Optimization of Metformin HCl 500 mg Sustained Release Matrix Tablets Using Artificial Neural Network (ANN) Based on Multilayer Perceptrons (MLP) Model

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The aim of the present study was to apply the simultaneous optimization method incorporating Artificial Neural Network (ANN) using Multi-layer Perceptron (MLP) model to the development of a metformin HCl 500 mg sustained release matrix tablets with an optimized *in vitro* release profile. The amounts of HPMC K15M and PVP K30 at three levels (−1, 0, +1) for each were selected as casual factors. *In vitro* dissolution time profiles at four different sampling times (1 h, 2 h, 4 h and 8 h) were chosen as output variables. 13 kinds of metformin matrix tablets were prepared according to a 2^3 factorial design (central composite) with five extra center points, and their dissolution tests were performed. Commercially available STATISTICA Neural Network software (Stat Soft, Inc., Tulsa, OK, U.S.A.) was used throughout the study. The training process of MLP was completed until a satisfactory value of root square mean (RSM) for the test data was obtained using feed forward back propagation method. The root mean square value for the trained network was 0.000097, which indicated that the optimal MLP model was reached. The optimal tablet formulation based on some predetermined release criteria predicted by MLP was 336 mg of HPMC K15M and 130 mg of PVP K30. Calculated difference (f_1 2.19) and similarity (f_2 89.79) factors indicated that there was no difference between predicted and experimentally observed drug release profiles for the optimal formulation. This work illustrates the potential for an artificial neural network with MLP, to assist in development of sustained release dosage forms.

Key words artificial neural network; multilayer perceptron; metformin HCl; sustained release; matrix tablet

Introduction of matrix tablet as sustained release (SR) has given a new breakthrough for novel drug delivery system (NDDS) in the field of pharmaceutical technology.[1,2] It excludes complex production procedures such as coating and pelletization during manufacturing and drug release rate from the dosage form is controlled mainly by the type and proportion of polymer used in the preparations.

In the development of a sustained release tablet dosage form, an important issue is to design an optimized formulation with an appropriate dissolution rate in a short time period and minimum number of trials. Many statistical experimental designs have been recognized as useful techniques to optimize the process variables. Artificial neural networks (ANNs) have seen an explosion of interest over the last few years, and are being successfully applied in the field of pharmaceutical development and optimizing of dosage forms by predicting the nonlinear relationship between casual factors and response variables.[3—7] Compared with classical statistical optimization techniques, such as response surface methodology where theoretical relationships between response variables and casual factors are not clear, ANN shows superiority as a modeling technique for data sets showing nonlinear relationships, and thus for both data fitting and prediction abilities.[8—10]

ANN is a learning based system on a computational technique that can simulate the neurological processing ability of the human brain and can be applied to quantify a nonlinear relationship between causal factors and pharmaceutical responses by means of iterative training of data obtained from a designed experiment.[11]

Metformin HCl is an orally administered biguanide, which is widely used in the management of type-2 diabetes, a common disease that combines defects of both insulin secretion and insulin action.[12] It improves hepatic and peripheral tissue sensitivity to insulin without the problem of serious lactic acidosis commonly found with its analogue, phenformin. It has three different actions: it slows the absorption of sugar in our small intestine; it also stops our liver from converting stored sugar into blood sugar; and it helps our body use our natural insulin more efficiently. It is a hydrophilic drug and is slowly and incompletely absorbed from the gastrointestinal tract and the absolute bioavailability of a single 500 mg dose is reported to be 50—60%.[13] An obstacle to more successful use of metformin therapy is the high incidence of concomitant gastrointestinal symptoms, such as abdominal discomfort, nausea, and diarrhea that especially occur during the initial weeks of treatment. Also the compound has relatively short plasma elimination half-life of 2 to 4 h.[14] Side effects and the need for administration two or three times per day when larger doses are required can decrease patient compliance. Sustained release (SR) formulation that would maintain plasma levels of drug for 8 to 12 h might be sufficient for once daily dosing for metformin. SR products are needed for metformin to prolong its duration of action and to improve patient compliance.[15]

The aim of the present study was to apply the simultaneous optimization method incorporating ANN using Multilayer Perceptrons (MLP) model to the development of a metformin HCl 500 sustained release matrix tablet with an optimized *in vitro* release profile using HPMC K15M and PVP K30 as casual factors.

ANN Using Multilayer Perceptrons (MLP) A commercial Microsoft Window's based neural network software package, STATISTICA 7 (Stat soft) was used throughout the

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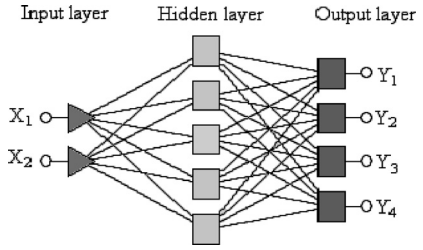

Fig. 1. Artificial Neural Network (ANN) with Multilayer Perceptrons (MLP)

X_1 and X_2 are two units of input layer. Y_1, Y_2, Y_3 and Y_4 are four units of output layer. Hidden layer contains five units.

study with a Pentium 4 personal computer. For real world problem solving, ANN is classified to the different models. Among them most frequently used models are mentioned below:

- Multilayer Perceptrons (Feed forward)
- Radial Basis Function Networks
- Probabilistic Neural Networks (PNNs)
- Generalized Regression Neural Networks (GNNs)

Multilayer Perceptrons (MLP) is perhaps the most popular network architecture in use today, due originally to Rumelhart *et al.*[16] and discussed at length in most neural network textbooks.[17] In overview, an MLP is composed of different layers of processing units that are interconnected through weighted connections (Fig. 1). The first layer consists of the input variables. The last layer consists of the output variables representing the output class. Intermediate layers called hidden layer receive the entire input pattern that is modified by the passage through the weighted connections. The hidden layer provides the internal representation of neural pathways.

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. Certain empirical techniques have been reported to improve the convergence of ANN in the global minima.[11,18] The network is trained using different algorithms (Back propagation, Conjugate gradient descent, Quasi-Newton, Levenberg-Marquardt, Quick propagation, Delta-bar-delta *etc.*).[18—21] Back propagation learning algorithm is widely used in multilayer feed forward networks. The calculations begin at the output layer and progress backward through the network to the input layer. A method called momentum decreases back propagation's sensitivity to small details in the error surface. This helps the network avoid getting stuck in local minima, which would prevent the network from finding a lower error solution. The momentum helps the network to overcome obstacles (local minima) in the error surface and settles down at or near the global minima (solution with lowest possible error). Another essential approach is to use an extended Kalman filter algorithm for ANN training.[22—25] We can greatly reduce the length of iterative training by using the extended Kalman filter algorithm and also can avoid to a certain extent, ANN getting stuck in a local minima. Although multiple layers can be set between the input layer and the output layer, many ANNs consist of only one hidden layer.[26] One layer is usually sufficient to provide adequate prediction even if continuous variables are adopted as the units in the output layer.[25—27]

Table 1. Composition of 500 mg Metformin HCl Sustained Release Matrix Tablet[a]

Ingredient	Amount (mg)
Metformin HCl	500 mg
HPMC K15M	240 to 480 mg
PVP K30	50 to 150 mg
Magnesium stearate	5 mg
Talcum powder	5 mg
MCC (Avicel PH 101)	qs to 1150 mg

a) qs: quantity sufficient; HPMC K15M: hydroxypropyl methyl cellulose of K15M viscosity grade; PVP K30: polyvinyl pyrrolidone of K30 viscosity grade; MCC: microcrystalline cellulose.

Experimental

Materials Metformin HCl was received from Deys Medical, Kolkata, India, as donated sample. Hydroxy propyl methyl cellulose (HPMC K15M) was a gift sample received from M/S Colorcon Asia Pvt. Ltd., Mumbai, India. MCC (Avicel PH 101), PVP K30 (polyvinyl pyrrolidone K30) were purchased from S. D. Fine Chemicals Ltd., Mumbai, India. Magnesium stearate and talc were procured from Mohanlal Dayaram and Company, Hyderabad, India. All other chemicals/reagents used were of analytical grade, except for those used in HPLC analysis, which were of HPLC grade.

Preparation of Sustained Release Matrix Tablets Table 1 enlists the composition of different trial formulations prepared using varying amounts of HPMC K15M as release controlling polymer and PVP K30 as binder along with fixed quantity of talcum and magnesium stearate as lubricant. MCC was used as filler. HPMC K15M polymer at different ratio was blended with metformin HCl, MCC and PVP K30 in a planetary mixer for 5 min after passing all the materials through a 60 mesh (250 μm). There after the powders were granulated with isopropyl alcohol, sieved using a 12 mesh (1700 μm) and dried at 50 °C for about 2 h with residual moisture content of 2 to 3% w/w. The dried granules were sized by an 18 mesh (1000 μm) and mixed with magnesium stearate and talc for 2 min. All granules were weighed finally to adjust the final weight of individual tablet considering its loss during operational handling. Granules thus obtained were compressed into 1150 mg tablets to average hardness of 6 to 8 kg/cm^2 on an 8 station rotary tablet machine (CIP Machineries Pvt. Ltd., Ahmedabad, India) with 19.5×8.9 mm caplet tooling at a rotational speed of 72 rpm.

Drug Release Study Drug release from 6 tablets of each formulation, in triplicate, was determined using the USP I (basket) apparatus (Electrolab, TDT 06P, USP XXIII) where 900 ml of 0.1 N HCl and phosphate buffer of pH 6.8 were used as dissolution media maintained at 37 °C (±0.5 °C) at 100 rpm. The release rates from the tablets were conducted in a dissolution medium of 0.1 N HCl for 2 h and thereafter in phosphate buffer of pH 6.8 for 6 h. Five milliliters of aliquot were withdrawn at 1, 2, 4 and 8 h with replacement of fresh media. Solution samples were analyzed by high performance liquid chromatography (HPLC) method mentioned below:

Column: Hypersil BDS C18 (250×4.6 mm, 5 μm particle size)
Mobile phase: 10 mM phosphate buffer of pH 6.0 : acetonitrile = 50 : 50 (v/v)
Detector: UV detection with 232 nm
Loop size: 20 μl

Drug Release Kinetics In order to propose a possible release mechanism, drug release from HPMC matrix tablets was fitted to the following equations:

Higuchi's equation[28]:

$$Q = k_H t^{1/2} \quad (1)$$

Where, Q is the amount of drug release at time t, and k_H is the Higuchi rate constant.

Korsmeyer *et al.*'s equation[29]:

$$M_t / M_\infty = kt^n \quad (2)$$

Where, M_t is the amount of drug released at time t, M_∞ is the amount of drug released after infinite time, M_t/M_∞ is the fractional drug release percentage at time t, k is a constant related to the properties of the drug delivery system, and n is the release exponent indicative of the drug release mechanism.

Design of Experiment A central composite design (CCD) with $\alpha = 1$ was employed as per the standard protocol.[30,31] The amounts of HPMC K15M (X_1) and PVP K30 (X_2) were selected as the input variables, studied at

Table 2. Factor Combinations as per the Chosen Experimental Design

Trial No.	Coded factor levels	
	X_1	X_2
I	−1	−1
II	−1	0
III	−1	1
IV	0	−1
V	0	0
VI	0	1
VII	1	−1
VIII	1	0
IX	1	1
X	0	0
XI	0	0
XII	0	0
XIII	0	0
Translation of coded levels in actual units		
Coded level	−1	0	1
X_1: HPMC K15M (mg)	240	360	480
X_2: PVP K30 (mg)	50	100	150

3 levels each. The central point (0, 0) was studied in quintuplicate. The range of HPMC K15M (240 to 480 mg) and PVP K30 (50 to 150 mg) was selected based on pre-formulation trial to prepare 500 mg metformin HCl sustained release tablet. Beyond that level of polymer and binder, the drug release rate was too slow whereas below those levels, the release rate was too high. That's why the range of HPMC K15M and PVP K30 was fixed at 240 to 480 mg and 50 to 150 mg respectively. All other formulation and processing variables were kept invariant throughout the study. Table 2 summarizes an account of the 13 experimental runs studied, their factor combinations, and the translation of the coded levels to the experimental units employed during the study. The percentage of drug released at 1 h (Y_1), the percentage of drug released at 2 h (Y_2), the percentage of drug released at 4 h (Y_3) and the percentage of drug released at 8 h (Y_4) were taken as the output variables.

Model Training, Validation and Optimization Commercially available STATISTICA Neural Network software (StatSoft Inc., Tulsa, OK, U.S.A.) was used throughout the study. Multilayer perceptrons (MLP) with feed forward back propagation method[16,32] was used in modeling and optimization of metformin sustained release tablets. ANN with MLP works in three phases.

First phase: an input vector is presented to the network, which leads *via* the forward pass to the activation of the network as a whole. This generates a difference (error) between the output of the network and the desired output.

Second phase: compute the error factor (signal) for the output unit and propagates this factor successively back through the network (error backward pass).

Third phase: compute the changes for the connection weights by feeding the summed squared errors from the output layer back through the hidden layers to the input layer.

This process is continued until the connection weights in the network have been adjusted so that the network output has converged, to an acceptable level, with the desired output.

Important issues in MLP design include specification of the number of hidden layers and the number of units in these layers.[17,20] Too few hidden layers lead to under fitting. Two many hidden layers can lead the system towards memorizing the patterns in the data.[26] According to Kolmogorov's theorem, it is understood that twice the number of input nodes plus one is sufficient to compute any arbitrary continuous function. Input variables and output variables were used to train the network until it can approximate a function, associate input variables with specific output variables. Initially one hidden layer was used and the number of units in the layer was varied from 1 to 10, using 100 iterations. When the training is over, the network is given the new data and processing and flow of information through the activated network should lead to the assignment of the input data to the output class.

In order to validate the ANN model, the model was trained again using 13 trial formulations and withholding 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. This process was repeated 13 times, each time withholding a different trial formulation from the training set. This validation method is called the "leave-one-out method." A regression plot was then constructed for the predicted output variables and observed output variables to obtain a slope and R^2. The determination of the final optimized model was based on the slope and R^2 values for all 13 formulations.

Once the ANN model was trained, the model was optimized by choosing optimum formulation based on optimum release criteria[33,34] fixed as given below:

Release at 1 h: 25 to 30% [optimum value=(25+30)/2=27.5]
Release at 2 h: 45 to 50% [optimum value=(45+50)/2=47.5]
Release at 4 h: 65 to 70% [optimum value=(65+70)/2=67.5]
Release at 8 h: 95 to 100% [optimum value=(95+100)/2=97.5]

The optimization of the 500 mg metformin HCl tablet was performed according to the generalized distance function method[35] as per following equation.

$$S = \left\{ \sum \left(\frac{FD_t - FO_t}{SD_t} \right)^2 \right\}^{1/2} \quad (3)$$

where S is the distance function generalized by the standard deviation, SD_t, of the observed values for each response variable, FD_t is the optimum values of each response optimized individually over the experimental region and FO_t is the simultaneous optimum value. The simultaneous optimum can be estimated by minimizing S under the restriction of the experimental region.

After training was completed, ANN gave the optimum composition of HPMC K15M and PVP K30 according to distance function method defined in Eq. 3. The tablets were prepared according to the optimal formulation, and their dissolution tests were performed. Observed release profile was compared with the predicted release profile as per Eq. 3 to optimize the ANN model. For every pair of observed/predicted drug release profiles for optimal formulation, difference (f_1) and similarity (f_2) factors were calculated and slopes of regression curves of the observed versus predicted release profiles. According to the US Food and Drug Administration's guide for industry,[36] generally f_1 values up to 15 (0—15) and f_2 values greater than 50 ensures sameness of the 2 curves.

Results and Discussion

***In Vitro* Drug Release Studies** Dissolution samples were analyzed by HPLC method described in Experimental. The retention time of metformin was at 2.367 min. Table 3 lists the mean values (N=3) various dissolution parameters computed for all the matrix formulations. To know the mechanism of drug release from the trial formulations, the data were treated according to Higuchi's[28] (cumulative percentage of drug released *versus* square root of time) and Korsmeyer *et al.*'s[29] (log cumulative percentage of drug released *versus* log time) equations. In our experiments the *in vitro* release profiles of drug from all the formulations could be best expressed by Higuchi's[28] equation as the correlation coefficient values (R^2) presented in Table 3 had high linearity (R^2: 0.990 to 0.999, with k_H 25.85 to 38.52). In the current study, the values of release rate exponent (n), calculated as per the equation proposed by Korsmeyer *et al.*,[29] ranged between 0.4993 and 0.5874 (Table 3). For matrix tablets, an n value of near 0.5 indicates diffusion control, and an n value of near 1.0 indicates erosion or relaxation control. Intermediate values suggest that diffusion and erosion contribute to the overall release mechanism.[37,38] In our experiments the results of n clearly indicated that the diffusion is the dominant mechanism of drug release from these formulations. Diffusion is related to transport of drug from the dosage matrix into the *in vitro* study fluid depending on the concentration of the hydrophilic polymer. As gradient varies, the drug is released, and the distance for diffusion increases. This could explain why the drug diffuses at a comparatively slower rate as the distance for diffusion increases.

Table 3. Mean Drug Release Parameters of Various Trial Formulations Prepared as per the Experimental Design (N=3)[a)]

Trial No.	Factor amount (mg)		Y_1	Y_2	Y_3	Y_4	n	k_H	R^2
	X_1	X_2							
I	240	50	35.21	56.14	75.14	100.15	0.4993	35.43	0.994
II	240	100	34.17	53.41	73.12	100.21	0.5117	35.78	0.998
III	240	150	33.21	52.21	71.65	99.12	0.5145	35.20	0.998
IV	360	50	32.35	51.14	69.32	99.16	0.5263	35.72	0.999
V	360	100	30.47	49.52	68.3	99.19	0.5513	36.45	0.997
VI	360	150	27.65	47.35	64.23	85.32	0.5259	30.75	0.995
VII	480	50	29.56	43.38	67.54	99.11	0.5824	37.92	0.995
VIII	480	100	25.25	46.12	60.59	80.59	0.5387	29.31	0.990
IX	480	150	23.15	38.67	51.17	73.11	0.5314	25.85	0.997
X	360	100	28.18	47.15	67.54	99.14	0.5874	37.58	0.995
XI	360	100	30.41	48.17	67.45	98.47	0.5528	36.39	0.998
XII	360	100	28.75	47.68	69.71	99.31	0.5813	37.42	0.995
XIII	360	100	27.98	46.68	68.59	100.15	0.5998	38.52	0.995

a) X_1: HPMC K15M; X_2: PVP K30; Y_1: release at 1 h; Y_2: release at 2 h; Y_3: release at 4 h; Y_4: release at 8 h; n: release exponent obtained from Korsmeyer *et al.* equation ($M_t/M_\infty=kt^n$), k_H: Higuchi rate constant ($Q=k_Ht^{1/2}$); R^2: regression coefficient of Higuchi equation.

Total amount of metformin released from all the formulations up to 8 h ranged between 73.11% and 100.21%. Rate of drug release (until 8 h) tended to decrease with increase in the content of either HPMC or PVP K30. This is in agreement with literature findings[39,40] that the viscosity of the gel layer around the tablet increases with increase in the hydrogel concentration, thus limiting the release of active ingredient. The gel formed during the penetration of dissolution media into the matrix structure, consists of closely packed swollen particles. With further increase in polymer amount, thicker gel forms inhibiting dissolution media penetration more strongly, resulting in significant reduction in the values of release at 8 h indicating slower drug release.

Figure 2 exhibits the dissolution profiles obtained for various trial formulations, prepared as per CCD. The formulations with lower levels of polymer and binder exhibited initially higher rate of drug release. This result could be attributed to the dissolution of drug present initially at the surface of the matrices and rapid penetration of dissolution media to the matrix structure. However, the formulations showed little burst effect at higher polymer levels, ratifying better substance of drug release. Overall, all the formulations showed quite regulated drug release from 4 h onwards.

MLP Structure Two casual factors corresponding to three levels of HPMC K15M (X_1) and PVP K30 (X_2) were used as each unit of the input layer in the MLP. *In vitro* release at four different time points mentioned below were used as 4 output units

- Y_1: the percentage of metformin released at 1 h
- Y_2: the percentage of metformin released at 2 h
- Y_3: the percentage of metformin released at 4 h
- Y_4: the percentage of metformin released at 8 h

Above mentioned input and output variables were fed into STATISTICA 7 software using MLP with feed forward back propagation method. Several training sessions were conducted with different numbers of units (1—10) in the hidden layer in order to determine the optimal MLP structure.[41,42] For selecting the number of units in the hidden layer, we started with 1 hidden unit and we gradually increased the number of units. The learning period was completed at 5000 iterative training processes when minimum root mean square (RMS) was reached:

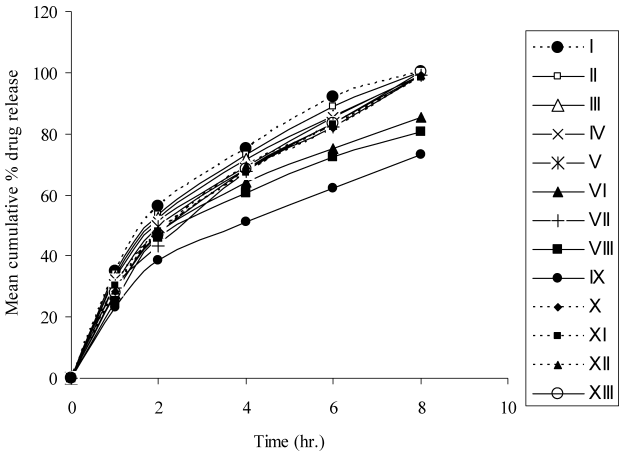

Fig. 2. Release Profiles of Metformin from Trial Formulations (I to XIII) Prepared as per the Experimental Design; the Mean of 6 Determinations

$$\mathrm{RMS}=\left[\sum (y_i^{\mathrm{p}}-y_i^{\mathrm{m}})^2/n\right]^{1/2} \quad (4)$$

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

Based on the above criteria the selected optimal MLP structure was with 3 layers (Fig. 1): the first layer with 2 input units and the second layer with 5 hidden units. A third layer had four output units. Training was completed when RSM reached 0.000097, which is an acceptable value. Further increase in hidden nodes produced high error, when the network was validated with another set of trial data. The developed ANN was cross-validated utilizing "leave-one out" method. Correlation plots were constructed for predicted *versus* observed values of drug release for all trial formulations. Predicted values of all release parameters based on the optimal ANN were coincided well with the experimental values as depicted in Fig. 3. The MLP model yielded a regression plot with squared coefficients (R^2) that were close to a value of 1.0 (for all formulations >0.99), which indicated that the optimal MLP model was reached.

Optimization Figure 4 (A to D) shows the three-dimensional diagrams of each response variable as a function of HPMC K15M and PVP K30 obtained from optimal ANN.

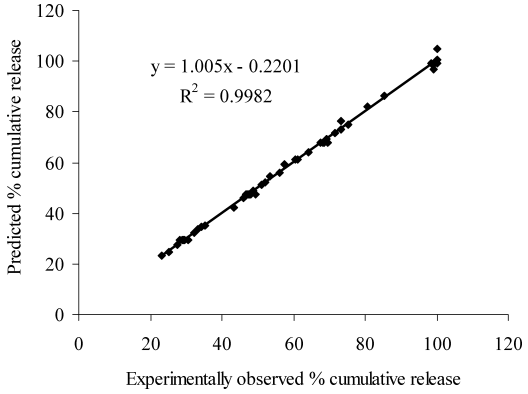

Fig. 3. Plot of Experimentally Observed % Cumulative Release *versus* ANN Predicted % Cumulative Release of Metformin from 13 Trial Formulations for 4 Output Variables (Y_1, Y_2, Y_3 and Y_4)

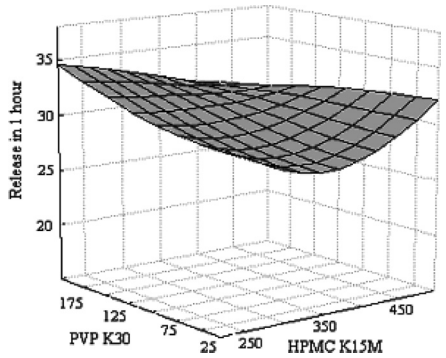

Fig. 4A. Response Surface Plot Showing the Influence of HPMC K15M and PVP K30 on Release at 1 h from the Optimal ANN

HPMC K15M=amount of hydroxypropyl methyl cellulose of K15M viscosity grade (in mg). PVP K30=amount of polyvinyl pyrrolidone of K30 viscosity grade (in mg).

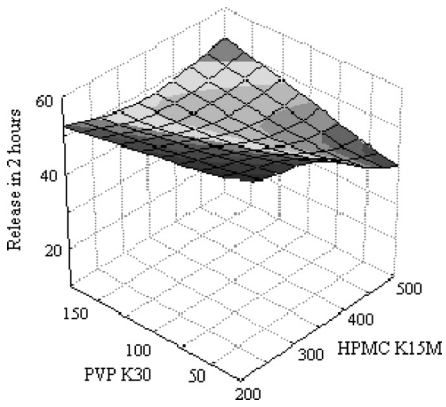

Fig. 4B. Response Surface Plot Showing the Influence of HPMC K15M and PVP K30 on Release at 2 h from the Optimal ANN

HPMC K15M=amount of hydroxypropyl methyl cellulose of K15M viscosity grade (in mg). PVP K30=amount of polyvinyl pyrrolidone of K30 viscosity grade (in mg).

An increase of HPMC K15M along with PVP K30 resulted in decrease in the percentage of metformin dissolved in 1 to 8 h. This suggests that amount of two input variables acts as the controlling agent in the release of metformin from matrix tablets.

After the ANN structure was determined, we examined the release parameters for 625 formulations provided by ANN (STATISTICA) to find the optimal formulation based on predetermined criteria of release profile (Y_1=27.5%, Y_2=47.5%,

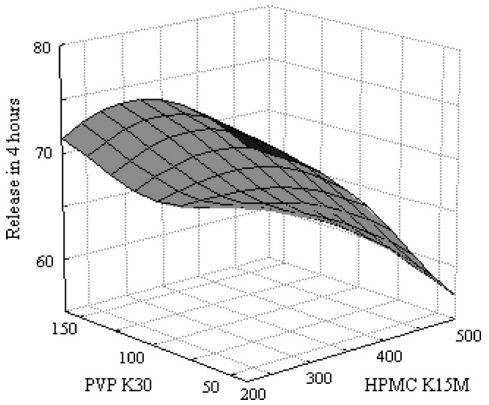

Fig. 4C. Response Surface Plot Showing the Influence of HPMC K15M and PVP K30 on Release at 4 h from the Optimal ANN

HPMC K15M=amount of hydroxypropyl methyl cellulose of K15M viscosity grade (in mg). PVP K30=amount of polyvinyl pyrrolidone of K30 viscosity grade (in mg).

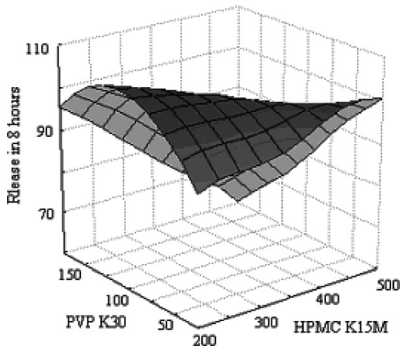

Fig. 4D. Response Surface Plot Showing the Influence of HPMC K15M and PVP K30 on Release at 8 h from the Optimal ANN

HPMC K15M=amount of hydroxypropyl methyl cellulose of K15M viscosity grade (in mg). PVP K30=amount of polyvinyl pyrrolidone of K30 viscosity grade (in mg).

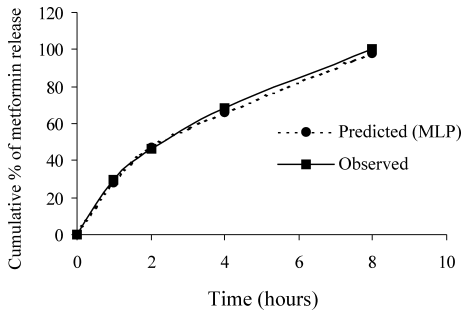

Fig. 5. Predicted and Experimentally Observed Metformin Release from Optimal Formulation

Y_3=67.5% and Y_4=97.5%). We selected optimal formulation according to distance function method defined in Eq. 3, where composition of HPMC K15M and PVP K30 were 336 mg and 130 mg respectively. The matrix tablet was prepared according to the optimal formulation, and their dissolution tests were performed.

Experimentally observed metformin release from this optimal formulation, and the metformin release predicted by MLP, is presented in Fig. 5. Release profiles predicted by the MLP coincided well with the experimentally observed values with f_1 and f_2 values as 2.19 and 89.79 respectively. The f_1 and f_2 values were within the limit of U.S. Food and Drug

Administration's guide for industry.[36)]

Conclusions

The satisfactory prediction of the drug release for test and optimal formulations by the MLP in this study has clearly shown the applicability of an MLP to modeling sustained release tablet formulation. Thus ANN application offers a new dimension of pharmaceutical systems study because of its unique advantages, such as nonlinear processing capacity and the ability to model poorly understood systems. It is very suitable for simulation and optimization and for the exact study of systems from all points of view, without performing additional experiments. A nonlinear relationship exists between the chosen formulation components and the amount of drug released as response in the formulation studied. Several combinations of the formulation components can be chosen to reach desired responses using this technique, which permits several possibilities of optimization.

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