RESEARCH ARTICLE

Application of an Artificial Neural Network for Design of Sustained-Release Matrix Tablets Containing *Vaccinium Myrtillus* Leaf Powder Extract

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Abstract

Context: *Vaccinium myrtillus* leaf extracts are promising source of natural remedies for diabetes mellitus Type 2 management and prevention. **Aim:** The aim of this study was to design the sustained-release matrix tablets containing *V. myrtillus* leaf powder extract with the application of an artificial neural network (ANN). **Methods and Materials:** The amounts of Methocel K4M, Methocel K100LV, and Eudragit L100 were used as input factors affecting the release from matrix tablets. Each input factor was varied on three levels according to Box–Behnken design. The *in vitro* percent release at time points of 2, 8, and 16 h were used as output data in training, testing, and validating the neural network. The software Matlab was used to create an ANN and the number of nodes in the hidden layer was selected based on trial and error approach to develop a model with the best predictive ability. **Results:** The multilayer perceptron with one hidden layer was constructed. The network with nine nodes in the hidden layer was used to simulate *in vitro* release from hypothetical formulations and the matrix forming agent ratio was selected by the brute-force method. The dissolution profile for the selected formulation of matrix tablets was studied. The evaluation of the release kinetics and mechanism indicated a coupling of the diffusion and erosion as release mechanisms. **Conclusions:** ANNs can be successfully applied to develop herbal sustained release matrix tablets.

Key words: Artificial neural networks, diabetes mellitus Type 2, matrix tablets, sustained release, *Vaccinium myrtillus* leaves

INTRODUCTION

Bilberry (*Vaccinium myrtillus* L.) leaves have long been used as an antidiabetic remedy in folk medicine. In the early scientific research, the bilberry leaf preparations were found to be effective in diabetic conditions as they considerably prolonged the survival time of fully depancreatized dogs and completely normalized the blood glucose level in partially depancreatized dogs.[1,2] The current *in vitro* studies revealed that aqueous and hydroethanolic extracts of *V. myrtillus* leaves possess antioxidant and α-glucosidase-inhibiting activities.[3] It was also reported that bilberry leaf extracts have some agonistic activity on human peroxisome proliferator-activated receptor gamma.[4] Hypolipidemic and hypoglycemic therapeutic potential of bilberry leaf extracts was confirmed by in vivo studies.[5,6]

Recently, the method for preparation of the hypoglycemic composition from *V. myrtillus* leaves in the form of water-soluble powder extract has been developed.[7] It was identified that the most abundant phytochemical constituent of *V. myrtillus* leaf extract obtained using this method is chlorogenic acid.[8] Unlike many other plant phenolic compounds (e.g., resveratrol, quercetin, and genistein), chlorogenic acid has good aqueous solubility and is highly absorbed and rapidly eliminated from the human organism.[9-12] Thus, taking into account physical–chemical

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Received: 29-04-2018
Revised: 02-06-2018
Accepted: 12-06-2018

properties of *V. myrtillus* leaf powder extract (VMLPE) and pharmacokinetic data of its main phytochemical component, it is appropriate to develop an extended release dosage form that will reduce the dose frequency, decrease the fluctuations in blood plasma concentrations of active substances, and improve the patient's compliance.

The most common approach to prolong drug release is to design of matrix type dosage forms. In matrix tablets, therapeutic agents are uniformly distributed in a hydrophilic or a hydrophobic matrix formed by natural, semisynthetic, or synthetic polymers. To date, the most widely used matrix-forming excipient is hypromellose (hydroxypropyl methylcellulose [HPMC]) - a hydrophilic semisynthetic polymer that swells in aqueous solutions and forms gels of various viscosities depending on HPMC grade used in the formulation. In this case, the necessary prolongation can be achieved by incorporating into the formulation a single HPMC grade or combination of grades with different viscosities, as well as combinations of HPMC with chemically different polymers.[13,14]

In general, extended release dosage forms are designed with the purpose of maintaining relatively steady concentrations of the drug in the blood, tissues, or target organs. However, the release rate of active pharmaceutical ingredient (API) from a matrix system may significantly vary at different release stages. Moreover, drug release from most of extended-release dosage forms involves more than one mechanism (e.g., diffusion, erosion).[15] In this regard, according to the United States Pharmacopeia (USP), *in vitro* dissolution profile of extended release dosage forms should meet certain acceptance criteria, which are often based on three time points: (1) An early time point to exclude dose dumping of the drug, (2) a time point at which not <50% of drug is released in order to characterize the release profile and demonstrate the extension of release, and (3) a time point to prove that most of the intended entire dose is delivered.[16] For example, the USP dissolution acceptance criteria for metformin hydrochloride 500 mg extended-release tablets include time points of 2, 8, and 16 h, at which the cumulative drug release should be not more than 30%, 60–85%, and not <90%, respectively.[17]

An important challenge in the designing extended release dosage forms is to achieve a desirable drug release profile within shorter terms and minimum number of experiments. Such a challenge is associated with a set of interacting factors affecting the rate and mechanism of API release from the matrix. Among these factors, API physicochemical properties as well as qualitative and quantitative composition of the matrix are the most significant. As a rule, the interrelation of the mentioned factors and API release profile has a rather complex, non-linear character, so the design of an extended-release formulation may require a large number of long and laborious experiments.

One of the modern approaches for solving this challenge is the application of artificial intelligence, in particular, artificial neural networks (ANNs). ANN is a computer model that simulates the interconnected neurological structures of the human brain and its ability to learn, recognize, and reproduce complex dependencies between input and output data. In comparison with the design of experiments (DoE) techniques (e.g., response surface methodology), ANNs are efficient in modeling highly non-linear behaviors, whereas capability of the DoE techniques to model highly non-linear behaviors is limited. However, it should be noted that the predictive ability of the ANN depends on the range of input data, thereby data from DoE methodologies are often used to construct ANN models since such approach usually ensures independence of the formulation factors.[18-20]

The most commonly used network architecture for multivariable objectives of pharmaceutical development is the multilayer perceptron. Each perceptron layer, namely, an input, hidden, and output layer, consists of neurons or nodes that are fully interconnected with neurons in the neighboring layers as shown in Figure 1. The input layer nodes represent independent variables, for example, amounts of matrix-forming polymers in a formulation. The hidden layer consists of several nodes which perform a weighted summation of the inputs followed by a non-linear transformation and relay that data to the output layer. The number of nodes in the hidden layer is critical to the efficiency of a network, as if the hidden layer has too few nodes, the ANN will lack the power needed to classify the data provided to it. Conversely, if there are too many nodes, patterns in the input data will be memorized and therefore the ability of the network to interpolate data will be diminished. In most cases, an appropriate number of nodes in the hidden layer is determined by a trial and error method. The output nodes are measurable properties of pharmaceutical formulations, for example, percent drug release at different stages of a dissolution test.[19,21]

Thus, the objective of this study was to develop extended-release matrix tablets containing VMLPE with optimal *in vitro* release profile using an ANN.

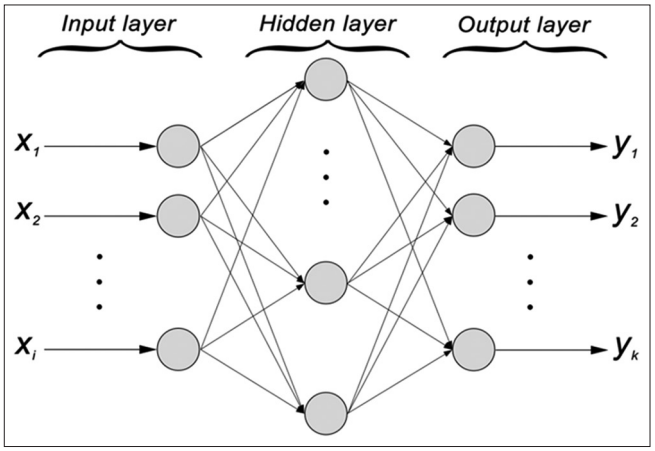

Figure 1: Multilayer perceptron architecture for a feedforward backpropagation artificial neural network where $x_1 \ldots x_i$ are inputs and $y_1 \ldots y_k$ represent response factors

MATERIALS AND METHODS

Materials

VMLPE was obtained by triple maceration method with 50% (v/v) ethanol (plant material to total solvent ratio was 1:10 (w/v)) at room temperature. The resulting liquid extracts were combined, allowed to settle for 24 h, and filtered. The filtrate was evaporated to dryness using a rotary vacuum evaporator with adding the mixture of L-arginine and myoinositol in amount equal to dry residue of the crude liquid extract, wherein L-arginine was taken in three-equimolar quantity relative to the total phenolic content expressed as pyrogallol (determined according to European Pharmacopoeia chapter 2.8.14 "Determination of tannins in herbal drugs").[22] The obtained powder extract was stored at 4°C until use.

The excipients used for matrix tablet preparation were Methocel K4M and Methocel K100LV with nominal viscosity 4000 cP and 100 cP, respectively (Dow Chemical Company, USA), Eudragit L100 (Evonik, Germany), Avicel PH101 (FMC BioPolymer, Philadelphia, PA, USA), Kollidon 25 (BASF, Germany), and magnesium stearate (S.D. Fine. Chemicals Ltd., India). All chemicals and reagents used in this study were at least of analytical grade purchased from Sigma-Aldrich.

Preparation of sustained-release matrix tablets

Matrix tablets were prepared by the wet granulation method. VMLPE (275 mg per tablet) was dry blended with polymer matrix-forming agents (viz., Methocel K4M, Methocel K100LV, and Eudragit L100) and Avicel PH101. The obtained blend was wetted by 15% aqueous solution of Kollidon 25, thoroughly mixed, and granulated through a sieve with pore diameter of 2.0 mm. Wet granules were dried at 40°C till residual moisture content of 4.0% was reached. The dried granules were sifted through a sieve with pore diameter of 1.0 mm and then mixed with previously sieved magnesium stearate. Flat-faced cylindrical tablets with a diameter of 12 mm were produced on the laboratory single-punch tablet press at a pressure enough to achieve tablet hardness of 100 ± 5 N. The levels of Avicel PH101, Kollidon 25, and magnesium stearate were constant for all matrix tablet formulations.

Bulk properties of granules for VMLPE sustained-release formulations

To characterize bulk properties of granules such parameters as angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio were determined for all VMLPE sustained-release formulations. Angle of repose was measured using fixed funnel method. The granules were allowed to flow through a funnel fixed at a constant height (h) until the apex of the conical pile so formed touched the tip of funnel. Mean diameters (2 r) of the pile of powder cone were measured and the angle of repose was calculated. The Carr's index and Hausner's ratio were calculated from poured bulk density (ρ_0) and tapped bulk density (ρ_t). Electrolab tap density tester (model ETD-1020, India) was used to determine poured and tapped bulk densities of granules as described in European Pharmacopoeia chapter 2.9.34 "Bulk density and tapped density of powders."[22] All tests were performed with $n = 5$.

In vitro dissolution studies

USP paddle apparatus Type 2 at rotation speed of 75 rpm was used for a dissolution test in this study. The dissolution medium was 0.1 M HCl (pH 1.2) for acid stage and phosphate buffer solution (pH 6.8) for buffer stage. Volume and temperature of dissolution medium were 1000 ml and 37.0 ± 0.5°C, respectively. The dissolution test was performed for 2 h at acid stage and then for 14 h at buffer stage. At certain time points, a 5 ml aliquot of dissolution medium was removed from the dissolution vessels, filtered through a 0.45 μm Millipore filter (Millipore, Bedford, MA, USA) and then used for the determination of drug released. All tests were performed with $n = 6$.

As it is known, herbal extracts usually contain a range of biologically active compounds. According to previous pharmacological studies, VMLPE possesses the antidiabetic action through several mechanisms which may be attributed not only to its dominant constituent (i.e. chlorogenic acid) but also its total phenolic composition (Koshoviy *et al*., 2016). Due to this, quantification of total phenolics released was chosen as the most suitable to study drug release kinetics. The spectrophotometric method using Folin–Ciocalteu reagent and pyrogallol as a standard (λ_{max} = 760 nm) was used as described in European Pharmacopoeia chapter 2.8.14 "determination of tannins in herbal drugs."[22] *In vitro* cumulative release was calculated as percentage to the average content of biologically active substances (expressed as pyrogallol equivalents) of 10 tablets.

ANN

Designing ANN was carried out using Neural Network Toolbox (NNTool) of commercially available software Matlab R2016b through following five basic steps: (1) Collecting data, (2) pre-processing data, (3) building the network, (4) train, and (5) test the model performance. Feedforward back propagation networks were created for this study. The amounts of matrix forming excipients Methocel K4M, Methocel K100LV, and Eudragit L100 were selected as input factors affecting the release of VMLPE active substances. Each input factor was varied on three levels according to Box–Behnken design [Table 1]. The percent API released from corresponding matrix tablet formulations at time points of 2, 8, and 16 h was used as output data. Input and output data were normalized through "mapminmax" function automatically applied by NNTool for

providing values in the range from −1 to +1. All data were randomly divided into training (65%), testing (20%), and validation (15%) sets. Levenberg–Marquardt algorithm was used for training ANN and a sigmoidal function ("logsig") was used as the transfer function for the hidden layer and backpropagation of errors. The mean squared error was used as the performance function. Stopping criteria for ANN training were 6 validation failures or 1000 epochs, whichever came first. The predicted data were compared with the original data set by plotting the predicted versus original values and computing the correlation coefficient for each of the responses in the output layer. The closer correlation coefficient values were to 1 then the better the predictive capability of the ANN. Several training sessions were conducted with different numbers of nodes in the hidden layer and training times in order to determine the optimal ANN architecture. The ANN with the closest correlation coefficient value to 1 was then selected for further prediction *in vitro* release from hypothetical formulations. For this purpose, a function for simulating the *in vitro* release from matrix tablets with different ratios of prolonging agents was written in Matlab code. The selection of optimal composition of prolonging agents was done by the brute-force method with a step of variation 1/20 of the original input data range for each factor. The selecting criteria were the responses of *in vitro* release at time points of 2, 8, and 16 h – not more than 30%, 60–85%, and not <90%, respectively.

RESULTS

Experimental data used to design ANN are shown in Table 1. Granules of all VMLPE sustained-release formulations were subjected to evaluation of bulk properties and such parameters as angle of repose, bulk and tapped density, Carr's index, and Hausner's ratio were determined. Angle of repose was found to be ranging from 22º.19' ± 0.05 to 31º.16' ± 0.02. Carr's index was found to be ranging from 6.92 ± 0.09 to 11.29 ± 0.02% for the granules of all the formulations. Hausner's ratio was found to be lesser than 1.18 for the granules of all the formulations. These results generally indicate good to excellent flow properties of VMLPE sustained-release formulations.

Based on the data presented in Table 1, ANNs with different number of nodes in the hidden layer were constructed. To determine the optimal ANN architecture, a trial and error approach was used and ANN with correlation coefficient values closest to 1 was selected for further simulations. The impact of changing the number of nodes in the hidden layer on the predictive ability of the ANN is depicted in Figure 2.

ANN with nine nodes in the hidden layer was selected for further simulations. Regression plots for selected ANN generated through Matlab NNTool are shown in Figure 3. The criteria for the selection of the prolonging agent ratio were the percentage

Table 1: Data used for designing ANN

Formulation	Input data set			Output data set		
	X_1	X_2	X_3	Y_1	Y_2	Y_3
F1	−1	−1	0	61.50	89.76	98.86
F2	+1	−1	0	24.49	60.71	76.77
F3	−1	+1	0	34.18	76.09	93.47
F4	+1	+1	0	12.69	40.96	54.02
F5	0	0	−1	24.09	69.01	87.16
F6	+1	0	−1	19.56	51.33	66.35
F7	−1	0	+1	34.74	76.14	94.62
F8	+1	0	+1	20.24	52.51	65.82
F9	0	−1	−1	28.92	72.81	86.43
F10	0	+1	−1	27.31	66.18	82.36
F11	0	−1	+1	23.17	70.95	86.96
F12	0	+1	+1	22.52	64.35	81.27
F13	0	0	0	22.76	71.99	87.33
F14	0	0	0	21.15	72.42	85.91
F15	0	0	0	23.48	70.91	86.09

Input data set	Levels			Output data set
	−1	0	+1	
X_1: Amount of HPMC K4M, mg per tablet	0	32.5	65.0	Y_1: Cumulative percent release after 2 h*
X_2: Amount of HPMC K100LV, mg per tablet	0	32.5	65.0	Y_2: Cumulative percent release after 8 h*
X_3: Amount of Eudragit L100, mg per tablet	130.0	162.5	195.0	Y_3: Cumulative percent release after 16 h*

*The mean value from *n*=6. HPMC: Hydroxypropyl methylcellulose, ANN: Artificial neural network

of *in vitro* release at time points of 2, 8, and 16 h – not more than 30%, 60–85%, and not <90%, respectively. On the basis of ANN simulations, the following prolonging agent ratio was selected: Methocel K4M – 26.0 mg per tablet; Methocel K100LV – 26.0 mg per tablet; and Eudragit L100 – 162.5 mg per tablet.

For matrix tablets with the indicated ratio of prolonging agents, *in vitro* dissolution at time points of 1, 2, 3, 4, 5, 6, 7, 8, and 16 h was studied [Figure 4]. The comparison of predicted and experimental values of *in vitro* dissolution at the corresponding time points for optimized matrix tablet formulation is presented in Table 2.

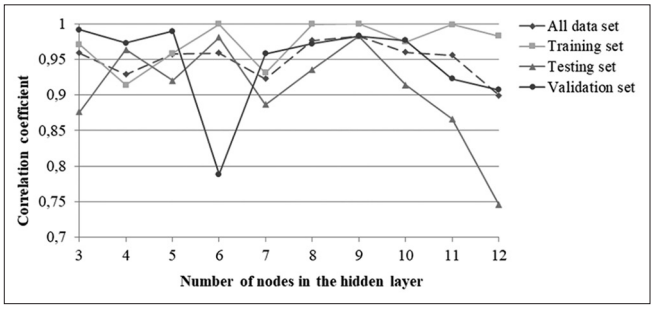

Figure 2: The impact of the number of nodes in the hidden layer of an artificial neural network on the correlation coefficient

To study the release kinetics and mechanism, experimental data of *in vitro* release from optimized formulation of matrix tablets were plotted in various kinetic models. The regression coefficient values in the analysis of release kinetics as per zero order, first order, Higuchi, Hixson–Crowell models, and Korsmeyer–Peppas model are given in Table 3.

DISCUSSION

As it is seen from Table 1, the release of VMLPE biologically active substances is significantly affected by the type and ratio of prolonging agents. That is, the slowest release, which did not exceed 80% at time point of 16 h, was observed for the formulations containing a maximum level of high-viscosity HPMC Methocel K4M, while the use of single Methocel

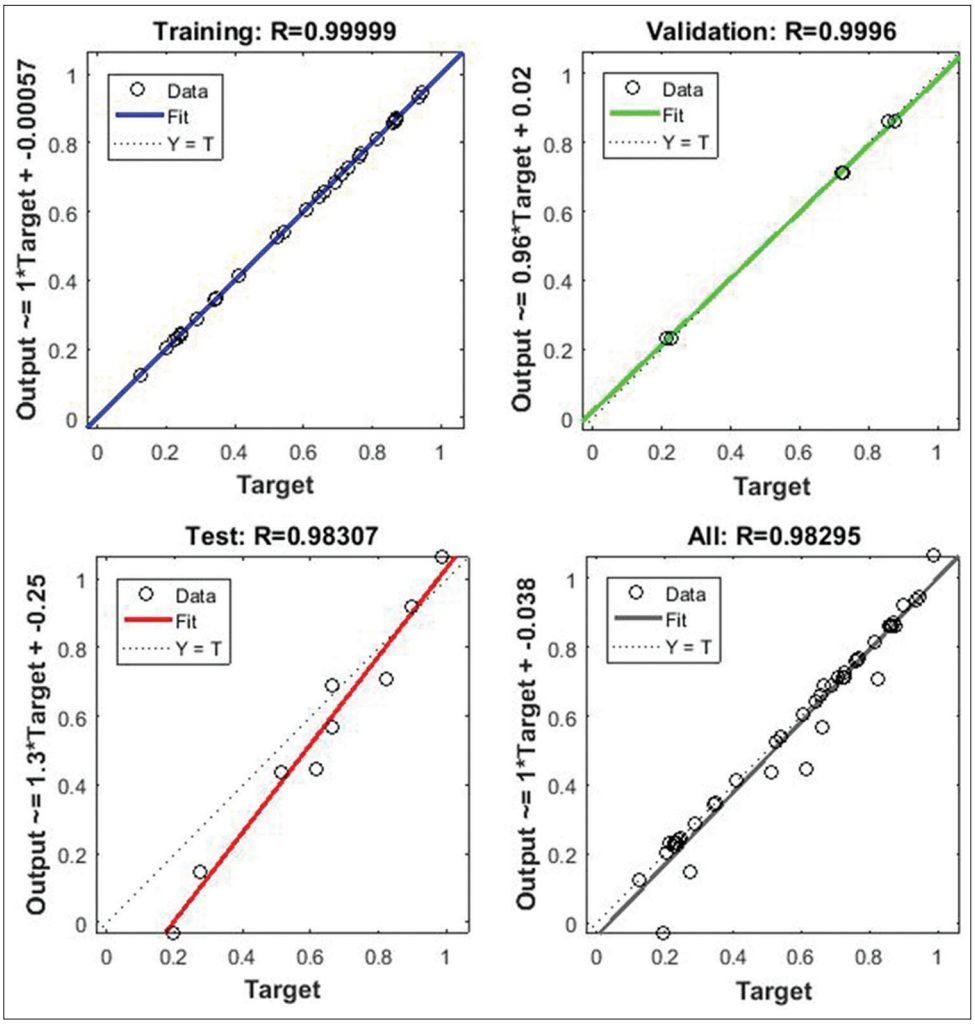

Figure 3: Regression plots for selected artificial neural network generated via Matlab Neural Network Toolbox

Table 2: Comparison of predicted and experimental *in vitro* release values at time points of 2, 8, and 16 h for optimized formulation of matrix tablets containing VMLPE

Optimized formulation		Time point, h	Predicted *in vitro* release value, %	Experimental *in vitro* release value, %	Correlation coefficient
Ingredient	Amount, mg per tablet				
VMLPE	275.0	2	26.76	25.08*	0.9993
Eudragit L100	162.5	8	76.96	73.91*	
Methocel K4M	26.0	16	94.83	94.57*	
Methocel K100LV	26.0				
Avicel PH 101	128.0				
Kollidon 25	26.0				
Mg stearate	6.5				

*The mean value from *n*=6. VMLPE: *Vaccinium myrtillus* leaf powder extract

Table 3: Release kinetics for the optimized formulation of matrix tablets containing VMLPE

Zero order	First order	Higuchi	Hixson–Crowell	Korsmeyer–Peppas	
R^2	R^2	R^2	R^2	R^2	*n*
0.8864	0.9893	0.9776	0.9935	0.9964	0.7094

VMLPE: *Vaccinium myrtillus* leaf powder extract

K100LV grade even at maximum level gave the release of more than 30% already at the end of the acid stage. Eudragit L100, which is an anionic low-swellable polymer soluble at pH >6, was added as pH-dependent prolonging agent. In such a way, formulations containing equal amounts of Methocel K4M and Methocel K100LV, but higher levels of Eudragit L100 showed less release in acid medium under the close release values in buffer solution. On the other hand, the use of only Eudragit L100 without adding HPMC grades gave the release of more than 60% at the first 2 h of dissolution test.

From Figure 2, it is clear that the efficiency of ANN is dependent on the number of nodes in the hidden layer of the network. The ANN having nine nodes in the hidden layer gives correlation coefficients closest to 1 for all data sets. Therefore, such ANN architecture is characterized by good predictive capabilities and useful for the simulation of the impact of formulation variables on the dissolution rate of VMLPE biologically active substances from matrix tablets.

A number of mathematical models have been proposed to describe drug release from pharmaceutical delivery systems, however, in the case of matrix type sustained-release dosage forms, the most commonly used models are zero-order and first-order kinetic models, Higuchi model, and the Hixson–Crowell model.[23-25]

Zero-order kinetic model (Equation 1) assumes that the rate of API release from matrix system does not depend on its concentration and is constant in time:

$$C = K_0 t, \quad (1)$$

Where K_0 – is the zero-order rate constant expressed in units of concentration/time and t is the time in hours.[26] To study the release kinetics using zero-order model, the experimental data were plotted as cumulative percentage of API released versus time [Figure 4].

According to the first-order kinetic model (equation 2), the rate of drug release is proportional to its concentration:

$$\text{Log}C = \text{Log}C_0 - kt/2.303 \quad (2)$$

Where C_0 is the initial drug concentration, k is the first-order constant, and t is the time. This relationship is often used to describe the immediate drug release from conventional dosage forms; however, it is also applicable for sustained-release dosage forms containing water-soluble drugs in porous matrices.[26] For this model, the experimental data were plotted as log cumulative percentage of API remaining in the matrix versus time [Figure 5a].

Higuchi kinetic model is one of the most known and often used to describe the release rate of drugs from matrix systems. This model is based on the following assumptions: (1) Initial concentration of the drug in the matrix is much higher than the drug solubility; (2) diffusion of drug occurs only in one dimension (edge effect is negligible); (3) drug particles much smaller than system thickness; (4) swelling and dissolution of matrix polymer are negligible; (5) drug diffusivity is constant; and (6) in the release environment, perfect sink conditions are

maintained. Initially, Higuchi model was intended to describe planar systems, but later, it was modified and expanded for systems of different geometric shape and structure porosity. The modified Higuchi model is described by equation 3:

$$Q = Kt^{1/2} \quad (3)$$

Where Q is the cumulative percentage of drug released, K is the constant reflecting the design variables of the system, and t is the time in hours.[26] To study the release kinetics using modified Higuchi model, the data obtained from *in vitro* release studies were plotted as cumulative percentage API released versus the square root of time [Figure 5b].

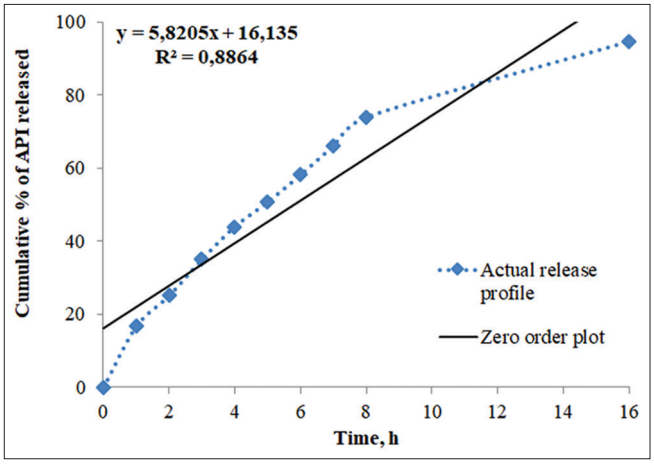

Figure 4: Experimental release profile versus zero-order plot for the optimized formulation of matrix tablets containing *Vaccinium myrtillus* leaf powder extract

Hixson–Crowell model is applied to pharmaceutical dosage form such as tablets, where dissolution occurs in planes that are parallel to the drug surface if the tablet dimensions diminish proportionally in such a manner that the initial geometrical form keeps constant all the time. This model is expressed by equation 4:

$$Q_0^{\frac{1}{3}} - Q_t^{\frac{1}{3}} = kt \quad (4)$$

Where Q_0 is the initial amount of drug in the matrix, Q_t is the remaining amount of drug in the matrix at time t, k is the rate constant for Hixson–Crowell equation.[26] To study the release kinetics, the data were plotted as the cube root of percentage API remaining in the matrix versus time [Figure 5c].

The mechanism of release of VMLPE biologically active substances (expressed as pyrogallol) from optimized formulation of matrix tablets was evaluated using Korsmeyer–Peppas model (equation 5) by plotting the first 60% of experimental data as log cumulative percentage of API released versus log time [Figure 5d]:

$$Q_t/Q_\infty = Kt^n \quad (5)$$

Where Q_t/Q_∞ is the fraction of API released at time t, K is a kinetic constant, and n is an exponent that characterizes the mechanism of release. For cylindrical matrix tablets, if the exponent n = 0.45, then the drug release mechanism is Fickian diffusion and if $0.45 < n < 0.89$, then it is non-Fickian or anomalous diffusion. An exponent value of 0.89 is indicative of typical zero-order release.[25,26]

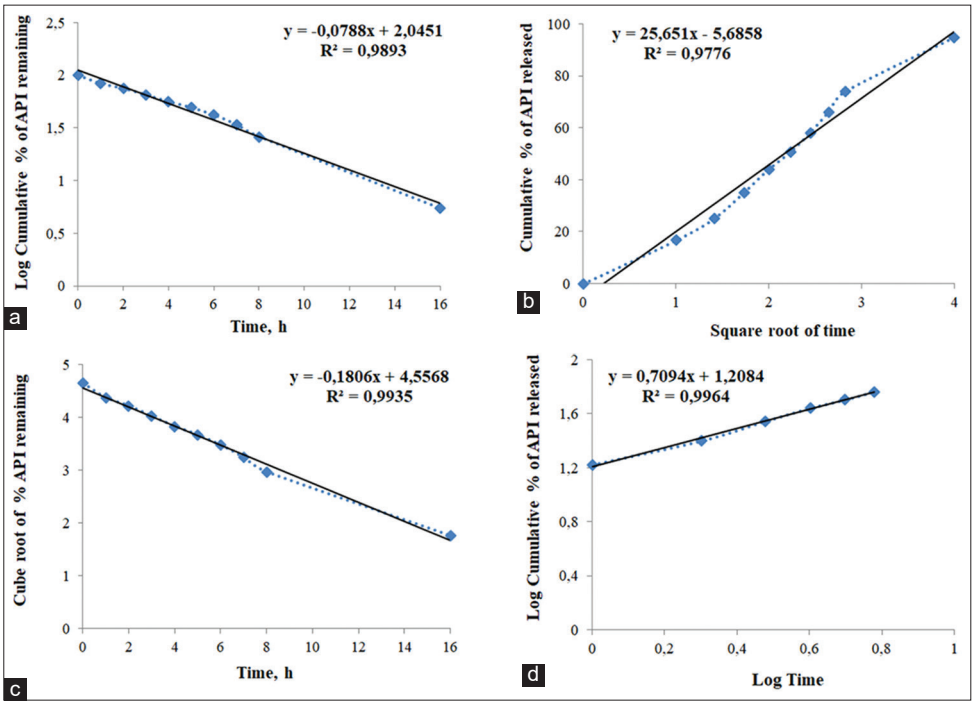

Figure 5: First order (a), Higuchi (b), Hixson–Crowell (c), and Korsmeyer–Peppas (d) model plots for the optimized formulation of matrix tablets containing *Vaccinium myrtillus* leaf powder extract

It was found that the kinetics of VMLPE biologically active substances *in vitro* release was best explained by Korsmeyer–Peppas and Hixson–Crowell equations (R^2 were 0.9964 and 0.9935, respectively). A good linearity for Hixson–Crowell equation indicates that the release rate changes with the change of the tablet surface area and diameter, which is typical for tablets with polymer erosion/dissolution.[27] However, drug release was also found to be close to Higuchi model kinetics ($R^2 = 0.9776$), indicating diffusion as a release mechanism. The Korsmeyer–Peppas release exponent n was 0.71, which confirms the release by a coupling of the diffusion and erosion mechanisms.[25]

Thus, our study demonstrated the effectiveness of ANN application in the design of the sustained-release formulation. Our findings generally correspond to the earlier studies on ANN applications in pharmaceutical development,[18-21] however, this is the first report of the use of ANN for designing delivery systems for herbal extracts.

CONCLUSIONS

Sustained-release matrix tablets containing VMLPE were designed using an ANN. Formulation variables such as amounts of three matrix-forming agents and the percent of biologically active substances released at time points of 2, 8, and 16 h were used for training, validating, and testing the networks through NNTool of Matlab R2016b. The efficiency of the network was dependent on the number of nodes in the hidden layer and the optimal number of nodes was determined by a trial and error approach. The optimal number of nodes that produced a good predictive model was found to be nine. The network with established architecture was used to simulate *in vitro* release from hypothetical formulations and the matrix-forming agent ratio was selected by the brute-force method. The dissolution profile for the optimized formulation of matrix tablets was studied. The evaluation of the release kinetics and mechanism indicated a coupling of the diffusion and erosion as release mechanisms from the designed matrix tablets.

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