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Optimization and extraction of pharmaceutical micro-pollutant - norfloxacin using green emulsion liquid membranes

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ABSTRACT

Amongst the present water treatment technologies membrane separation is gaining focus nowadays. Emulsion liquid membrane is one of the advanced strategies used for pollution removal from waste water in which the use of biosurfactant makes this approach eco-friendly technique. The norfloxacin belongs to the fluoroquinolones class of antibiotic and extensively used for urinary tract infections, which is the model pollutant in this study. Saponin was solvent extracted from soapnuts and used as biosurfactant. The main and interactive effects of parameters such as saponin concentration (0.01–0.03 g/100 mL), NaOH concentration (0.25–0.75 M) and Initial Norfloxacin concentration (25–75 mg/L) were investigated using Response Surface Methodology (RSM) - Box Behnken Design (BBD) and Artificial Neural Networks (ANN) design. The results suggested that developed 3-8-1 ANN model evaluated in terms of performance measure (R^2: 0.9806, Chi square: 0.02) and error functions (RMSE: 0.11, MAE: 0.09, SEP: 1.16, MPE: 1.76) demonstrated superiority more precisely than the RSM model in terms of both data fitting and prediction capability. The optimal conditions for ELM were found to be: initial norfloxacin concentration 67.65 mg/L, saponin concentration 0.021 mg/100 mL, and NaOH concentration 0.36 M and the extraction efficiency at these parameter settings would be 91.27%.

Keywords: Pharmaceutical waste; Norfloxacin; Emulsion liquid membrane; Saponin

1. Introduction

Urbanization and rapid Industrialization generate enormous amounts of hazardous wastes and pharmaceutical containing waste water is one among them [1]. Pharmaceutical effluents are complex in nature and hazardous to the ecosystem. Pharmaceutical micro pollutants are extremely harmful as they are present at very smaller quantity in waste waters which have the potential to create adverse effects in the aquatic system, human, and animal health [2]. Even though, norfloxacin is a potent fluoroquinolone antibiotic which is used to treat urinary tract infections in human beings, administered to poultry, and farm animals for prophylaxis, it has the ability to create antimicrobial resistance in human populations and may also act as potential endocrine disruptors in aquatic life forms [3,4,5]. Similarly, wastewater from hospital, sewage treatment plant

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and wastewater treatment plant are reported with micro- and nano-levels of this component [6].

The conventional treatment for the removal of fluoroquinolone antibiotics using mechanical and biological treatment [7–9] showed very low level removal of norfloxacin under methanogenic conditions in sludge digesters [10]. It also proved that complete removal of norfloxacin at micro level has not been achieved so far with any other technique. The methods such as advanced oxidation process and ozonisation may have harmful consequences as they might convert the norfloxacin into some other harmful chemical substance [11]. Hence a novel green surfactant assisted Emulsion Liquid Membranes (ELM) system is developed in this study for norfloxacin removal from aqueous solution. ELMs are useful especially in the efficient recovery of solutes from low concentration which is one of the merits of this technique [12]. Another major advantage of this technique is that, the separation is carried out in a single step. Classical methods for the treatment of micro pollutants using ELM utilizes synthetic surfactants such as span 80 [12]. Such synthetic chemical surfactants are hazardous to the environment and are costly [13]. The solvents are recoverable and the only chemical used for ELM formation is these chemical surfactants. If they are replaced by renewable and cheap biosurfactant, the ELM process goes eco-friendly. Hence, a novel green surfactant - saponin was extracted from soapnuts and used in this study. Saponin is a saponaceous substance produced naturally by plants such as *Sapindus mukorossi* [14].

Soap nut or *Sapindus indicus* belongs to *Sapindaceae* family, is widely available in Asian countries and had been used as a traditional surfactant for cleansing hair and body for several years [15,16]. An untried and cheap surfactant saponin extracted from soap nut is employed in this study substituting synthetic surfactant. The present investigation, introduces a novel strategy by choosing saponin as the green surfactant that further allows for the cost effective and possible removal of the pharmaceutical micro-pollutant norfloxacin from aqueous solutions using a single step ELM process.

Even though, operating cost of the ELM is low, the dynamics for the removal need to be addressed to understand the optimum utilization of ELM. Predicting the removal efficiency of the norfloxacin micro-pollutant using ELM involves several experimental procedures which are a cumbersome process. While considering the classical "one factor at a time" method the number of variables taken is too many which is unrealistic [17,18]. Further such process generates huge volume of data which makes the interpretation a very daunting process. Hence, Response Surface Methodology (RSM) and Artificial Neural Network (ANN) design have been developed in this study to understand the extraction of norfloxacin using ELM. Response surface methodology (RSM) is more advantageous than the traditional single parameter optimization because it can save time, space and raw material [18]. In experimental design, a BBD is a type of RSM. BBD along with the design of experiments remove systematic errors with an estimate of the experimental errors, and also reduce the number of experiments, in order to obtain the optimum operating condition [19].

ANN is a machine learning tool which is a biologically inspired model formed from hundreds of single units, and artificial neurons that are connected with coefficients (weights) which comprises of the neural network [20,21]. ANN can deal with the optimization of nonlinear multivariate systems with its interactions greater than the quadratic range which can be applicable to both small and large data sets [22,23]. Recently, focus on the comparison of RSM data with ANN have been used to understand the results of different process parameters.

To the best of our knowledge, this manuscript is one of a kind to demonstrate the removal of micro-pollutant norfloxacin using ELM and to investigate on the combined effects of the involving variables using RSM-BBD mathematical model and predicts the removal of the pharmaceutical micro-pollutant norfloxacin using ANN model.

2. Materials and methods

2.1. Chemical

The NaOH (internal reagent, SD fine, ≈97%), Isoamyl alcohol (membrane phase, Hi Media, ≈99%), poly-butyl succinimide (membrane stabilizer, Hi Media, 99%), norfloxacin for feed/external phase (Sigma Aldrich, ≈97%) and ethyl acetate (for saponin extraction, Hi Media, 99%) used during this present investigation were of analytical grade and were used without any pre-treatment. Doubly distilled water was used for all the experiments unless otherwise stated. The saponin was extracted from soap nut powder and used as a green surfactant in this experiment.

2.2. Biosurfactant extraction and characterization

Ten gram of soapnut powder was added with 100 ml of ethyl acetate in a 250 ml beaker. The beaker was placed in a water bath at 60±1ºC with intermittent stirring at 180 rpm for 7 h. After heating, it was allowed to cool until it attained room temperature. Then the solution was filtered using the Whatmann filter paper No.1 and the solvent was recovered by the rotary flash evaporator (Heidolph Laborota 4000, India). The sample was concentrated and placed in a Petri plate under 27±1ºC for drying. Finally, the sample was weighed for calculating the yield of saponin. The critical micellar concentration of saponin was determined using a procedure explained by Chakrabarty [23]. The extracted saponin was characterized using FTIR (IRAFFINITY-1S, Double beam, Shimadzu, US) in the range of 750–4500 cm^{-1}.

2.3. Batch ELM experiments

A glass mixer-settler of 12.5 cm diameter with proper covering and a variable speed turbine impeller was used for batch ELM extraction. The constituents of the liquid membrane used in this study were: amyl alcohol as the solvent and saponin as surfactant to stabilize water-in-oil emulsions and poly-butyl succinimide (1.5 wt%) as membrane strengthening agent. The internal reagent was sodium hydroxide. The primary emulsion (Water in oil) was prepared by gradually dripping NaOH solution into the amyl alcohol (oil phase) in a beaker by high speed stirring at around 4000 rpm for about 20 min. The resultant milky white emulsion was then dispersed (at 200 rpm) in the external aqueous phase containing pharmaceutical compound as feed in the mixer-settler for 20 min. During this period, the norfloxacin (solute) transport occurs through the membrane phase into the internal stripping phase where it is concentrated. The treated sample was then separated from the emulsion and filtered before analysing for norfloxacin concentration by using UV-spectrophotometer (SHIMADZU, India) at 270 nm. The initial concentration of the aqueous feed phase norfloxacin solution was altered between 25 to 75 mg/L and experiments carried out to understand the concentration effects. Saponin loading also varied between 0.01 to 0.03 g/100 mL mixture to investigate the surfactant loading effects. Sodium hydroxide was used as stripping agent and its concentration was varied from 0.25 M to 0.75 M.

2.4. BBD Optimization of ELM parameters

The entire optimization was carried out using Box-Behnken design (BBD) [24] using Design Expert 10 (State Ease, USA) software [20]. Experiments were conducted in random order to reduce error. The regression analysis was executed to evaluate the response function. The following quadratic model (Eq. (1)) can predict the extraction efficiency (%E):

$$\%E = \beta_0 + \sum_{j=1}^{k} \beta_j X_j + \sum_{j=1}^{k} \beta_{jj} X_j^2 + \sum_{i} \sum_{<j=2}^{k} \beta_{ij} X_i X_j \qquad (1)$$

where %E is the extraction efficiency, β_i, β_j, and β_{ij} are the coefficients from regression analysis, k is the number of factors, X_i and X_j represent the uncoded value of the i^{th} (linear coefficient), and j^{th} (quadratic coefficient) parameter respectively [24].

2.5. Artificial neural networks

In this study, an Artificial Neural Network (ANN) model was constructed for predicting the norfloxacin extraction efficiency. ANN was performed for the same data according to BBD matrix with 17 data points with 3 process variables as input variables - NaOH concentration (0.25–0.75 M, X_1), initial norfloxacin concentration (25–75 mg/L, X_2) and saponin concentration (0.01–0.03 g/100 mL, X_3). The input signals were modified by interconnecting the weights known as weight factors, which represented the interconnection of i^{th} nodes of the first layer to j^{th} nodes of the second layer. The sum of modified signals (total activation) was then amended by a sigmoid transfer function and output was obtained at the output layer [17]. The coefficient of determination for ANN was obtained from regression graph. In this study the ANN model was performed using Neural Network Toolbox of (MATLAB R2014a) mathematical software [22]. The hidden layer then did all the pre-processing and gave the output based on the sum of the weighted values from the input layer, modified by a sigmoid transfer function (transig) at the hidden layer and a linear transfer function (purelin) as output. The performance of the ANN process was expressed in terms of the Root Mean Square Error (RMSE) and correlation coefficients (R^2) [20].

3. Results and discussion

3.1. Saponin yield and critical micellar concentration

The Saponin yield was obtained as 26 g/kg powder of dried soapnut powder. The critical micellar concentration of the extracted saponin was found to be 0.2 g/L (=4.37 × 10^{-4} mol/L). The FTIR results (Fig. 1) clearly indicated that the extract was saponin which is comparable with other researchers [15,16,25].

3.2. Statistical analysis of ELM

In this study, we demonstrated the statistical optimization for norfloxacin removal using saponin assisted ELM system. Three factors namely, NaOH concentration (0.25–0.75 M, X_1), initial norfloxacin concentration (25–75 mg/L, X_2) and saponin concentration (0.01–0.03 g/100 mL, X_3) were considered to analyse the extraction efficiency of norfloxacin from aqueous solution. In order to investigate the combined effects of the selected variable on percentage norfloxacin removal the experiments were carried out according to the BBD [26–29]. The results for BBD are shown in Table 1.

Multivariate regression analysis of the empirical data generated the following quadratic equation:

$$\%E = 95.90 + 1.72\times X_1 + 3.32\times X_2 + 0.58\times X_3 - 0.52\times X_1\times X_2 - 0.28\times X_1\times X_3 + 0.93\times X_2\times X_3 - 5.06\times X_1^2 - 8.16\times X_2^2 - 7.61\times X_3^2 \qquad (2)$$

Experimentally designed data were analysed using multiple regression through the least square method. The significance of the regression coefficients was also tested by F-test [24]. The results were analysed, the analysis of variance (ANOVA) is presented in Table 2. The quality of fit of the polynomial equation was expressed with the coefficient of determination (R^2). The effect and regression coefficients of linear, quadratic, and interaction terms were determined. The quadratic models and response surfaces were generated for each response [26].

The extraction efficiency values predicted from Eq. (2) were almost close to the linearity in the normal probability plot (Fig. 2) which indicated the best fit. Hence, this quadratic polynomial equation was deemed to be fit for this set of extraction experiments.

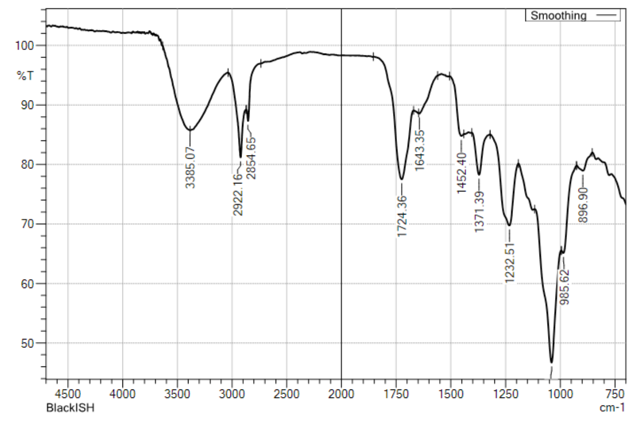

Fig. 1. The FT-IR spectra of saponin.

Table 1
BBD matrix for extraction efficiency of norfloxacin

Saponin concentration (g/100 mL)	Norfloxacin concentration (mg/L)	NaOH concentration (M)	$\%R_{act}$	$\%R_{pred}$	
				RSM	ANN
0.01	25	0.5	77.2	76.8	77.2
0.03	25	0.5	81.9	77.6	81.2
0.01	75	0.5	84.5	84.1	84.5
0.03	75	0.5	87.1	87.6	87.1
0.01	50	0.25	80.8	80.9	80.8
0.03	50	0.25	84.6	83.7	84.6
0.01	50	0.75	82.4	82.1	82.4
0.03	50	0.75	85.1	89.3	85.2
0.02	25	0.25	76.9	77.3	76.4
0.02	75	0.25	82.1	81.9	82.1
0.02	25	0.75	76.3	77.2	76.3
0.02	75	0.75	85.2	84.4	85.2
0.02	50	0.5	95.9	95.9	95.9
0.02	50	0.5	95.9	95.9	95.9
0.02	50	0.5	95.9	95.9	95.9
0.02	50	0.5	95.9	95.9	95.9
0.02	50	0.5	95.9	95.9	95.9

Table 2
ANOVA results

Source	Coefficient estimate	F Value	p-value Prob > F
Model	95.90	1523.54	< 0.0001
Saponin concentration (X_1)	1.72	396.75	< 0.0001
NorfloXacin concentration (X_2)	3.32	1474.08	< 0.0001
NaOH concentration (X_3)	0.58	44.08	< 0.0001
$X_1 X_2$	–0.52	18.37	< 0.0001
$X_1 X_3$	–0.28	5.047	0.0002
$X_2 X_3$	0.93	57.04	< 0.0001
X_1^2	–5.06	1798.52	< 0.0001
X_2^2	–8.16	4675.53	< 0.0001
X_3^2	–7.61	4066.67	< 0.0001
Residual	–	–	–
Lack of Fit	–	–	–
CV	0.28	–	–
PRESS	6.72	–	–
R^2	0.9424	–	–
R^2_{adj}	0.9323	–	–
R^2_{prd}	0.9214	–	–

Probability less than 0.05 signifies the model coefficients are important. From Table 2, factors (X_1, X_2, X_3) and their interactions (X_1X_2, X_2X_3, X_1^2, X_2^2, X_3^2) were noteworthy. The value of probability of the model F value (1523.54) indicated that the selected quadratic polynomial model was significant [27]. The value of regression coefficient

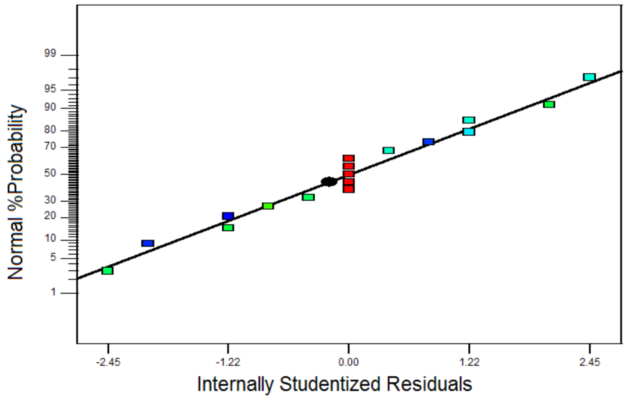

Fig. 2. Normal probability plot.

(0.9424) close to unity showed that predicted model coefficients were reasonable. The predicted R^2 (0.9214) and adjusted R^2 (0.9323) were in practical tuning with each other. Greater than 4 of adequate precision value specified an adequate signal [28]. Hence, the predicted quadratic models could navigate the design space to understand the factors interaction.

3.3. Significant interactions of ELM parameters

Contour and 3D plots were produced to get a clear picture about the interaction of the independent parameters and optimum conditions for the norfloxacin extraction [29]. The nonlinear nature of the contours suggested that the interaction between the parameters is significant and the optimum parameters cannot be found simply.

The 3D plots explaining the combined effect of the two selected parameters were generated for saponin assisted removal of norfloxacin from aqueous solution using ELM batch system and the shaded surface indicated the maximum extraction efficiency. Based on F value the process variable initial norfloxacin concentration (1474.08) and saponin concentration (396.75) had a higher effect on norfloxacin removal from aqueous solution, whereas NaOH (44.08) had least effect on norfloxacin removal.

3.3.1.Effect of saponin concentration

As the concentration of saponin increased the emulsion stability also increased due to the aid to emulsification [30,31]. From Figs. 3a and b, when there was an increase in the surfactant concentration, the rate of norfloxacin removal increased, whereas the rate of extraction decreased beyond a certain concentration. The higher dosage of saponin aided good dispersion of primary emulsion and intern increased the number of membrane globes which consistently increased the norfloxacin extraction rate.

3.3.2. Effect of initial norfloxacin concentration

It is inferred from Figs. 3b and c that, when the initial norfloxacin concentration increased it affected the norfloxacin removal efficiency positively. The higher initial concentration favored the driving force (concentration gradient)

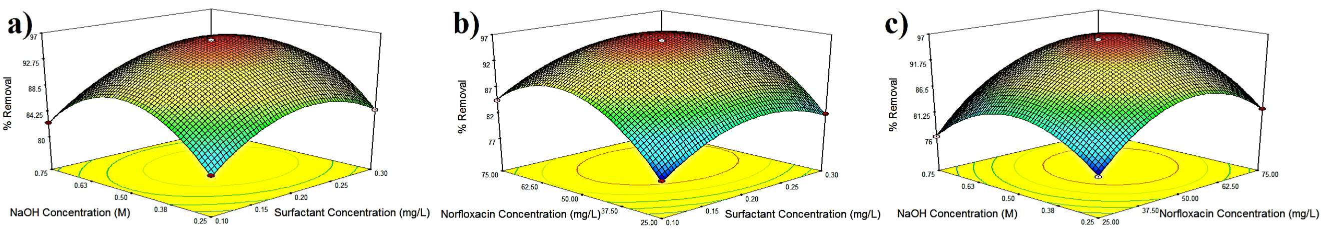

Fig. 3. Effect of process parameters of norfloxacin extraction.

across the ELM which enhanced the rate of transfer, subsequently resulted in increased extraction efficiency.

3.3.3. Effect of NaOH concentration

From Figs. 3a and c, as the NaOH concentration increased there was also an increase in the extraction efficiency. The internal stripping agent (NaOH) concentration created stress to the norfloxacin molecules which was present in the aqueous phase due to ionic potential. The ionic potential rose up when the NaOH concentration augmented up which subsequently resulted in the high extraction efficiency [32]. So the concentration of norfloxacin present in the membrane phase could be more than the external phase.

3.3. ANN modelling

In this study we developed ANN based model for norfloxacin extraction from an aqueous phase. The ANN model used in this study was Feed-forward networks (FFN) – Multilayer feed forward network and it was performed with 17 data points for norfloxacin extraction with 3 components as input data through the input layer – initial norfloxacin concentration (X_1), saponin concentration (X_2), and NaOH concentration (X_3). The Number of neuron present in the hidden layer was selected for ANN initially using trial and error method [33] by testing various algorithms, topology, and hidden layer. Neuron number were optimized for better result in order to select the optimal architecture based on the minimization of the error function - the mean square error (MSE).

The first trial informational collection were sorted into three subsets including training set (60% of the first exploratory informational collections), testing set (20% of the first test informational collections) and validation set (20% of the first trial informational collections). The reason for a part of the test information was to quantify the execution of the neural system for the expectation of concealed information, that was not utilized for preparing and to evaluate the speculation capacity of the ANNs. The optimum ANN architecture was taken as 3-8-1 (three neurons in the input layer, 8 in the hidden layer and 1 in the output layer) for norfloxacin extraction, by trial and error, when the mean square error (MSE) decreased gradually, and became constant [34].

The value of MSE obtained from the ANN was 0.0086 which was close to the acceptance limit for the MSE set to zero. The closeness of the training and testing errors validated the accuracy of the model. The correlation coefficient (0.9806) indicated that the goodness of fit between the experimental and predicated responses given by the ANN model. Since the R^2 for all the model was about equivalent to 1, it showed the significance of the model (Fig. 4). Along these lines, great, sufficient, higher estimation of R^2 of the ANN anticipated and trial runs proposed that the developed ANN could predict the norfloxacin extraction (Table 2 and Fig. 4). The ANN model for norfloxacin extraction was built utilizing the same data used by the RSM and hence it indicated that ANN was better than BBD. A parity plot was constructed to visualize the precision of the ANN model which is depicted in Fig. 5.

3.4. Comparison of ANN and RSM model

The study revealed that ANN model demonstrated good fit than BBD, as the predicted values were more close to the actual values of norfloxacin extraction. In statistics, the parameters root mean square error (RMSE), mean absolute error (MAE), standard error percentage (SEP), mean percentage error (MPE) are error functions used to estimate the deviation of the developed models. Whereas chi square is a statistical test analyzing the goodness of fit between experimental values and those expected predicted value. Furthermore, coefficient of determination (R^2) explains how good the experimental data fits the developed models. From Table 3, it was confirmed from the lower values of these error functions of the ANN model that ANN was better than BBD model.

Higher precision of ANN can be recognized to its complete ability to predict the experimental values by empirical model prediction, though the RSM is limited to a second order polynomial condition. It was likewise apparent that the ANN did not require a standard test configuration to assemble the model. Additionally, from Fig. 6, it was clear that every one of the information predicted by the ANN was near the straight line, meaning that the ANN predicted better, compared with the RSM. In this way, the ANN based model was more flexible, and permitted to add new experiment values to assemble another reliable model. The execution of the model for foreseeing the norfloxacin extraction was observed to be very remarkable. In this way ANN works best for a non-linear structure, interaction higher than quadratic range and applicable both little and extensive experimental values.

4. Conclusions

The saponin assisted ELM technique was utilised for norfloxacin removal from aqueous solution by using amyl alcohol as a solvent phase. In this study we developed a BBD model to study the combined effect of the influencing

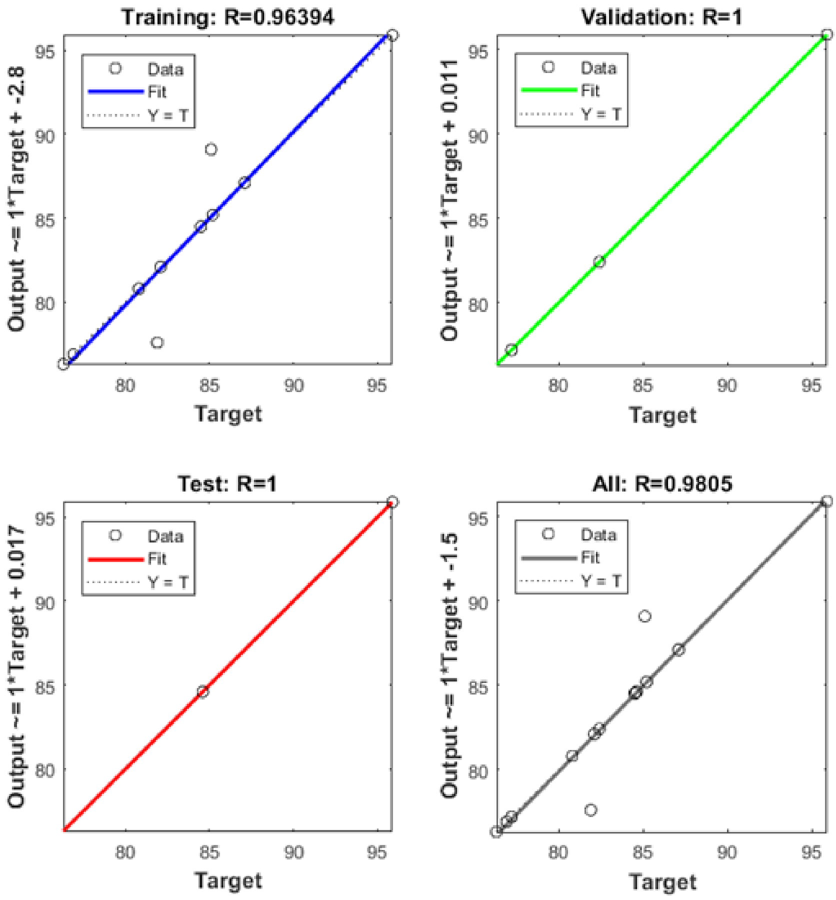

Fig. 4. ANN model prediction.

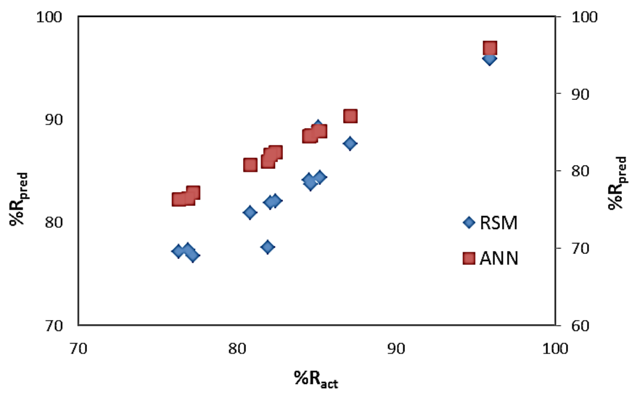

Fig. 5. Predicted extraction efficiency versus actual values.

process variables such as initial norfloxacin concentration (X_1), saponin concentration (X_2), and NaOH concentration (X_3) on norfloxacin removal using saponin assisted ELM. The individual and combined effect of each process variables were decoded from RSM 3D surface plots and model equation. Additionally, 3-8-1 ANN model was developed to predict the same and both the models were compared for the ability to predict norfloxacin removal from aqueous solution using saponin assisted ELM based on perfor-

Table 3
Comparison of statistical parameters for ANN and RSM models

Error	Function	RSM	ANN
RMSE	$\sqrt{\sum_{i=1}^{n}\left(\%E_{\exp}-\%E_{pre}\right)^2 / n}$	0.23	0.11
MAE	$\frac{1}{n}\sum_{i=1}^{n}\left\|\%E_{\exp}-\%E_{pre}\right\|$	0.11	0.09
SEP (%)	$\frac{RMSE}{\%E_{\exp}}\times 100$	1.38	1.16
MPE (%)	$\frac{100}{n}\sum_{i=1}^{n}\left\|\frac{\%E_{\exp}-\%E_{pre}}{\%E_{\exp}}\right\|$	2.25	1.76
Chi square	$\sum_{i=1}^{n}\frac{\left(\%E_{\exp}-\%E_{pre}\right)^2}{\%E_{\exp}}$	0.10	0.02
R^2	$\sum_{i=1}^{n}\frac{\left(\%E_{\exp}-\%E_{pre}\right)}{\left(\%E_{\exp}-\%E_{pre}\right)^2}$	0.9424	0.9806

mance measures (P value, F value, adjusted R^2, predicted R^2, adequate precision, lack of fit) and error functions (RMSE, MAE, SEP, and MPE). The optimal conditions for ELM were found to be: initial norfloxacin concentration 67.65 mg/L, saponin concentration 0.21 mg/100 mL, and NaOH concentration 0.36 M and the extraction efficiency at these parameter settings would be 91.27%.

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