The application of "artificial neural network" in dosage form development of bi-layer floating tablets of baclofen

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ABSTRACT

The aim of the present investigation was to prepare & evaluate bilayer floating tablet of Baclofen. In which one layer was made up of immediate release layer to provide loading dose, while another layer was made up of floating layer of BCF to provide maintenance dose. The focus of present work was to prepare and evaluate bilayer floating tablet of Baclofen to increase residence time in stomach and there by gives prolog action. Tablets were prepared by wet granulation technique. Drug-excipients compatibility study was done by using Fourier transform infrared spectroscopy (FTIR). Optimization was carried out using artificial neural network (ANN) and multiple regression analysis using 3^2 factorial designs. Cumulative percentage release (CPR) at 24 hr, time required for 50% of drug release ($T_{50\%}$), floating lag time study of the tablet formulations were selected as dependent variables. The Content of HPMC K 4M (X_1) and Content of PEO WSR N 10 (X_2) were selected as independent variables. Tablets were evaluated for swelling index, *in vitro* buoyancy and *in vitro* drug release. The similarity factor (f_2) was used as a base to compare dissolution profiles. Optimized batch was subjected for kinetic modeling. Different process parameters of optimized batch were also studied. From FTIR spectra it was observed that there were no any interaction between drug and excipients used. The results demonstrate that 3.5% of crosspovidone released 99% of drug in 20 minutes. It was found that HPMC K 4M with concentration 30% and PEO WSR N 10 with concentration 20% showed good sustained as well floating ability and its releases 99.39% of drug within 24 hrs. Drug release was best explained by Higuchi plot. It was seen that the process parameters have great influence on performance of bilayer floating tablet. To check the accuracy of these predictions, experimentally three formulations were prepared by random selection of causal factors as per counter plot and also validated ANN. The experimental data were compared with predicted data by paired t test, no statistically significant difference was observed. ANN showed less error compared with multiple regression analysis. These findings demonstrate that ANN provides more accurate prediction and was quite useful in the optimization of pharmaceutical formulations than the multiple regression analysis method.

Key words: Bilayer floating tablet, Baclofen, HPMC K 4M, PEO WSR N 10, artificial neural network (ANN)

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INTRODUCTION

The high cost involved in the development of a new drug molecule has diverted the pharmaceutical industry to investigate various strategies in the development of new drug delivery systems. However, the real issue in the development of oral controlled release dosage forms is to prolong the residence time of dosage forms in the stomach or upper gastrointestinal (GI) tract until the drug is completely released (1). Several approaches are currently used to retain the dosage form in stomach. These include bioadhesive systems, swelling and expanding systems, floating systems and other delayed gastric emptying devise (2). The principle of buoyant preparation offers a simple and practical approach to achieve increased residence time for the dosage form in stomach and sustained drug release.

BCF is a specific agonist at GABA-B receptors. It is mainly used as skeletal muscle relaxant. It is used in the treatment of spasticity, especially that due to spinal cord damage & multiple sclerosis. Its PK_a is 3.87; therefore it remains unionized in stomach and maximum absorption take place from stomach only (3). The recommended adult dose of BCF is 10-20 mg 3 times a day. It causes fluctuation in plasma concentration and producing peaks and troughs (4). Peaks associated with side effects like drowsiness, muscle weakness & dizziness. Due to troughs there is inadequate control of muscle spasm (5). In context of the above principles, a strong need was recognized for the development of a dosage form to deliver BCF in the stomach and to increase the efficiency of the drug, providing sustained action. Thus by preparing once in day BCF bi-layer floating tablet, we can achieve better patient compliance through less frequent administration and lowers the cost of total therapy.

The objective of this study was to prepare and evaluate bi-layered tablet of BCF which give quick (via fast disintegration) and sustained effect (via high viscosity floating polymer) for 24hrs. Polyethylene oxide (PEO) and Hydroxylpropyl methylcellulose (HPMC K 4M) are various hydrophilic polymers that, in presence of water, control the release of the active moiety either by swelling or by swelling/erosion by forming a hydrogel. In the present study sodium bicarbonate was used as a gas generating agent. Di-calcium phosphate (DCP) was used as diluents.

MATERIALS AND METHODS

Materials

BCF was supplied by Sun pharmaceuticals (baroda, India). HPMC K 4M and HPMC K 100M were received from Colorcon Asia Pvt. Limited (Goa, India). PEO WSR N 10 and PEO WSR 303 were obtained as gifts from Ranbaxy Research Laboratories (Gurgaon, India). Other ingredients used were of analytical grade.

Methods

Preformulation study

In preformulation study solubility and melting point study was done. Flow properties of drug were also determined by using their respective equations (6).

Drug- excipient compatibility study

The pure drug, BCF and a mixture of it with the polymer HPMC K 4M and PEO WSR N 10 powder was mixed separately with IR grade KBr and corresponding pellets were prepared (4). The pellets were scanned over a wave number range of 400 to 4000 cm^{-1} in Fourier Transform Infrared Spectroscopy 8400S model instrument.

Preparation of immediate release (IR) layer

Different IR tablets formulations (Table 1) were prepared by wet granulation technique. Required quantity of drug and various super disintegrating agents like

cross providone, sodium starch glycolate, and croscarmellose sodium were mixed thoroughly. Granules were prepared by using solution of PVP K 30 in Iso-propyl alcohol (IPA). Prepared granules were dried at room temperature and passed through 20 mesh sieve. Talc and magnesium stearate were finally added as glidant and lubricant respectively. The blend was compressed (7.5 mm diameter, flat punches) using Remiek mini press tablet machine. Batches A1 to A9 were prepared by taking 2, 4 and 6% of SSG and 2, 3, 5% of Crs-pvp and Crs-carmellose sodium (8).

Evaluation of powder blend & physical parameters of tablets

Prepared powder blend was evaluated for different parameters like loose bulk density, tapped bulk density, compressibility index, and Hausner's ratio. Tablets were evaluated for various physical parameters of tablets like tablet disintegration time, weight variation test, friability, and hardness (9-13).

Preparation of sustained release (SR) layer

The procedure is same as described for the IR layer tablet. Here for preliminary study different grades of HPMC and PEO were used as polymers as shown in Table 1.

Optimization of tablet formulation using 3^2 full factorial designs and ANN

A 3^2 randomized full factorial design was utilized in the present study. In this design two factors were evaluated, each at three levels, and experimental trials were carried out at all nine possible combinations. The coded value of independent factor and design layout was shown in Table 5. The factors were selected based on preliminary study. The Content of HPMC K 4M (X_1) and Content of PEO WSR N 10 (X_2) were selected as independent variables. The selected dependent variables are Y_1 = Cumulative percentage release (CPR) at 24 hr (Q_{24}), Y_2 = Time required for 50% of drug release ($T_{50\%}$) and Y_3 = Floating lag time study (FLT).

A commercial Microsoft Window's based ANN software package, Matlab version7.0 was used throughout the study (14). Schematic representation of ANN was explained in figure 1. Briefly, the general structure of the ANN has one input layers which contains two neuron X1 and X2, one hidden layer which contains 6 hidden neuron and one output layer contain three dependent variables Y1,Y2,Y3. Too few nodes can lead to under fitting. Too many nodes can lead the system toward memorizing the patterns in the data. According to Kolmogorov's theorem, it was understood that twice the number of input nodes plus one is sufficient to compute any arbitrary continuous function. As explained in figure 4, we started off with Kolmogorov's number of hidden nodes and increased the number until a network with the least mean-squared error was attained The strength of connections between two units is referred to as weights. A multi-layer feed forward back-propagation network that was created by generalizing the Levelberg-Marquardt's learning rule was used to predict Y1, Y2, and Y3 (15).

Validation of ANN with check point batch

To check the accuracy of these predictions, we prepared experimentally three formulations as per Table 6 by random selection of causal factors as per counter plot shown in figure 3. Experimental results were compared with the predicted results by paired t-test.

Normalized Error Determination

The quantitative relationship established by both techniques (ANN and multiple regression analysis) was confirmed by comparing the results obtained for three dependent variables using Normalized Error (NE). The equation of NE is expressed as follows:

$$NE = [\Sigma \{(Pr - Er)/Er\} 2]1/2 \quad (1)$$

where Pr and Er represent predicted and experimental response, respectively.

***In-vitro* dissolution profile**

The release rate BCF from sustained release tablets was determined using dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl ($_P$H=1.2), at 37 ± 0.5°C and 50 rpm. A sample was withdrawn from the dissolution apparatus at an interval of every hrs for initially three hours and then every two or three hours till 24 hrs. The samples were replaced with fresh dissolution medium of same quantity. The samples were filtered. Absorbance of these solutions was measured at 220 nm using a Shimadzu UV-1700 UV/Vis double beam spectrophotometer.

Comparison of dissolution profiles

The similarity factor (f_2) given by SUPAC guidelines for modified release dosage form was used as a basis to compare dissolution profile. The dissolution profiles are considered to be similar when f_2 is between 50 and 100 (16). This similarity factor is calculated by following formula,

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{t=1}^{n} (R_t - T_t)^2 \right]^{-0.5} \times 100 \right\} \quad (2)$$

where, n is the number of dissolution time and R_j and T_j are the reference and test dissolution values at time *t*.

***In vitro* buoyancy studies**

The *in vitro* buoyancy was determined by floating lag time method (17). The tablets were placed in 100 ml beaker containing 0.1 N HCl (pH=1.2). The time required for the tablets to rise to the surface and float was determined as floating lag time.

Swelling index

The swelling index of tablets was determined in 0.1 N HCl (pH 1.2) at room temperature. The swelling index was calculated by the following equation. Determinations were made in triplicate.

$$Swelling\ index = \frac{W_t - W_0}{W_t} \quad (3)$$

Where, W_0 is the initial weight of tablet, and W_t is the total weight of the tablet at time *t* (18, 19).

Kinetic modeling and mechanism of drug release

The dissolution profile of all the batches was fitted to Zero order, First order, and Higuchi and Krosmeyer Peppas model to ascertain the kinetic modeling of the drug release (20, 21).

Preparation of Bi-layer gastro retentive tablet of BCF

First, immediate release formulation placed on cavity of die and 10 kg/cm^2 pressure was applied for 30 second then finally sustained release layer were placed, and 20 kg/cm^2 pressures were applied in Hydraulic Pellet Press.

Process Optimization of bi-layer gastro retentive table of BCF

The effect of process parameters on release behavior of BCF sustained release tablets, effect of mixing time and effect of compression force were studied.

Accelerated stability study of the optimized batch

Bi-layer gastro retentive tablets of BCF formulated in the present study were subjected to accelerated stability studies in Aluminum / Aluminum pouch pack as aluminum strip is considered the best protecting packaging material but in the present study simulation was made using aluminum foil pouch. As the dosage form is formulated for site-specific drug delivery to stomach, no change should occur in its floating lag time and drug dissolution profile. Dose dumping and failure of buoyancy are probable effects anticipated during the stability study of such dosage forms. The tablets of best batch were packed in aluminum pouch and charged for accelerated stability studies at 40 °C and 75% RH for 3 months in a humidity jar.

RESULT AND DISCUSSION

Preformulation study

From preformulation study, it was observed that BCF was slightly soluble in water (4.5 mg/ml) and soluble in 0.1NHCl (20 mg/ml) so 0.1NHCl was selected as dissolution medium for further study. Hausner's ratio of BCF was found to be 1.33. Carr's index (%) and angle of repose (θ) was found 25.32 and 43.36, respectively. From the results of preformulation studies of the API, It was concluded that BCF has poor flow and compressibility properties. So, to improve the flow property, it was decided to go for wet granulation technique for preparation of bilayer tablet. Drug excipient interaction study using FTIR 8400S model instrument presented in figure 2 showed that there were no changes in the main peaks in IR spectra of mixture of drug and polymers, which indicate absence of any physical interactions between drug and polymers.

Optimization of immediate release formulation

Immediate release formulations were prepared as per the composition given in Table 1. Prepared tablets were evaluated for *in-vitro* dissolution profile. Physical properties of tablets of IR layer containing BCF was explained in table 3. In case of batch A11, release of drug was 99.9% within 20 minutes (3.5% of crospovidone); while in batch A14 release of drug was 96.15% in 20 minutes (2.5% of croscarmellose). Due to the fast release of drug within stipulated period of time (28±2.15 sec.) and good hardness property batch A11 was selected as best batch.

***In vitro* drug release profile of preliminary trials of SR layer**

In preliminary study, different batches were prepared by taking different grades of HPMC and PEO. From *in vitro* drug release profile study of batches S1 to S7, it was found that Batch S1 gives desirable sustained effect for 23.5 hrs having 97% releases. Moreover, hardness of tablet was found 4.5 kg/cm^2.

Batch S1, containing 25% of HPMC K 4M and 20% of PEO WSR N 10 shows

good floating time that is more than 24 hrs and floating lag time was 1.5 minutes. It also shows good similarity with the theoretical release profile, i.e. 57.41. Therefore these combinations of polymers were selected for further study.

Optimization using 3^2 full factorial designs and ANN

Composition of full factorial designs was shown in table 4. On the basis of the preliminary trials, 3^2 full factorial designs was employed to study the effect of independent variables, i.e. content of HPMC K 4M (X_1) and content of PEO WSR N 10 (X_2) on dependent variables like %drug release at 24 hr. $Q_{24,}$ T_{50} & floating lag time. The results clearly indicate that all the dependent variables are strongly dependent on the selected independent variables as they show a wide variation among the nine batches (F_1 to F_9). The fitted equations (full models) relating the responses (i.e. $Q_{24,}$ T_{50} & FLT) to the transformed factor were shown in tables 5. A multilayer feed-forward back-propagation network using Levelberg-Marquardt's learning rule was used to predict Cumulative percentage release (CPR) at 24 hr, Time required for 50% of drug release ($T_{50\%}$), floating lag time study of the tablet formulations. Two causal factors corresponding to different content of HPMC K 4M (X1) and different content of PEO WSR N 10 (X2) were used as each unit of input layer. The output layer was composed of three response variable Y1, Y2, Y3. In an ANN, the nerve cells are replaced by computational units called neurons and the strengths of the interconnections are represented by weights. This unique arrangement can therefore attempt to simulate some of the neurological processing ability of the biological brain such as learning and drawing conclusions from experience.

ANN was trained using preexisting data. At the beginning of the training process, the connections between the neurons are set to random weight values. During the training process, the input and output data from the training data subset were fed into the network. The difference between the actual output and the training output values was then calculated. The difference was an error value, which is decreased using a training algorithm during the training process by modifying the values of the weights at each neuron. These modifications bring the output of the network closer to the desired output. Once trained, the network can hopefully be used to predict accurate output values for new input data.

A set of release parameters and causal factors were fed into a computer. Several iterations were conducted with different numbers of nodes of hidden layer and training times in order to determine the optimal ANN structure. If a hidden layer has too few neurons, the network will lack the power it needs to classify patterns in the data. If a hidden layer has too many neurons, existing patterns will merely be memorized and the network will be unable to generalize. Therefore, the number of neurons to be incorporated into the hidden layer is a key decision. For selecting the number of hidden nodes, we started with 3 hidden nodes and gradually increased the number of nodes until a network of least mean squared error was attained. Increase in the number of nodes led to decrease in least mean squared error. Finally, with 6 hidden nodes, we could achieve the least mean squared error and excellent prediction of the response variable. Graphical representation of above data was explained in figure 4. Further increase in hidden nodes produced high error.

It was found that 6 units in the hidden layer and 500 iterative training processes were needed to obtain an excellent prediction of the response variables. The error limit observed with the optimal ANN structure was 0.00001, while the optimal learning rate was 0.02.

Thus, ANN has many advantages over conventional statistical techniques. They give good results when the response variable is highly nonlinear. In addition, historic or literature data can be used for training. Other advantages are that ANN can make use of incomplete data and that no a priori knowledge of the underlying statistical nature of the problem is required.

Validation of ANN with check point batch

The relationship between formulation variables (X_1 and X_2) and $Q_{24,}$ T_{50} and floating lag time was elucidated using contour plot. From that three batches were selected randomly. As shown in table 6 the Student *t* test was carried out between the predicted results from the ANN and the experimental results obtained from counter plot. It showed no statistically significant difference between them.

Comparison of ANN and multiple regression analysis

The NE between the predicted and experimental response variables was employed as an evaluation standard. The NE value observed with the optimal ANN structure was 0.000339, 0.000222, and 0.000274 for $Q_{24,}$ T_{50} & FLT respectively. While NE value observed with multiple regression analysis was 0.000389, 0.000304, 0.000296 for $Q_{24,}$ T_{50} & FLT respectively. The comparison of NE was given in table 6. From results it was said that the normalized error obtained from ANN was less, compared with the multiple regression analysis, and showed the higher accuracy in prediction. ANN can easily handle more input variables and was extremely helpful when the number of experiments is greater, but in the case of factorial design, a large number of input variables lead to a polynomial with many coefficients, which involves tedious computation. Another major advantage with ANN is the flexibility to work with the theoretical data for better prediction, but multiple regressions do not accommodate theoretical or historical data.

***In-vitro* dissolutions profile of factorial batches**

The statistical analysis of the factorial design batches were performed by multiple linear regression analysis carried out in Microsoft Excel 2007. The Q_{24}, t_{50}, and FLT (sec.), values for the 9 batches (F1 to F9) showed in Table 4. The data clearly indicated that the values of Q_{24}, t_{50}, and FLT (sec.), were strongly dependent on the independent variables.

In vitro drug release profile of all batches of factorial design was compared with theoretical drug release profile. Which indicates that the all the batches shows good similarity to theoretical release profile. But batch F8 showed the highest *f2* among all the batches that is 77.10.

Swelling index study

Tablets composed of polymeric matrices build a gel layer around the tablet core when they come in contact with water. This gel layer governs the drug release. Kinetics of swelling is important because the gel barrier is formed with water penetration. Swelling is also vital factor to ensure floating. To obtain floating, the balance between swelling and water acceptance must be restored (22). The swelling index of the best batch (F8) at different time intervals was explained in figure 5. which may be because of high viscosity and high water retention property of HPMC polymer.

Kinetic modeling and mechanism of drug release

Kinetic data obtained for batch F8 was fitted to different models. The release profile of the best batch (F8), which showed highest similarity factor f_2, was fitted to Higuchi plot (F= 0.0019). Priority should be given to the model with the least F-value. Thus, it was observed that the drug release from sustained release tablet of BCF was best explained by Higuchi plot. Diffusion controlled drug release was observed.

Optimization of Bi-layer gastro retentive tablet of BCF

Bilayer tablets were prepared as per the composition given in table 2. To study the effect of process parameters on release behavior of BCF sustained release tablets, following parameters were selected for study.

- ***Effect of mixing time***

To know the effect of mixing time taken for the granulation, three trials were taken with the mixing time of 5, 10 and 20 min. in the Octagonal Blender. Comparison of Physical parameters having different mixing time was given in table 7. It was seen that the higher amount of shear i.e. mixing time has a retarding effect on dissolution of drug. There is significant retarding effect was observed in case of 15.0 min. In case of 5 min mixing time, release become very fast whereas, in case of 10 min mixing time, release of drug follows with therapeutic release profile. f_2 value found was 78.52, so 10 min mixing time was kept optimum.

- ***Effect of compression force***

To know the effect of compression force, four trials were taken. First immediate release formulation placed on cavity of die and 10 kg/cm^2 pressure was applied for 30 second then finally sustained release layer (gastro retentive layer) were placed, and different pressure like 20kg/cm^2, 30kg/cm^2, 40kg/cm^2, 50kg/cm^2 were applied in Hydraulic Pellet Press. The physical parameters of the tablets observed were given in table 7. It was seen that as compression force increases, hardness of tablet also increase. And thus friability of tablet decreases, drug release rate was also retarded. So when 20 kg/cm^2 pressure is applied tablet became too soft and drug release rate was too fast. So, CF2 and CF3 batches having almost similar f_2 values were selected as optimum. So, it was concluded that applied compression force should between 30-40 Kg/cm^2.

Accelerated stability study of the optimized batch

The similarity factor was calculated for comparison of dissolution profile before and after stability studies. The *f2* value was found more than 50 (~ 74.87) that indicate a good similarity between both the dissolution profiles. Similarly, no significant difference was observed in the floating lag time after stability studies. Hence, the results of stability studies reveal that the developed formulation has good stability.

CONCLUSION

In preparation of bilayer tablet, it was concluded that 3.5% concentration of crospovidone gives desirable release within 20 minutes due to very fast disintegration of tablet Different formulation of HPMC polymer and PEO WSR N 10 was studied with help of 3^2 factorial designs by using ANN approach. Increase in the number of nodes led to decrease in least mean squared error. Finally, with 6 hidden nodes, the least mean squared error was achieved. Software validation was also done using counter plots. There was no significant difference found between experimental and predicted results. It was concluded 30% of HPMC K 4M, and 20% of PEO WSR N 10

was best combination to prepare SR layer. Drug release was best explained by Higuchi plot. Thus diffusion controlled drug release was observed. Different process parameters were also studied and it was seen that they have great influence on performance of bilayer floating tablet. Mixing time optimized was 10 minutes. Granules passed from 20# Shows better physical properties of tablet than passed from 40# and 60#**.** Drying time & temperature has not much influence on drug release profiles. Optimized compression force was 30-40 kg/cm^2. The f_2 value of optimized batch was found to be 81.48. Bi-layer tablet releases loading dose within 30 minutes and maintenance dose release till 24hrs with good floating ability. Thus it was concluded that Bi-layer floating tablet of baclofen can be successfully formulated with HPMC K 4M and PEO WSR N 10 as polymers for SR layer and super disintegrating agent crospovidone.

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Table 1: Composition of immediate release layer formulation

Ingredients	Immediate release layer formulation									Sustained release layer formulation					
	F1	F2	F3	F4	F5	F6	F7	F8	F9	A10	A11	A12	A13	A14	A15
BCF	36	36	36	36	36	36	36	36	36	7	7	7	7	7	7
HPMC K 4M	40	40	40	50	50	50	60	60	60	--	--	--	--	--	--
PEO WSR N10	30	40	50	30	40	50	30	40	50	--	--	--	--	--	--
Crospovidone	--	--	--	--	--	--	--	--	--	3	3.5	4	--	--	--
Croscarmellose	--	--	--	--	--	--	--	--	--	--	--	--	2	2.5	3
PVP K-30	14	14	14	14	14	14	14	14	14	7	7	7	7	7	7
IPA	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
$NaHCO_3$	20	20	20	20	20	20	20	20	20	--	--	--	--	--	--
DCP	54	44	34	44	34	24	34	24	14	80	79.5	79	81	80.5	80
Mg Stearate	2	2	2	2	2	2	2	2	2	1	1	1	1	1	1
Talc	4	4	4	4	4	4	4	4	4	2	2	2	2	2	2
Total weight	200	200	200	200	200	200	200	200	200	100	100	100	100	100	100

* All the ingredients in mg.

Table 2: Composition of bi-layer gastro retentive tablet

Ingredients	IR formulation Batch (A11)	SR formulation Batch (F8)	Bi-layer floating tablet
Drug	7	36	43
Crospovidone	3.5	-	3.5
HPMC K 4M	-	60	60
PEO WSR N 10	-	40	40
$NaHCO_3$	-	20	20
PVPK-30	7	14	21
IPA	q.s.	q.s.	q.s.
DCP	79.5	24	103.5
Mg-sterate	1	2	3
Talc	2	4	6
Total Weight	100	200	300

* All the ingredients in mg.

Table 3: Physical Properties of tablets of IR layer containing BCF (n=3)

Formulation code	Disintegration Time (sec)	Hardness (kg/cm^2) (n=5)	Weight variation (mg) (n=20)	% Friability (n=10)	Q_{20}*
A10	42.6±2.52	3.4±0.06	99 ± 0.254	0.75±0.02	94.3 ±1.15
A11	28±2.15	4±0.28	100 ± 0.005	0.69±0.02	99.9±2.23
A12	25.3±2.08	3.6±0.28	98 ± 0.252	0.78±0.01	97.5 ±3.01
A13	45.3±2.52	3.6±0.15	99 ± 0.268	0.72±0.01	96.6 ±3.42
A14	37.6±1.53	3.9±0.1	102 ± 0.152	0.77±0.02	96.2±2.95
A15	35.3±3.51	3.6±0.15	100 ± 0.264	0.77±0.03	95.8 ±3.11

* Q_{20}: Cumulative % release of drug within 20 minutes

Table 4: Effect of independent variable on dependent variable by 3^2 full factorial design for BCF

Formulation code	Independent variable		Dependent variables		
	X_1	X_2	Q_{24}	$t_{50\%}$	FLT (sec.)
F1	-1	-1	104.36	8.96	50
F2	-1	0	103.75	9.19	55
F3	-1	+1	96.95	9.73	62
F4	0	-1	96.18	10.65	72
F5	0	0	95.85	10.87	85
F6	0	+1	93.17	11.14	89
F7	+1	-1	92.98	11.68	90
F8	+1	0	99.39	12.41	92
F9	+1	+1	91.96	12.6	95

Coded value	Content of HPMC K 4M(mg) X_1	Content of PEO WSR N 10(mg) X_2
-1	40	30
0	50	40
1	60	50

Table 5: Test data set for validating ANN for the determination of Q_{24}, T_{50} & FLT

X1	X2	Q_{24}		T_{50}		FLT	
		Experimental	Predicted (ANN)	Experimental	Predicted (ANN)	Experimental	Predicted (ANN)
55	**45**	95.29	95.28	12.09	12.08	92	92.36
60	**35**	95.47	95.48	12	12.03	90	91.73
50	**35**	95.90	95.88	11.10	11.09	80	79.30

Parameters	Calculated	Tabulated
Q_{24}	0.001875	2.776445105
T50	-0.1269	2.776445105
FLT	0.0026	2.776445105

$$t_{calculated} \leq t_{tabulated}\ \mu 1 = \mu 0$$

Here, both mean are equal. So, hypothesis is accepted.

Table 6: Comparison of two methods in terms of normalized error and regression analysis

Serial Number	Q_{24}		$T_{50\%}$		Floating Lag Time	
	Multiple regression analysis	**ANN**	**Multiple regression analysis**	**ANN**	**Multiple regression analysis**	**ANN**
1.	103.947	104.36	8.9575	8.85	47.91667	50.0025
2.	104.173	103.74	9.313333	9.41	56.33333	54.99
3.	96.9391	96.96	9.609167	9.83	62.75	61.99
4.	95.73	96.18	10.51333	10.28	76	72.02
5.	97.5533	95.86	10.90667	10.80	82.66667	84.99
6.	91.9166	93.16	11.24	11.35	87.33333	88.99
7.	93.8425	92.98	11.81917	11.68	88.08333	90
8.	97.2633	99.39	12.25	12.34	47.91667	50.0025
9.	93.2241	91.96	12.62083	12.59	56.33333	54.99
Normalized error	0.000389	0.000339	0.000304	0.000222	0.000296	0.000274
Correlation coefficient	0.927	0.99	0.915	0.9814	0.915	0.9814

Table 7: Comparative physical parameters of three batches having different mixing time and compression force (n=3)

Evaluation parameters	Batches						
	Mixing time			Compression force			
	MT1 (5 Min)	MT2 (10 Min)	MT3 (15 Min)	CF1 (20kg/cm^2)	CF2 (30kg/cm^2)	CF3 (40kg/cm^2)	CF4 (50kg/cm^2)
Disintegration Time(Min)	--	--	--	1.4±0.20	1.8±0.11	1.8±0.25	2.0±0.18
%Compressibility	18.25	20.63	20.58	17.89	13.42	15.48	18.36
Angle of repose (θ)	29.85	30.98	30.85	34.95	30.95	29.65	35.75
Hardness(n=5)kg/cm^2	8±0.15	5±0.13	4±0.27	3±0.076	4±0.15	5±0.076	5±0.133
Thickness(n=5) mm	2.55-2.60	2.75-2.80	2.85-2.90	2.85-2.90	2.70-2.75	2.65-2.70	2.55-2.60
%Friability(n=10)	0.30±0.003	0.38±0.004	0.54±0.003	0.30±0.003	0.32±0.003	0.29±0.002	0.12±0.003
Weight Variation(n=20)	300±2.00	301±2.54	299±2.23	305±0.076	300±0.516	299±0.076	302±0.516
Similarity factor (f_2)	64.65	78.52	57.46	59.29	72.57	70.92	64.29
MDT (hrs)	9.27	9.72	10.16	9.23	9.58	9.64	8.71

List of Figures

Figure 1: Schematic representation of ANN (X_1 code for content of HPMC K4M and X_2 code for content of PEO WSR N 10

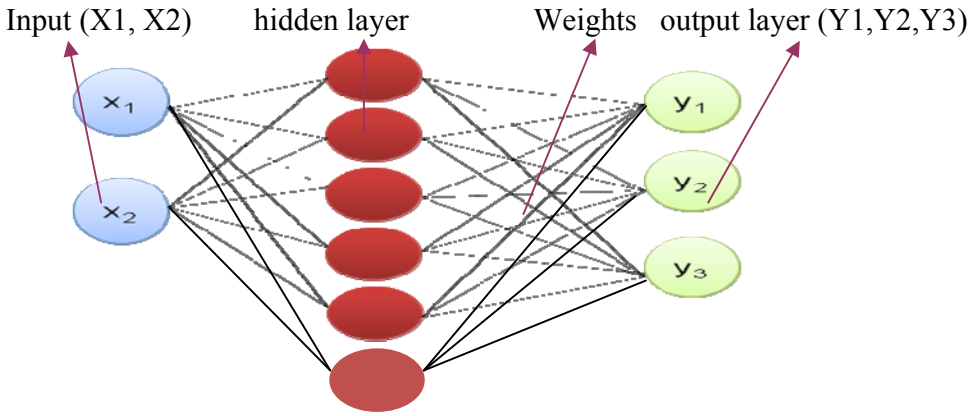

Figure 2: (A) FT-IR Spectra of BCF (B) FT-IR Spectra of BCF +HPMC K4M (C)FT-IR Spectra of BCF+PEOWSRN10 (D) FT-IR Spectra of BCF + polymer blend

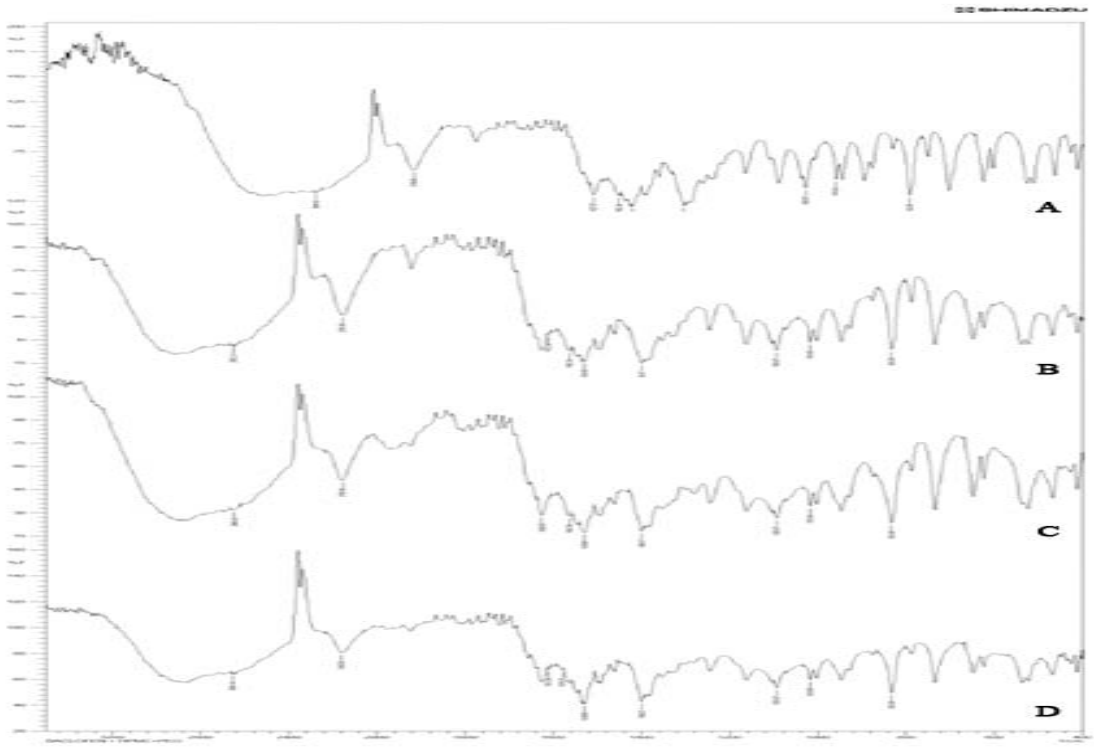

Figure 3: Contour plot showing effect of X_1 and X_2 on Q_{24}, T50 & FLT for BCF

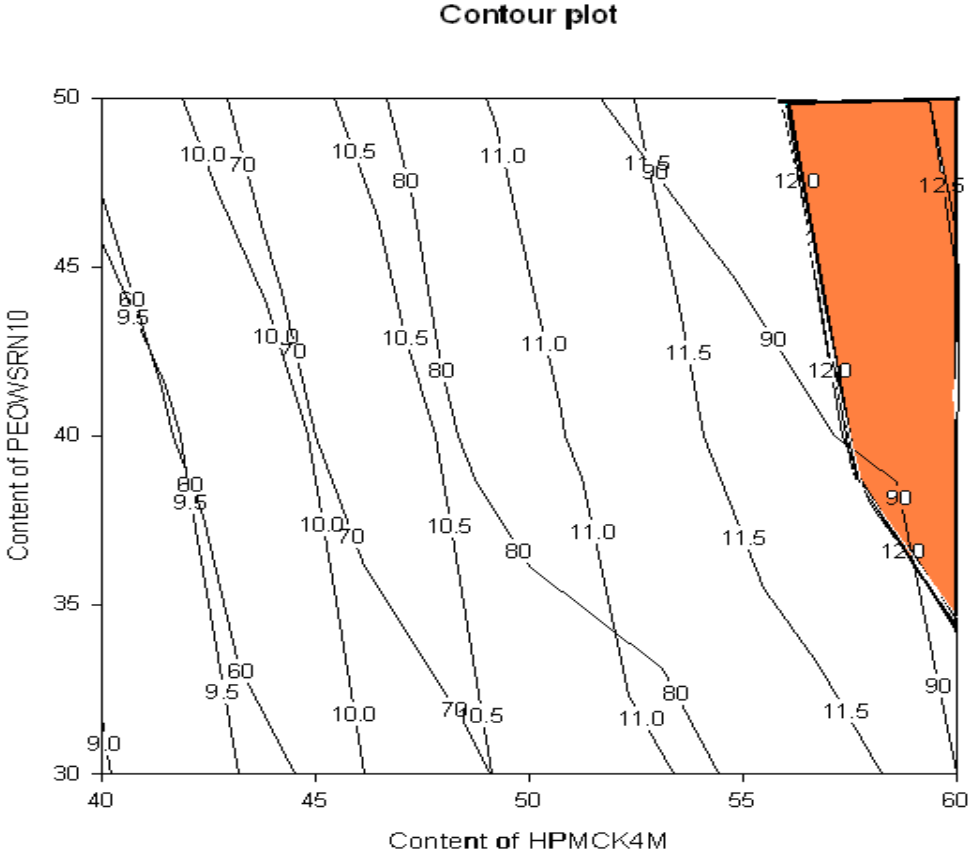

Figure 4: Regression (r^2) for all batch as a function of the number of hidden Nodes using ANN. $Q_{24, T50}$ & FLT for BCF

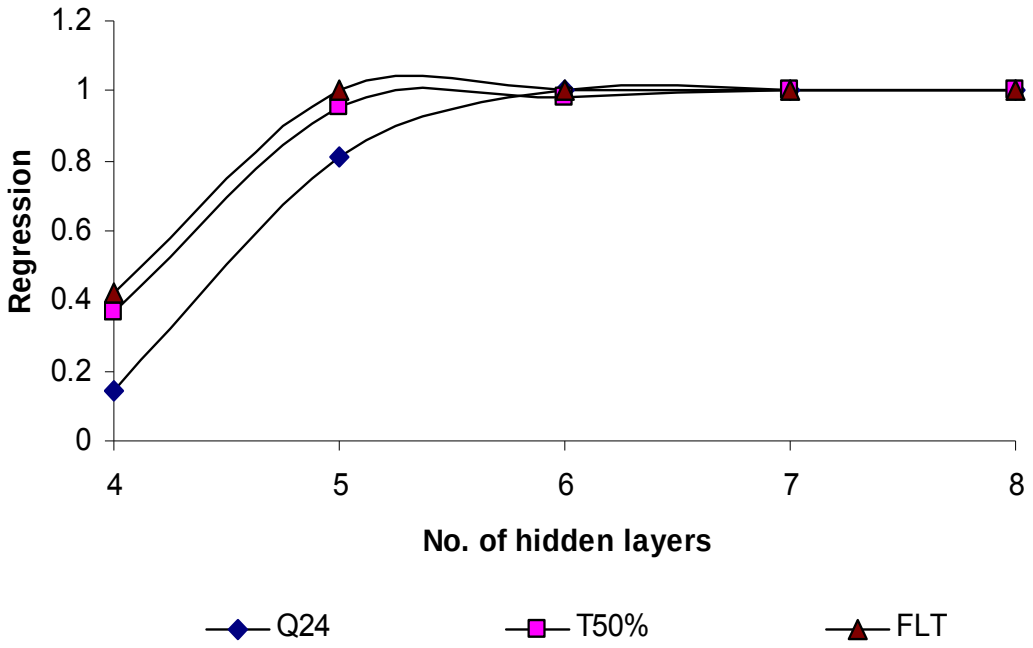

Figure 5: Swelling index of best batch F8 (n=3)