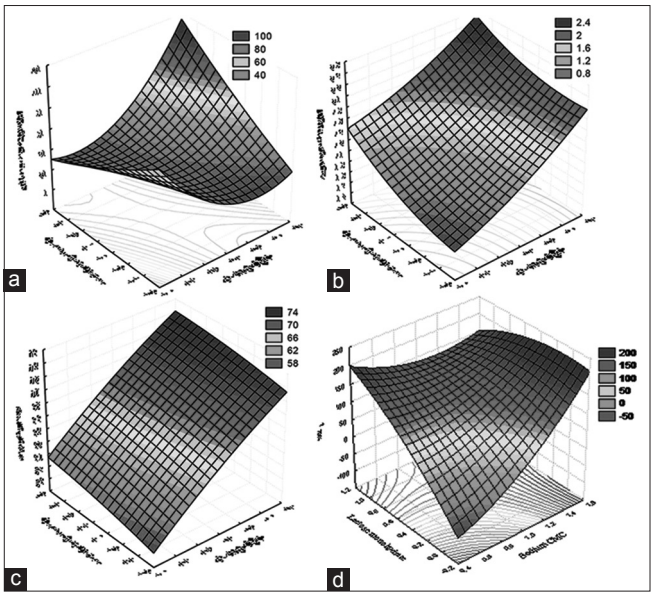

Figure 4: Response surface plots of different outputs (a) Response surface plot of Y1 (b) Response surface plot of Y2 (c) Response surface plot of Y3 (d) Response surface plot of Y4

CONCLUSION

Based on the ANN models obtained in this study, it was possible to predict the desired effect of each input on the different properties of the prepared buccoadhesive pharmaceutical wafers. QbD approach offered a complete knowledge of the factor responsible for different effects of the ingredients on the development of the wafer formulations

In this research, the capability of neural network model was explored for reproducing the physicochemical property of experimental formulations in order to check the effectiveness of the model and its simplification capability under different parameters. Development of new comprehensible computer based programs and the emergent use of ANNs in design and development of pharmaceutical formulation enabled the quick and easy evaluation of the response of ingredients in formulation properties, with reduction in cost by restricting to the minimum number of experimentations.

ACKNOWLEDGMENTS

The authors would like to acknowledge the Chairman and Director, SKS Group of Institutions, India for providing necessary facility to carry out the research work.

REFERENCES

1. Belic A, Skrjanc I, Bozic DZ, Karba R, Vrecer F. Minimisation of the capping tendency by tableting process optimisation with the application of artificial neural networks and fuzzy models. Eur J Pharm Biopharm 2009;73:172-8.
2. Chansanroj K, Petrović J, Ibrić S, Betz G. Drug release control and system understanding of sucrose esters matrix tablets by artificial neural networks. Eur J Pharm Sci 2011;44:321-31.
3. Mendyk A, Kleinebudde P, Thommes M, Yoo A, Szlęk J, Jachowicz R.

Analysis of pellet properties with use of artificial neural networks. Eur J Pharm Sci 2010;41:421-9.
4. Ihme M, Marsden AL, Pitsch H. On the optimization of artificial neural network for application to the approximation of chemical systems. Center for Turbulence Research Annual Research Briefs; 2006. p. 105-18.
5. Mohammad R, Mahmood A, Mohsen J, Alireza S. Application of artificial neural networks in controlled drug delivery systems. Appl Artif Intell Int J 2010;24:807-20.
6. Wei H, Zhong F, Ma J, Wang Z. Formula optimization of emulsifiers for preparation of multiple emulsions based on artificial neural networks. J Dispers Sci Technol 2008;29:319-26.
7. Arulsudar N, Subramanian N, Muthy RS. Comparison of artificial neural network and multiple linear regression in the optimization of formulation parameters of leuprolide acetate loaded liposomes. J Pharm Pharm Sci 2005;8:243-58.
8. Sibanda W, Pillay V, Danckwerts MP, Viljoen AM, van Vuuren S, Khan RA. Experimental design for the formulation and optimization of novel cross-linked oilispheres developed for *in vitro* site-specific release of *Mentha piperita* oil. AAPS Pharm Sci Tech 2004;5:E18.
9. Laitinen N, Rantanen J, Laine S, Antikainen O, Räsänen E, Airaksinen S, *et al*. Visualization of particle size and shape distributions using self-organizing maps. Chemometr Intell Lab 2002;62:47-60.
10. Kachrimanis K, Karamyan V, Malamataris S. Artificial neural networks (ANNs) and modeling of powder flow. Int J Pharm 2003;250:13-23.
11. Bourquin J, Schmidli H, van Hoogevest P, Leuenberger H. Advantages of Artificial Neural Networks (ANNs) as alternative modelling technique for data sets showing non-linear relationships using data from a galenical study on a solid dosage form. Eur J Pharm Sci 1998;7:5-16.
12. Wilson WI, Peng Y, Augsburger LL. Comparison of statistical analysis and Bayesian Networks in the evaluation of dissolution performance of BCS Class II model drugs. J Pharm Sci 2005;94:2764-76.
13. Barmpalexis P, Kanaze FI, Kachrimanis K, Georgarakis E. Artificial neural networks in the optimization of a nimodipine controlled release tablet formulation. Eur J Pharm Biopharm 2010;74:316-23.
14. Chakraborty P, Parcha V, Chakraborty DD, Chanda I, Ghosh A. Mathematical optimization and characterization of pharmaceutically developed novel buccoadhesive wafers for rapid bioactive delivery of loratadine. J Pharm Investig 2013;43:133-43.
15. Chakraborty P, Dey S, Parcha V, Bhattacharya SS, Ghosh A. Design expert supported mathematical optimization and predictability study of buccoadhesive pharmaceutical wafers of Loratadine. Biomed Res Int 2013;2013:197398.
16. Mandal U, Gowda V, Ghosh A, Bose A, Bhaumik U, Chatterjee B, *et al*. Optimization of metformin HCl 500 mg sustained release matrix tablets using Artificial Neural Network (ANN) based on Multilayer Perceptrons (MLP) model. Chem Pharm Bull (Tokyo) 2008;56:150-5.
17. Bishop CM. Neural Networks for Pattern Recognition. Oxford: Oxford University Press; 1995.
18. Djuriš J, Medarević D, Krstić M, Vasiljević I, Mašić I, Ibrić S. Design space approach in optimization of fluid bed granulation and tablets compression process. Scientific World Journal 2012;2012:185085.

How to cite this article: Prithviraj C, Versha P, Debarupa CD, Amitava G. Application of artificial neural network model in predicting physicochemical characteristics of pharmaceutically developed wafers of loratadine. Asian J Pharm 2015;9:44-8.

Source of Support: Nil. **Conflict of Interest:** None declared.