Application of Design of Experiments and Multilayer Perceptrons Neural Network in the Optimization of Diclofenac Sodium Extended Release Tablets with Carbopol® 71G

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The purpose of the study was to screen the effects of formulation factors on the *in vitro* release profile of diclofenac sodium from matrix tablets using design of experiment (DOE). Formulations of diclofenac sodium tablets, with Carbopol® 71G as matrix substance, were optimized by artificial neural network. According to Central Composite Design, 10 formulations of diclofenac sodium matrix tablets were prepared. As network inputs, concentration of Carbopol® 71G and the Kollidon® K-25 were selected. *In vitro* dissolution time profiles at 5 different sampling times were chosen as responses. The independent variables and the release parameters were processed by multilayer perceptrons neural network (MLP). Results of drug release studies indicate that drug release rates vary between different formulations, with a range of 1 h to more than 8 h to complete dissolution. For two tested formulations there was no difference between experimental and MLP predicted *in vitro* profiles. The MLP model was optimized. The root mean square value for the trained network was 0.07%, which indicated that the optimal MLP model was reached. The optimal tablet formulation predicted by MLP was with 23% of Carbopol® 71G and 0.8% of Kollidon® K-25. Calculated difference factor (f_1 7.37) and similarity factor (f_2 70.79) indicate that there is no difference between predicted and experimentally observed drug release profiles for the optimal formulation. The satisfactory prediction of drug release for optimal formulation by the MLP in this study has shown the applicability of this optimization method in modeling extended release tablet formulation.

Key words matrix tablet; Carbopol 71G; extended release; diclofenac sodium; neural network

Application of and artificial neural network (ANN) have new approach in the study of pharmaceutical systems with significant advantages as modelling and optimization.[1,2] In this study the optimization method was applied on the development of diclofenac sodium extended release matrix tablets using multilayer perceptrons neural network (MLP) and Back Propagation algorithm. The matrix substance, Carbopol® 71G and binder Kollidon® K-25, were screened as the most important–independent variables responsible for the release of diclofenac sodium in 8 h using design of experiments (DOE). Extended release of diclofenac sodium in this study is accomplished using Carbopol® 71G which is a free-flowing granular form of Carbopol® 971P NF, as a matrix substance. Hydrophilic gel-forming matrix tablets are widely used as oral extended-release dosage forms.[3—5] The overall rate of drug release is regulated by the viscosity and thickness of the gel layer formed from the matrix tablets.[6—8] The aim of this study was obtaining the 8 h extended drug release profile of diclofenac sodium from Carbopol® 71G matrices. "Optimal" or "target" drug release profile specified in the beginning of this study was following: 0.5 h $<$10%, 1 h: $<$20%, 2 h: 30—40%, 4 h: 50—80%, 8 h: $>$80% of diclofenac sodium that have to be released from tablets.

Screening Study

The purpose of this study in the beginning was to investigate effect of formulation variables on drug release from matrix tablets which contained Carbopol® 71G as matrix substance. The tablet formulations were made by non-aqueous granulation method according to 2^{5-1} fractional factorial design (FFD) where five formulation variable factors were varied on two levels. Real and coded values of independent variables are presented in Table 1.

The dependent variables were: Y_1, percentage of diclofenac sodium release after 30 min and Y_2, percentage of diclofenac sodium release after 4 h.

Applying FFD 2^{5-1}, five independent variables were varied on two levels; there were eight formulations with different combinations of these variables. The experimental design with corresponding formulations is shown in Table 2.

Results of drug release studies (Fig. 1, Table 2) from formulations obtained according to FFD 2^{5-1} were fitted into the linear model, and following models were calculated:

$$Y_1 = 15.74 - 0.16X_1 - 2.46X_2 - 2.01X_3 - 11.57X_4 + 1.53X_5 \quad (1)$$

$$Y_2 = 82.48 - 6.89X_1 - 6.90X_2 - 8.25X_3 - 17.7X_4 - 11.31X_5 \quad (2)$$

The obtained results showed that the concentration of polymer was the most significant drug release factor: the higher the concentration of Carbopol (X_4), the greater the decrease of the released drug. The amount of drug released varied with different % v/v of the polymer. This phenomenon can be attributed to the formation of the gel layer on the

Table 1. Real and Coded Values of Evaluated Factors

Factors	Levels	
	−1	+1
X_1 (%) solvent concentration, anhydrous ethanol	20	40
X_2 (%) binder concentration, Kollidon® K-25	1	2.5
X_3 (N) tablet hardness	80	160
X_4 (%) polymer concentration, Carbopol® 71G	10	30
X_5 (mg) tablet weight	90	150

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tablet surface. As the concentration of polymer increases the gel layer becomes so thick and compact that the drug cannot diffuse through it. That's the reason for rapid decrease in the amount of released drug as the concentration of the polymer increases. *In vitro* release of drug now is mainly controlled by diffusion out the gel layer and is depending on gel thickness and viscosity. Factors (X_1) and (X_2) had less influence on the drug release from the tablet, while factors (X_3) and (X_5) had no significant influence in this study.

The results represent the screening study that demonstrates the significance of the polymer (X_4) and binder concentrations (X_2) as drug release factors. Their influence was further examined applying central composite design (CCD) and artificial neural network (ANN). Experimental matrix for CCD is presented in Table 3.

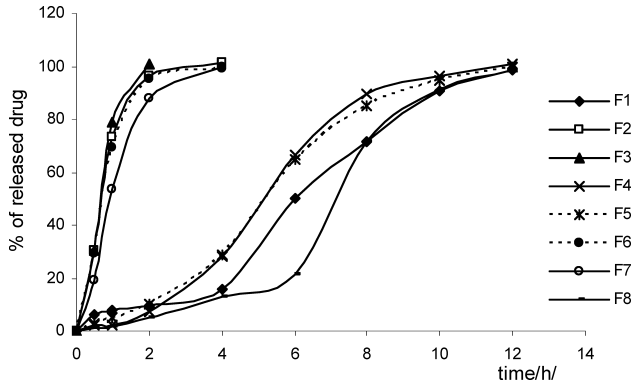

Fig. 1. Effect of Different Factors on the Release of Diclofenac Sodium from Formulations (F1—F8) According to FFD 2^{5-1}

Application of MLP, Structure, Training and Testing

According to the two factor spherical Central Composite Design (CCD), 10 formulations of diclofenac sodium tablet formulations were selected and used as inputs for network training (Table 3). Different levels of independent variables induced variation in release profiles of diclofenac sodium from F11—F20 formulations. Results of drug release studies indicated that drug release rates varied between different formulations, with a range of 1 h to more than 8 h to complete dissolution (Fig. 2).

Different percentage of screened factors X_1, % Carbopol® 71G (5.86—34.14%) and binder X_2, % Kollidon® K-25 (0.69—2.81%) were the input layer in the MLP. In the hidden layer there were three units. Outputs (responses) represent percentage of released diclofenac sodium after 0.5, 1, 2, 4 and 8 h. Selected MLP was trained through 1000 epochs with results from formulations F11—F20 according to central composite design. The learning period was completed when minimum root mean square (RMS) was reached 0.07%, which is an acceptable value. When process of learning was over, MLP was tested with a set of test data.[9] Test formulations, Test 1 and Test 2, were prepared for validating the ability for prediction of MLP: Test 1, 9% of Carbopol® 71G and 2% of binder and Test 2, 32% of Carbopol® 71G and 1.5% of binder. Test formulations were prepared and examined in the same conditions as formulations F11—F20. Selected values for percentage of Carbopol® 71G and binder were within of range of design of experiment and they were random, different from 10 formulation data set. RMS reached after the testing was 0.125%, which is an acceptable value. In order to select the optimum MLP model, correlation plots were constructed of the experimentally obtained responses and those

Table 2. Model Formulations (F1—F8) and Responses for 2^{5-1} FFD

Formulation	Independent variables (coded values)					Responses	
	X_1	X_2	X_3	X_4	X_5	Y_1 (0.5 h)	Y_2 (4 h)
F1	−1	−1	−1	+1	+1	7.96	71.66
F2	+1	−1	−1	−1	−1	30.15	101.17
F3	−1	+1	−1	−1	+1	30.90	100.93
F4	+1	+1	−1	+1	−1	1.98	89.34
F5	−1	−1	+1	+1	−1	5.62	85.35
F6	+1	−1	+1	−1	+1	29.06	99.32
F7	−1	+1	+1	−1	−1	19.11	99.52
F8	+1	+1	+1	+1	+1	1.14	12.95

Table 3. Model Formulations (F11—F20), Real and Coded Values of Independent Variables in CCD

Formulation	X_1	Carbopol® 71G (%)	X_2	Binder (%)	Responses				
					Y_1 (0.5 h)	Y_2 (1 h)	Y_3 (2 h)	Y_4 (4 h)	Y_5 (8 h)
F11	−1	10	−1	1	35.4	71.6	95.46	104.89	—
F12	+1	30	−1	1	21.03	58.58	90.43	103.27	—
F13	−1	10	+1	2.5	4.56	4.58	9.85	42.78	86.62
F14	+1	30	+1	2.5	4.62	5.68	11.23	45.65	97.01
F15	$-2^{1/2}$	5.86	0	1.75	16.58	36.2	74.23	96.47	—
F16	$+2^{1/2}$	34.14	0	1.75	8.28	25.1	63.02	98.68	—
F17	0	20	$-2^{1/2}$	0.69	38.8	78.59	98.22	103.83	—
F18	0	20	$+2^{1/2}$	2.81	5.12	6.18	11.98	58.28	95.92
F19	0	20	0	1.75	11.18	34.31	74.42	100.2	—
F20	0	20	0	1.75	10.85	31.92	71.7	98.49	—

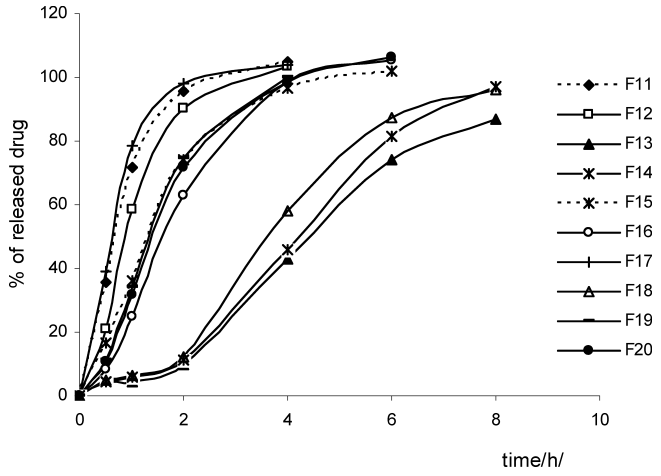

Fig. 2. Release Profiles of Diclofenac Sodium from Model Formulations (F11—F20) According to CCD

Table 4. Responses from Optimal Formulation Obtained from Experiments and Predicted by MLP

Responses (outputs)	Experimental results	Predicted results (MLP)
Y_1	9.44	8.95
Y_2	16.31	18.16
Y_3	36.26	45.29
Y_4	59.65	80.11
Y_5	102.64	95.89

predicted by MLP for test formulation Test 1 and Test 2. Square coefficient r^2 was for Test 1: $r^2=0.9999$ and for Test 2: $r^2=0.9923$, (both >0.98) showing that the MLP was properly trained and validated to generalize the problem. Correlation plots of predicted and obtained values of drug release for test formulations showed that the MLP model had a regression plot with square coefficient r^2 that was close to the value of 1.0 which indicated that optimum MLP model was reached.

Optimization Optimization was the final step in the application of MLP and it considers calculation of the optimal network input, percentage of polymer and binder which enables optimal diclofenac sodium release specified at beginning of this study. Learned MLP was used for modeling, simulation and optimization of the model extended release formulation by testing experimental results in experimental fields, searching for the optimal solutions. Contour plots were constructed to present separated contours and areas, which satisfies demands regarding the diclofenac sodium release after 0.5, 1, 2, 4 and 8 h. Folding over, these contours give area of combinations of independent variables. This area is limited with three contours and every combination of polymer percentage and binder percentage in this area should satisfy all demands regarding the diclofenac sodium release in phosphate buffer.

Optimal solution estimated with MLP, formulation with 23% Carbopol 71G and 0.8% binder Kollidon K-25 was examined and obtained results for diclofenac sodium release were satisfactory and similar to the responses predicted by MLP which Table 4 shows.

For diclofenac sodium release profile comparison of predicted and obtained formulation f_1 (difference factor) and f_2 (similarity factor) were calculated. Obtained values $f_1=7.37$ and $f_2=70.79$ showed that compared formulations were similar and that MLP-Back Propagation algorithm was a satisfactory method for optimization.

Conclusion

Based on the results presented in this study, extended release diclofeanc sodium matrix tablets were optimized using Carbopol 71G as matrix substance and Kolidon K-25 as a binder. The satisfactory prediction of drug release for optimal formulation by the DoE and MLP neural network in this study has shown the applicability of this optimization method in modeling extended release tablet formulation. Information and knowledge gained from this development study provide scientific understanding to support the establishment of the design space.

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