Chapter 9

Dissolution enhancement of lamotrigine

9.1 INTRODUCTION

The use of solid dispersions of drugs in highly water-soluble carriers to increase their solubility and dissolution rate, and therefore bioavailability, has been widely studied and reviewed[1,2].

Inclusion complexation of lipophilic drug molecules with cyclodexrins has been extensively applied to optimize the biopharmaceutical parameters such as solubility, stability, and bioavailability. Beta-cyclodextrin (β-CD) is one of the natural cyclodextrins and numerous works concerning its effect on improving the physicochemical characteristics of many lipophilic drugs have been published[3-7]. In this study, an attempt was made to enhance the dissolution of lamotrigine and its oral bioavailability characteristics by inclusion complex formation with β-CD. The inclusion complexes were formulated into tablets. Dissolution rate and dissolution efficiency (DE) values of these tablets were investigated.

Lamotrigine is practically insoluble in water and its oral absorption is dissolution rate limited. The poor dissolution characteristics of relatively insoluble drug have long been a problem to pharmaceutical industries. The poor aqueous solubility of the drug causes difficulties in formulation of dosage forms and may leads to a variable bioavailability, therefore the attempt was made to enhance the aqueous solubility of lamotrigine by complexation with β-CD. The prepared solid dispersions were characterized and formulated as tablets using direct compression method. Such tablets were subjected to quality control tests and were evaluated for dissolution

Neural network (NN) models might generalize better than regression models since regression analyses are dependent on predetermined statistical significance levels (i.e. less significant terms are not included in the model). With the NN method all data are used potentially making the models more accurate[8]. Hence NN was selected for modeling and evaluating tool.

NN operation is based upon the simulation of biological neural process abilities in the human brain. NN are very useful in modeling of systems where independent and dependent variable relationships are not well known. They are characterized by architecture, transfer function and learning paradigm[9-11]. NN consists of a number of processing elements (neurons) which are interconnected forming input and output layers and one or more hidden layers (figure 9.1).

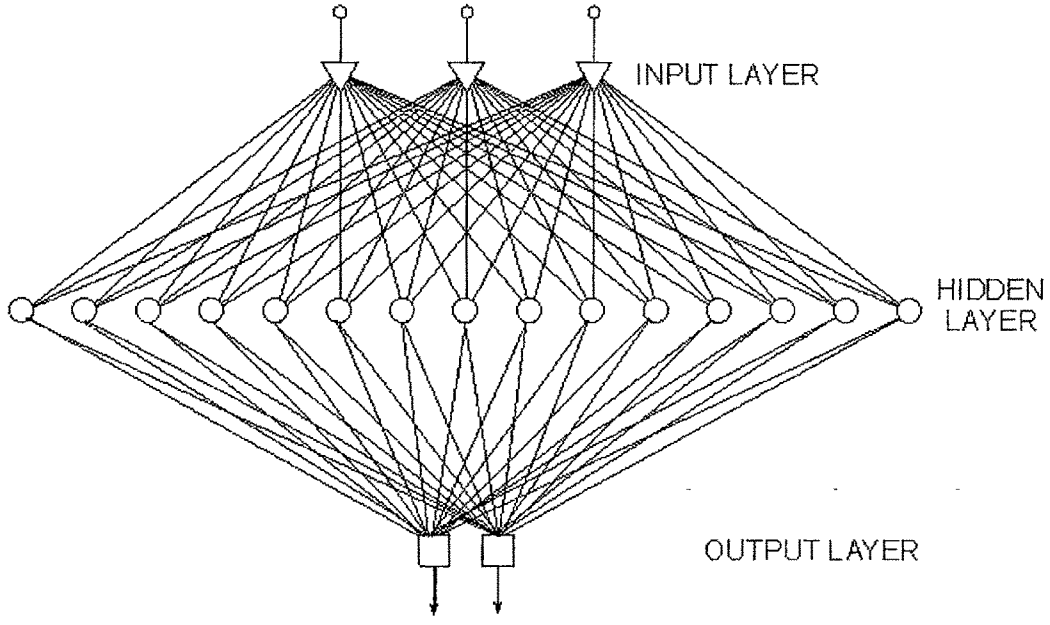


Figure 9.1. Architecture of three-layer neural network.

The use of at least one hidden layer enables the NNs to describe nonlinear systems[8,12]. One layer is usually sufficient to provide adequate prediction even if continuous variables are adopted as the units in the output layer[13] and also there is a little evidence to suggest that a larger number of hidden layers improves performance[14]. Processing elements on the input layer receive input signals, process them and send them to the output layer through hidden layers by the network connections (synapses). Each connection is characterized by a synaptic strength (weight). Learning of NN with known independent

and dependent variables based on an experimental design results in a condition for using that network for modeling. It begins with a random set of synaptic weights and proceeds in epoch (iterations). During each epoch connection weights are adapted via back propagation to minimize so-called 'error $e_i(n)$' which is the difference between the momentary network signal at neuron i at iteration n, $y_i(n)$, and the aimed signal based on experimental results $d_i(n)$.

$$e_i(n) = d_i(n) - y_i(n) \qquad (1)$$

In each hidden layer and output layer the processing unit sums its input from the previous layer and then applies the non-linear sigmoidal function to compute its output to the next layer according to equations:

$$y_j = \sum w_{ij} x_i \qquad (2)$$

$$f(y_j) = \frac{1}{1+e^{(-\sigma y_j)}} \qquad (3)$$

where w_{ij} is the weight of the connection between neuron j in the current layer to neuron i in the previous layer, x_i is the output value from the previous layer, $f(y_j)$ is conducted to the next layer as an output value, and σ is a parameter relating to the shape of the sigmoidal function. Nonlinearity of the sigmoidal function is strengthened with an increase in σ.

The three most common criterions to stop training are: to cap the number of iterations, to threshold the output mean square error, or to use cross validation. If a network is left to train for too long, it will overtrain and will lose the ability to generalize. Cross validation is more powerful of the three since it stops the training at the point of best generalization. When the performance starts to degrade in the validation set, training is stopped and

connection weights become the memory units. Then trained NN can be used for output prediction on the basis of new input values.

The multilayer perceptron (MLP) is one of the most widely implemented neural network topologies[14] and is important in the study of nonlinear dynamics. MLPs are normally trained with the backpropagation algorithm[18]. Two important characteristics of the multilayer perceptron are: its nonlinear neurons which have a nonlinearity that must be smooth (the logistic (sigmoidal) function is the most widely used); and their massive interconnectivity (i.e. any element of a given layer feeds all the elements of the next layer).

In present study, MLP with a training rule of momentum learning was applied which uses a memory term (the past increment to the weight) to speed up and stabilize convergence. The equation to update the weights (w_{ij}) can be represented as:

$$w_{ij}(n+1) = w_{ij}(n) + \eta\delta_i(n)x_j(n) + \alpha(w_{ij}(n) - w_{ij}(n-1)) \qquad (4)$$

The local error $\delta_i(n)$ can be directly computed from $e_i(n)$ at the output neuron or can be computed as a weighted sum of errors at the internal neurons. The constant η is called the step size and α is the momentum. Normally α should be set between 0.1 and 0.9.

NN has been successfully applied to many pharmaceutical areas in recent years[11] e.g.: quantitative structure activity relationship analysis[16], pharmacokinetic–pharmacodynamic studies[17], pharmaceutical formulation development[10,17], optimization of manufacturing processes[19], in vitro–in vivo correlations[20], etc.

9.2 EXPERIMENTAL

9.2.1 Materials

β-Cyclodextrin was purchased from S. D. Fine Chem. Ltd., Mumbai, India and lamotrigine was received as a gift sample from Torrent Pharmaceutical Ltd., Ahmedabad, India. All other compounds and solvents used in this study were of analytical reagent grade.

9.2.2 Phase Solubility Study

Solubility measurements were performed by the method of Higùchi et al [21]. Solution of β-CD of different concentrations (0.5, 1, 1.5, 2, 3, 3.5 mM/litre) with lamotrigine were shaken in sealed flasks in a water bath at temperature of 37 °C for 72 hrs. The aliquots were withdrawn and filtered through 0.45-μm filters. A portion of the filtrate was then diluted with water and analyzed spectrophotometrically at 305 nm. The solubility constant and the ratios of lamotrigine/ β-CD in the complexes were calculated from the phase solubility diagram.

9.2.3 Preparation of Solid Complexes

The solid complexes of lamotrigine and β-CD were prepared by using the following three different methods.

1. Physical mixture method

The Physical mixture was prepared by a simple dry mixing of lamotrigine and β-CD (1:1) in a mortar for 10 minutes.

2. Coprecipitation method

The mixture of lamotrigine and β-CD (1:1) was dissolved in 50 % ethanol, the solvent was allowed to evaporate, and then it was further dried under vacuum at 50 °C for 24 hour.

3. Cogrinding method

The mixture of lamotrigine, β-CD (1:1) and solubilizing agent was cogrinded in the mortal. The cogrind solid dispersion was processed as shown in coprecipitation method.

9.2.4 Experimental Design

To optimize the concentration of solubilizing agents, a central composite design was adopted using the concentration of transcutanol (X_1), maisine (X_2) and peceol (X_3) as independent variables. The time required for 50 % dissolution ($T_{50\%}$), and dissolution efficiency were selected as response variables. The factors and responses are shown in table 9.1.

Table 9.1. Matrix of the Experiments, Results for the Measured Responses. Each value is mean of three replicates.

Run no.	X_1	Trancutanol concentration (% v/w)	X_2	Maisine (%v/w)	X_3	Peceol concentration (%v/w)	$T_{50\%}$ (min)	Dissolut efficien (%)
1	1	3	1	3	-1	1	4	70.62
2	1.7	3.7	0	2	0	2	2.5	79.23
3	-1	1	1	3	1	3	5	60.81
4	-1	1	-1	1	-1	1	9	38.22
5	1	3	1	3	1	3	3.5	79.04
6	0	2	0	2	-1.7	3	7	56.29
7	1	3	-1	1	1	3	2.5	86.17
8	0	2	0	2	1.7	37	6	59.48
9	-1.7	3	0	2	0	2	8	44.83
10	0	2	1.7	37	0	2	5.5	56.3
11	0	2	0	2	0	2	4.5	67.92
12	0	2	0	2	0	2	4	73.84
13	1	3	-1	1	-1	1	7.5	38.06
14	0	2	0	2	0	2	4.5	63.35
15	0	2	-1.7	3	0	2	5	61.83
16	-1	1	-1	1	1	3	5.5	58.22
17	0	2	0	2	0	2	4	75.13
18	-1	1	-1	1	-1	1	10	34.47

9.2.5 Neural Network Software and Network Topology

The Microsoft®-Windows® based neural network software; NeuroSolutions® Version 4.24 (Neuro Dimension, Inc., USA) was used. A multilayer perceptron (MLP) with single hidden layer architecture was chosen. The experimental matrix of 18 input:desired output data sets (table 9.2) was inserted in to the model, with three input neuron (transcutanol concentration, maisine concentration and peceol concnetration), one hidden layer and two output neuron (T_{50}, and dissolution efficiency) as shown in Figure 1. Various adjustable parameters like number of neurons in hidden layer, step size and momentum of hidden layer and output layer, etc. were optimized.'

Table 9.2. Matrix of the Experiments, Neural Network Predicted Responses. Each value is mean of three replicates.

Run no.	X_1	Trancutanol concentration (%)	X_2	Maisine concentration (%)	X_3	Peceol concentration (%)	$T_{50\%}$ (min)	Dissolut efficien (%)
1	1	3	1	3	-1	1	4.48	66.44
2	1.7	3.7	0	2	0	2	3.56	73.7
3	-1	1	1	3	1	3	4.79	64.56
4	-1	1	-1	1	-1	1	8.91	40.25
5	1	3	1	3	1	3	3.40	75.33
6	0	2	0	2	-1.7	3	7.77	46.18
7	1	3	-1	1	1	3	3.57	73.68
8	0	2	0	2	1.7	37	3.62	73.42
9	-1.7	3	0	2	0	2	8.074	44.97
10	0	2	1.7	37	0	2	4.44	66.93
11	0	2	0	2	0	2	4.90	63.59
12	0	2	0	2	0	2	4.90	63.59
13	1	3	-1	1	-1	1	5.22	61.03
14	0	2	0	2	0	2	4.90	63.59
15	0	2	-1.7	3	0	2	5.63	58.61
16	-1	1	-1	1	1	3	5.44	60.14
17	0	2	0	2	0	2	4.90	63.59
18	-1	1	-1	1	-1	1	8.91	40.25

The neural network was trained with 1 to 15 hidden neurons with 2000 training epochs and performance was tested after each 1 addition of neurons. Training was repeated for 3 times for optimization of all parameters. At the start of the training run, weights were initialized with random values. During training, 5 additional data sets of input:desired output were used for the cross-validation and was back-propagated through the network to evaluate the trained network. A mean square error (MSE) termination criterion was

based on the cross validation set. By selecting this option training stops when the MSE of the cross validation set begins to increase, a sign of network overtraining when network simply memorizes the training set and is unable to generalize the problem. The network trained under optimum conditions was used to predict responses at different factor values and response surface were generated for interpretation.

9.2.6 Characterization of Complexes

Powder X-ray difftractometry was carried out using a Rigaku DMAX- III 3 KVA diffractometer (Geigerflex Horizontal Goniometer, Japan). The operating conditions were as follows: target, Cu; filter, Ni; voltage, 40 kV, current, 10 mA; receiving slit, 0.15 mm; scanning speed, 5°/min. The drug powder was measured using the KBr method. Differential scanning calorimeter (DSC) with a Shimadzu DT-60 was used for each sample at a constant scanning speed of 10 °C/min between 40°C and 300°C. The samples of 5-7 mg were accurately weighted into solid aluminum pans without seals.

9.2.7 Preparation of Tablets

The prepared solid complexes were formulated into tablets by direct compression method. The composition of the prepared tablets was as follow: lamotrigine (5 mg), β-CD (5mg), transcutanol (0.02) lactose anhydrous (10 mg), microcrystalline cellulose (20 mg), mannitol (10 mg), cross carmellose (8 mg), magnesium stearate (0.5 mg). Each time a batch of tablets containing 5 mg lamotrigine with an average weight of 63 mg was prepared using cadmach single punch tablet machine

9.2.8 In Vitro Dissolution Study

The dissolution of lamotrigine from inclusion complxes and tablets were studied using USP USP 25 Paddle apparatus (Model TDT-06P, Electrolab, Mumbai, India) at 37± 0.5 °C using 900 ml of 0.1 N hydrochloric acid containing 0.5 % sodium lauryl sulphate (SLS) as dissolution medium with stirring speed of 75 rpm. SLS (0.5%) was added to maintain the sink condition. The inclusion complex equivalent to 20 mg of lamotrigine or

one tablet containing 20 mg of lamotrigine was used in each test. At suitable intervals, samples of 5 ml were taken and immediately replaced with equal volume of fresh dissolution medium (maintained 37 ± 0.5°C) to maintain a constant volume for drug dissolution. The withdrawn samples were filtered through 0.45-μm membrane filters and assayed spectrophotometrically at 305 nm (Model UV-1601, UV Visible spectrophotometer, Shimadzu, Japan). The absorbance values were transformed to concentration by reference to a standard calibration curve obtained experimentally (r^2 = 0.9968). Samples of solid dispersions were stored for 3 months at room temperature and at 45°C, and evaluated again for reliability of dissolution profiles.

9.2.9 Solubility Study

Solubility of lamotrigine and lamotrigine β-CD complex were studied at pH 1.2. To this aim, an excess amount of lamotrigine (an amount of lamotrigine, more that could be dissolved) was added to a closed flask with pH 1.2, and then mixed with a magnetic mixer at 37 °C for 72 hr. Thereafter, the liquid phase was filtered through 0.45-μm filters and the amount of lamotrigine in this solution was determined. Solubility of lamotrigine was calculated by the point measured during formation of the equilibrium status.

9.3 RESULTS AND DISCUSSION

The phase solubility diagram for lamotrigine and β-CD is shown in figure 9.2.

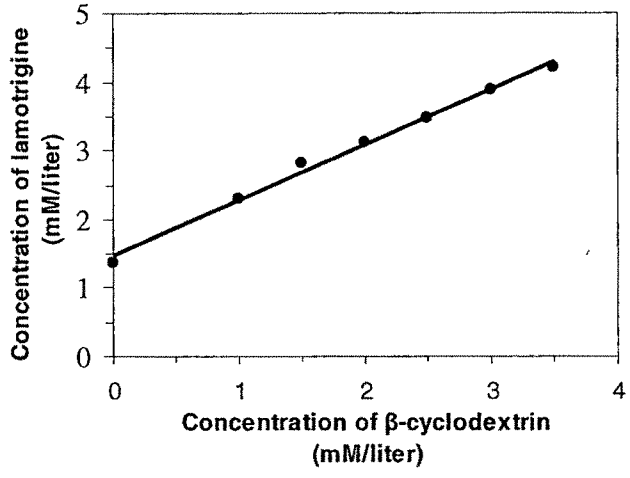


Figure 9.2. Phase solubility diagram of the lamotrigine-β-cyclodextrin system. Each values is mean ± S.D. of five experiments.

The solubility curve can be classified as type A_L according to Higuchi et al[21]. Because the straight line had a slope less than unity, it was assumed that the increase in solubility observed was due to the formation of a 1:1 complex. The 1:1 stability constant ($K_{1:1}$) of the soluble complex was calculated according to Eq. (5) and was found to be 3.05 M^{-1}.

$$K_{11} = \frac{\text{slope}}{S_0(1-\text{slope})} \qquad (5)$$

Where S_0 is the solubility of lamotrigine in absence of β-CD.

A three-factor spherical second order central composite experimental design was adopted using the concentration of transcutanol (X_1), maisine (X_2) and peceol (X_3) to study the effect of the solubilizing agents. The results of dependent variables such as the $T_{50\%}$ and

dissolution efficiency of different runs are shown in Table 1. Optimization of various parameters like number of neuron in hidden layer, step size and momentum of hidden and output layer was carried out. For optimization, the training was carried out three times and the minimum of average MSE was the optimization criteria. Results of various run are summarized in figure 9.3.

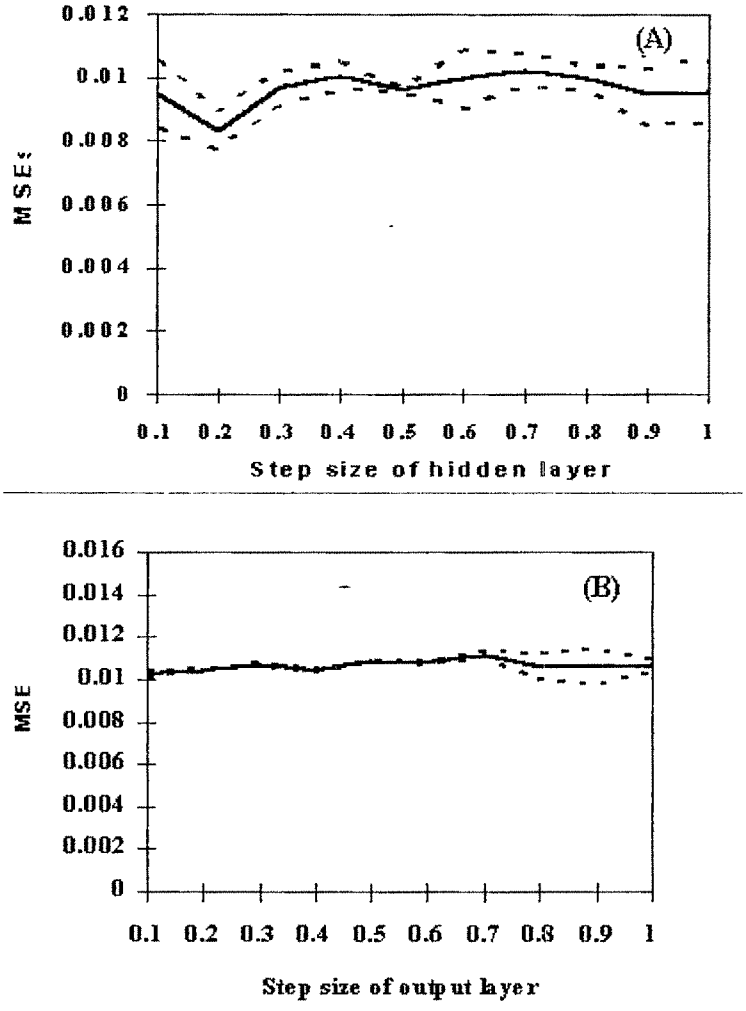


Figure 9.3. Optimization of neural network: (A) optimization of step of hidden layer, and (B) optimization of step size of output layer.

Optimum number of neurons in hidden layer was found to be 5, while optimum step size for hidden layer and output layer was 0.2 and 0.9 respectively (out of 0.1 to 1.0). Optimum momentum for hidden layer and output layer was found to be 0.8 and 0.4

respectively (out of 0.1 to 1.0). For prediction purpose, the neural network was constructed using the optimum conditions and trained (n=3) along with cross validation data set. The matrix of the experiments and neural network predicted responses are given in Table 2. The predicted responses were plotted to generate the contour plots for interpreting the effect of various process factors.

50 % of drug should be released in minimum time to exert maximum action at the site of release. The transcutanol concentration was the most positively influencing factor amongst all three. Similarly, all three factors had positive effect on the dissolution efficiency and transcutanol concentration was the most positively influencing factor. This may be due to the higher wetting of the drug by transcutanol. The liquid solid dispersion system containing drug and vehicles was studied by Spireas and Sadhu. The drug remained in a solubilized state within the substrate of the liquidsolid dispersion system. It is well known better bioavailability of an orally administered poorly water soluble drug can be achieved when it is in solution form. There is a possibility for the drug to precipitate out of the vehicle because of surface adsorption onto the carrier system. The precipitated drug particles may be in amorphous or solvated form possessing improved solubility. The relation between process variables and response factors was derived using multi-linear regression (MLR) which can be represented as:

$$T_{50\%} = 4.256 - 1.338X_1 - 0.391X_2 - 0.928X_3 + 0.303X_1^2 + 0.303X_2^2 + 0.735X_3^2 + 0.156X_1X_2 + 0.906X_2X_3 + 0.113X_1X_3$$
$$(R^2 = 0.8837; DF = 9,17; F = 6.754) \quad (6)$$

$$\text{Dissolution efficiency} = 69.999 + 8.463X_1 + 3.348X_2 + 6.115X_3 - 2.376X_1^2 - 3.402X_2^2 - 3.810X_3^2 - 0.585X_1X_2 - 8.078X_2X_3 + 4.276X_1X_3$$
$$(R^2 = 0.8265; DF = 9,17; F = 4.325) \quad (7)$$

The equation 7 showed that transcutanol has largest negative effect on the time required for 50% dissolution of lamotrigine while equation 8 showed that transcutanol has the largest positive effect on the dissolution efficiency of the lamotrigine. Therefore, In order

to assess the reliability of the model, five cross-validation experiments were conducted by varying the process variables at values other than that of the model and responses were predicted using the trained network. A comparison between the experimental and predicted values of the responses for these additional experiments is presented in table 9.3.

Table 9.3. Comparison of Responses between Predicted and Experimental Values for the Cross-Validation Set.

Responses	Test	Factors/levels			Experimental values	Predicted values	Bias%
		A	B	C			
$T_{50\%}$	1	-1	-0.6	-0.6	9.50	9.73	2.36
	2	-0.6	0.0	0.4	7.50	7.4	1.35
	3	-0.4	0.6	0.0	7.00	6.83	2.48
	4	0.0	-0.4	0.6	6.50	6.30	3.17
	5	0.4	0.4	-0.4	5.00	5.20	3.84
Dissolution efficiency (%)	1	-1	-0.6	-0.6	36.71	37.38	1.79
	2	-0.6	0.0	0.4	50.27	53.74	6.45
	3	-0.4	0.6	0.0	55.34	57.93	4.47
	4	0.0	-0.4	0.6	59.09	58.93	0.27
	5	0.4	0.4	-0.4	65.72	64.83	1.37

Bias was calculated by the following equation:

$$\text{Bias} = \left[\frac{(\text{predicted value} - \text{experimental value})}{\text{predicted value}}\right] \times 100 \qquad (8)$$

It can be seen that in all cases there was a reasonable agreement between the predicted and the experimental value, since low value of the bias were found. For this reason it can be concluded that the NN predicted responses describe adequately the influence of the

selected process variables on the responses under study and NN can be used successfully as a predictive and optimizing tool.

The DSC, XRD, SEM and in vitro dissolution studies were used to characterize the solid dispersions. Supporting evidence for complex formation was also obtained from DSC studies (figure 9.4).

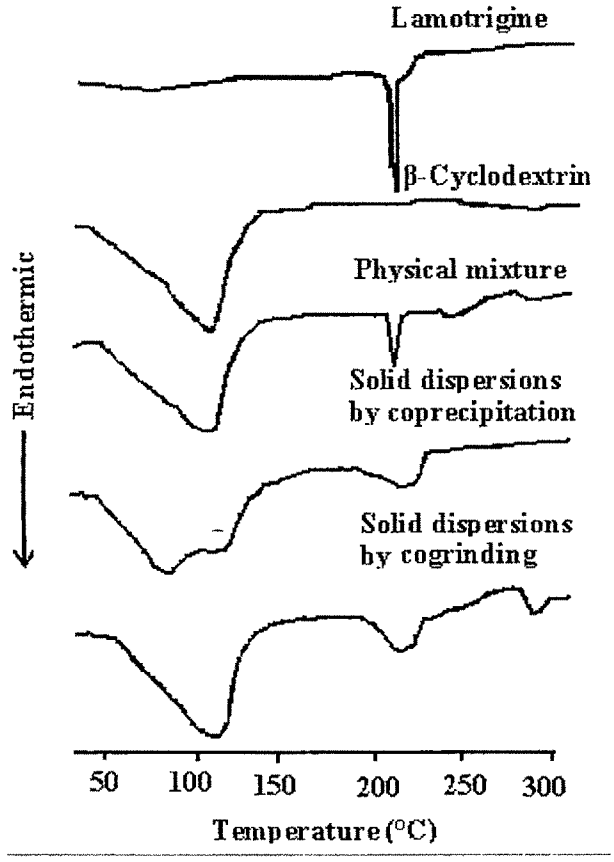


Figure 9.4. DSC thermograms of lamotrigine, β-cyclodextrin, physical mixture (lamotrigine: β-CD: 1:1), coprecipitation solid dispersions (lamotrigine: β-CD:transcutanol: 1:1:0.03)and cogrinding solid dispersions (lamotrigine: β-CD:transcutanol: 1:1:0.03).

The endothermic peak of lamotrigine at 210 °C, which correspondence to its melting point, was considerably broadened in the coprecipitated and cogrinding method. The

DSC thermogram of the physical mixture was a combination of the thermograms of lamotrigine and β-CD. DSC study indicated no interaction between lamotrigine and β-CD.

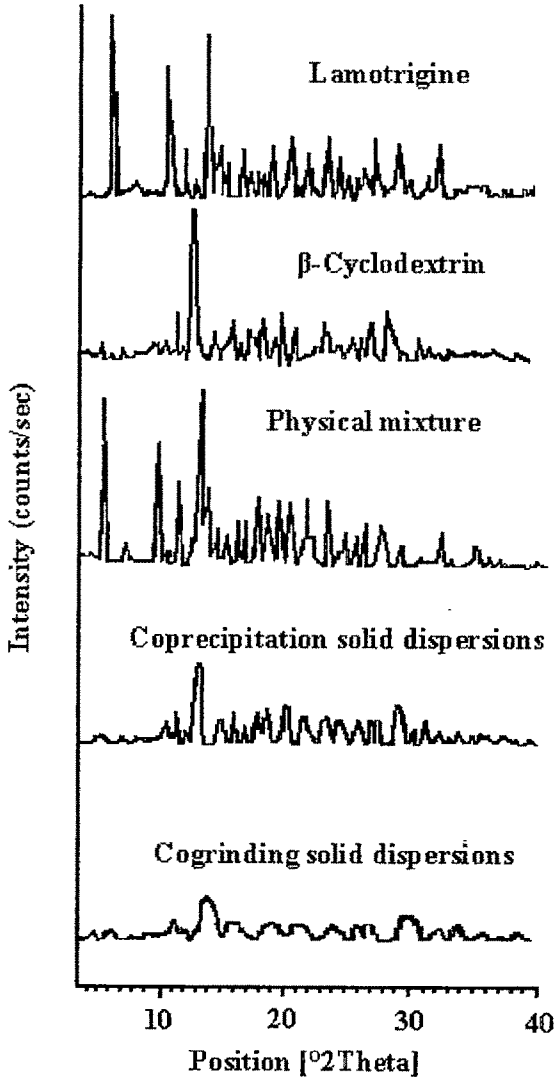
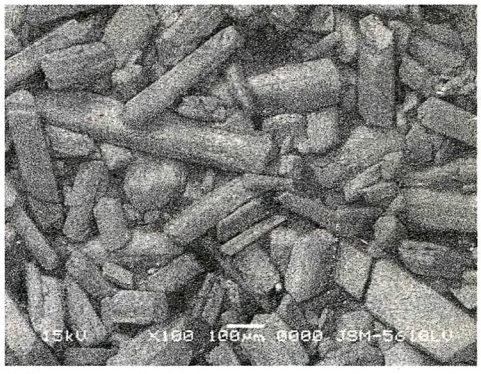


Figure 9.5. Powder x- ray diffraction patterns of lamotrigine, β-cyclodextrin, physical mixture (lamotrigine: β-CD: 1:1), coprecipitation solid dispersions (lamotrigine: β-CD:transcutanol: 1:1:0.03) and cogrinding solid dispersions (lamotrigine: β-CD:transcutanol: 1:1:0.03).

The diffraction pattern of lamotrigine showed that lamotrigine has high crystallinity because of the presence of numerous distinct peaks. The x-ray patterns of the physical mixture of lamotrigine and β-CD was simply a superimposition of each component with the peaks having lower intensity (figure 9.5). The solid dispersions produced my coprecipitated method and cogrinding method showed a broad, diffuse pattern indicating that the process of coprecipitation and cogrinding led to a grater amount of amorphous nature. The scanning electron photomicrographs (SEM) of lamotrigine, β-CD, physical mixture and various solid dispersions in figure 9.6.

(a)



(b)

(c)

(d)

(e)

Figure 9.6. Scanning electron photomicrographs of (a) lamotrigine, (b) β-cyclodextrin, (c) physical mixture (lamotrigine: β-CD: 1:1), (d) solid dispersions produced by coprecipitation method (lamotrigine: β-CD:transcutanol: 1:1:0.03), (e) solid dispersions produced by cogrinding method (lamotrigine: β-CD:transcutanol: 1:1:0.03).

Analysis of SEM revealed that the elongated crystalline forms of lamotrigine and relatively larger elongated crystals of β-CD, clearly visible in the physical mixture were transferred to less crystalline structures in the solid dispersions. These observations provided further evidence of solid solution formation, and are in accordance to the results obtained from DSC and x-ray diffraction studied.

Figure 9.7(a) shows the dissolution profiles of the different dispersion samples. The cogrinding solid dispersion dissolved completely to give a clear solution almost instantaneously. Lamotrigine dissolved only to the extent 36 % at the end of 3 hr. All other samples displayed better dissolution of the dug. The % drug dissolved from the physical mixture, coprecipitation method and cogrinding method was about 72 %, 91 % and 97 %, respectively. The coprecipitation treated lamotrigine and cogrinding-treated drug was slightly more soluble in comparison with intact lamotrigine, because the crystallinity of the dug was decreased by coprecipitation and cogrinding treatment. Samples stored at room temperature and at 45 °C showed no changes in dissolution patterns [figure 9.7 (b) and 9.7(c)] at the end of 3 months.

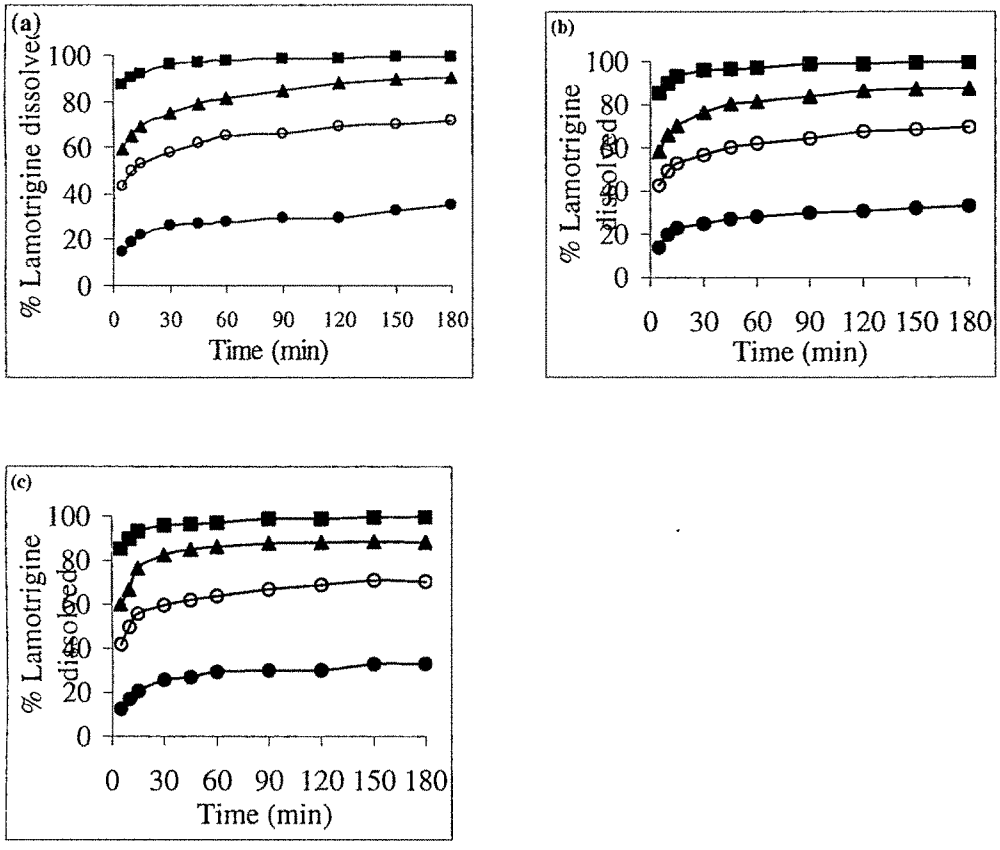


Figure 9.7. (a) Dissolution of lamotrigine from solid dispersions. (b) Dissolution of lamotrigine from solid dispersions (lamotrigine: β-CD:transcutanol: 1:1:0.03) stored at room temperatures for 3 month. (c) Dissolution of lamotrigine from solid dispersions (lamotrigine: β-CD:transcutanol: 1:1:0.03) stored at 45 °C for 3 month. Each value is mean ± of S.D. five experiments.

Coprecipitation method and cogrinding method gave a solid mass which was denser than the physical mixture and had better flow and compressibility. All the tablets prepared were found to contain lamotrigine within 100 ± 5% of the labeled claim. Hardness of the tablets was in the range of 4-7 kg/cm^2 and was satisfactory. The percentage weight loss in the friability test was less than 1% in all the batches prepared. The tablets disintegrated rapidly within 2 minutes fulfilling the official disintegration time specification for uncoated tablets. Figure 9.8 shows the dissolution of profiles of the tablets.

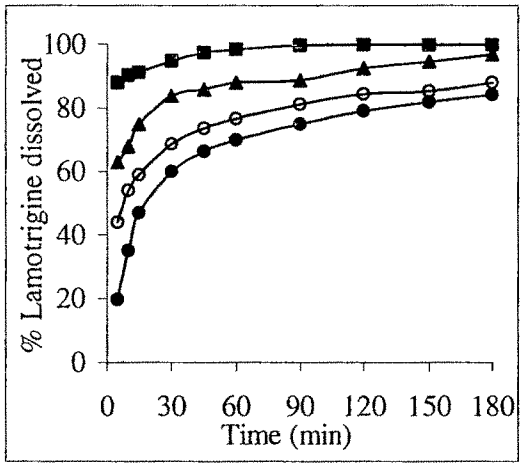


Figure 9.8. Percent lamotrigine dissolved from tablets made from the different solid dispersion versus time. Each value is mean ± S.D. of five experiments.

The time taken for 50 % ($t_{50\%}$) of lamotrigine is in table 9.4.

Table 9.4. $T_{50\ \%}$ values of tablets made from different method (n=5).

	Tablets made from:			
Time (min)	Lamotrigine	Physical mixture	Coprecipitation method	Cogrinding method
$t_{50\%}$	18 ± 1.06	7 ± 0.74	4 ± 0.37	2.5 ± 0.06

Tablets compressed from solid dispersions prepared with cogrinding method showed higher dissolution rates and high dissolution efficiency than tablets prepared from other solid complex method or lamotrigine alone. Thus the dissolution rates of lamotrigine can be significantly enhanced by its solid dispersion prepared with cogrinding method using β-CD and transcutanol. These dispersions could be formulated into tablets by direct compression method. The resulting tablets, apart from fulfilling all official and other specifications, exhibited higher dissolution rates of lamotrigine.

9.4 CONCLUSIONS

Solid dispersions with β-CD improved solubility of lamotrigine. The optimization of the process using the neural netowrk resulted to the optimum values of the factors at which the goal of the dissolution enhancement of lamotrigine could be fulfilled. Studies on solubility, DSC, x-ray diffraction, SEM, and powder dissolution indicated complex formation. Interaction between β-CD and lamotrigine was greater after the coprecipitation and cogrinding processes than physical mixture. Solubility of lamotrigine increased significantly due to complexation and amorphization. Solid dispersions with β-CD were compressed into tablets. Tablets so compressed had good in vitro dissolution profile.

9.5 REFERENCES

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