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Short communication

Application of artificial neural networks in optimizing the fatty alcohol concentration in the formulation of an O/W emulsion

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The purpose of this study was to optimize the concentration of a fatty alcohol, in addition to internal phase, for formulating a stable O/W emulsion, by using artificial neural networks (ANNs). Predictions from ANNs are accurate and allow quantification of the relative importance of the inputs. Furthermore, by varying the network topology and parameters it was possible to obtain output values that were close to experimental values. The ANN model's predictive results and the actual output values were compared. R^2 values depict the percentage of response variability for the model; R^2 value of 0.84 for the model suggested adequate modeling, which is supported by the correlation coefficient value of 0.9445.

Keywords: O/W emulsion, emulsifier, fatty alcohol, back propagation network, optimization, stability

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An emulsion is composed of several formulation factors and processing variables. Several responses relating to the effectiveness, usefulness, stability as well as safety must be optimized simultaneously. Hence, expertise and experience are required to design an acceptable emulsion for use in pharmaceuticals and also as cosmetics. The response surface method (RSM) has been widely used for selecting acceptable emulsions. However, prediction of pharmaceutical responses based on the second-order polynomial equation commonly used in RSM is often limited to low levels, resulting in poor estimation of optimal emulsions.

Artificial neural network is a learning system based on a computational technique that can simulate the neurological processing ability of the human brain. It can be applied to quantifying a non-linear relationship between causal factors and pharmaceutical responses by iterative training of data obtained from a designed experiment (1).

Compared to the classical statistical optimization techniques, such as RSM in the past decade, Artificial Neural Networks (ANNs) have been increasingly applied for the modeling of complex relationships between formulation parameters and their influence on the end product quality (2–4). Process validation is an important subject in the pharma-

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ceutical industry and the application of artificial neural networks has gained much interest in the field of pharmaceutical development and optimization of dosage forms (5, 6).

It is well known that in order to prepare an emulsion having a useful and persistent concentration of internal phase, the formulation has to include a third component, an emulsifier to bestow the required stability. Such emulsifiers may be associated with auxiliary emulgents and other agents for enhanced stability and elegance. Long chain alcohols are preferentially used as auxiliary emulsifiers in pharmaceutical as well as cosmetic products to achieve the desired consistency. Some studies have elucidated the stabilizing effect of fatty alcohol on O/W emulsions. Different mechanisms suggested for such stabilization are based on either the kinetics of droplet coalescence or the strength of liquid pseudocrystalline structure developed in the continuous aqueous phase (7, 8).

This study aims to identify the critical concentrations of fatty alcohol, its optimum volume share in O/W emulsions using ANNs and to develop a quantitative system that could serve as a guide for preparation of a stable emulsion.

EXPERIMENTAL

Materials

Liquid paraffin and sodium lauryl sulphate were purchased from High Purity Chemical, India. Lauryl alcohol (LA) was purchased from Amrut Industrial Products, India.

Preparation of emulsions

Emulsions were prepared as desplayed in Table I. Required amounts of sodium lauryl sulphate and lauryl alcohol were taken and dissolved in Milli Q water (Millipore, USA), and liquid paraffin, respectively. Both phases were then placed in a mixer (Sumeet SP-16, India) and the blend was subjected to mixing at a speed of 14,000 rpm for 2 minutes. The emulsions were left undisturbed for 24 hours to attain interfacial equilibrium and were then analyzed for their zeta potential, globule size and viscosity. Thereafter the emulsions were distributed for analysis at regular intervals and stored at 50 °C. The emulsions were prepared at seven different concentrations of fatty alcohol.

Each emulsion was prepared with a different emulsifier concentration. Fifteen vials, each containing 5 mL of emulsion, were kept for determination of zeta potential and particle size. A stoppered flask, containing 50 mL of emulsion, was kept for determination of

Table I. General formula of the emulsion

Ingredient	Quantity
Liquid paraffin (mL)	25
Sodium lauryl sulphate (g)	0.1
Lauryl alcohol (g)	0.00–10.00
Distilled water (mL)	q.s. to 100

specific conductance and rheological behavior. Test tubes containing 10 mL of each of the emulsions were kept for creaming analysis coupled with phase separation observation.

After distribution, all vials, stoppered flasks and test tubes were stored in a thermostatically controlled oven maintained at 50 ± 1 °C. At different time intervals, one vial representing each concentration was withdrawn and allowed to attain room temperature. Zeta potential and mean globule diameter of these emulsions were determined. Similarly, the stoppered flasks were also withdrawn along with other vials for determination of rheological behavior and specific conductance and all flasks were again placed in the oven to record the changes in rheological behavior and conductance of emulsions with time.

Evaluation of emulsions

Zeta potential. – A Zetasizer Nano ZS (Malvern, UK), was used for zeta potential measurements. About 1 mL of the sample was diluted to 100 mL with deionized water and the zeta potential was measured.

Particle size. – The microscopic method was employed for the determination of globule size using a microscope (Leica DME, Germany). 2–3 drops of the emulsion were diluted to 100 mL using deionized water. After selecting random fields 100 globules were screened for their diameters and from this the average globule size was calculated.

Conductance. – Conductivity of the emulsions was measured using a Cyberscan Con11 (Eutech Instruments, Singapore). The electrode was rinsed with de-ionized water and dried. The electrode was dipped in the sample taking care to ensure that the liquid level was above the upper steel band. The electrode was stirred gently and then the reading was noted.

Viscosity. – Apparent viscosity was measured using a viscometer (Brookfield LVT DV-II, USA). Spindle CP-40 with cone angle 0.8° and cone radius of 24 mm was used. 0.5 mL of the sample was used for the measurement.

Experimental design for ANN modeling

Data were modeled using the PC software package, NeuroShell® 2 release 4 (Ward Systems Group, Fredrick, USA). The neuro shell system uses a three layer Black propagation network, a universal architecture with the ability of generalizing on a wide variety of problems. It presets network parameters such as the learning rate, momentum, and the number of hidden nodes.

Training of the networks

Networks were trained using the delta rule back-propagation of errors (DBP). The term »back-propagation« refers to the process of propagating error information backwards from the output to hidden neurons, during which connection weights are modified by the delta learning rule (9). The gradient descent method was used to minimize the error. Each network was trained using new random sets of initial weights and each cycle con-

sisted of 1,000 iterations. The lowest Mean Square Error (MSE) was selected as the training end point for all networks. The training process stops when the correlation coefficient of the test data starts to decrease, indicating that the network is becoming over-trained.

The working data set from the experimental data was randomly divided into training (80 %) and testing (20 %) data sets before running the training. During training, the ANN performance was evaluated with a testing data set. The training set was used to train the network, and the testing set was used to determine the level of generalization produced by the training set and to monitor the overtraining of the network.

Twenty-nine variables of lauryl alcohol concentration and time in days were considered as input data and the properties of their respective emulsions such as the particle size, zeta potential, conductance and viscosity were considered as outputs in the training stage for analysis by the ANN.

Model validation

Eight points, different from the training data, were used to validate the system. For an unbiased estimate of the generalization error, the ANN was represented by a validation data set that was not used at all during the training process. This was used to validate the developed model and evaluate its prediction abilities. The rest of the data was used as a working data set. The differences between the network output and target values of the validation data set were monitored, and the training was stopped when these differences reached a minimum.

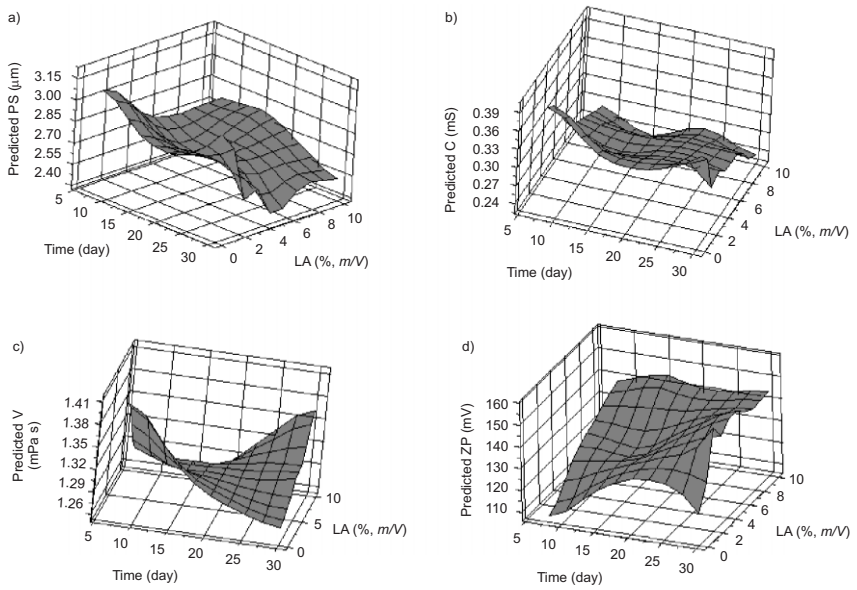

Fig. 1. Surface plot: a) predicted particle size, b) predicted conductance, c) predicted viscosity, d) predicted zeta potential, as a function of concentration of LA (m/V) and time in days.

RESULTS AND DISCUSSIONS

Changes in zeta potential (*ZP*), viscosity (*V*), conductance (*C*), particle size (*PS*) of lauryl alcohol stabilized O/W emulsions, with different phase volume ratios during ageing at 50 °C for fifteen days, are reported (Table II). These input-output sets were used as tutorial data to train the ANN model. The patterns were tuned using a hybrid

*Table II. Changes in zeta potential (*ZP*), viscosity (*V*), conductance (*C*) particle size (*PS*) of lauryl alcohol (*LA*) stabilized O/W emulsions with different phase volume ratios during ageing at 50 °C*

LA (%, *m*/*V*)	Time (day)	Particle size (μm)	Conductance (mS)	Apparent viscosity (mPa s)	Zeta potential (mV)
0.01	1	3.18	0.32	1.381	111.07
0.01	2	3.33	0.35	1.304	116.66
0.01	4	3.44	0.4	1.242	107.46
0.01	8	3.44	0.48	1.258	119.81
0.1	1	3.37	0.34	1.381	102.08
0.1	2	3.11	0.38	1.304	120.89
0.1	4	3.26	0.39	1.288	108.41
0.1	15	3.26	0.40	1.258	120.00
0.5	1	2.95	0.36	1.396	108.08
0.5	2	2.92	0.39	1.304	116.85
0.5	4	2.94	0.40	1.319	115.29
0.5	8	2.88	0.40	1.381	113.69
0.5	15	3.16	0.40	1.258	111.11
1.0	1	2.71	0.27	1.473	120.91
1.0	4	2.88	0.31	1.304	123.43
1.0	8	2.88	0.32	1.381	112.21
1.0	15	2.82	0.32	1.227	138.42
2.0	1	2.61	0.26	1.442	143.34
2.0	2	2.79	0.28	1.365	118.17
2.0	4	2.58	0.29	1.204	108.08
2.0	8	2.73	0.30	1.396	116.76
2.0	15	2.67	0.30	1.288	131.38
5.0	1	2.46	0.24	1.442	115.90
5.0	2	2.46	0.26	1.349	123.43
5.0	4	2.56	0.28	1.320	105.91
5.0	8	2.42	0.28	1.381	120.59
10.0	1	2.34	0.21	1.457	132.37
10.0	4	2.47	0.24	1.306	123.11
10.0	8	2.46	0.24	1.381	106.83

system that contained a combination of the back-propagation and least-squares-type methods. Models developed were evaluated by the correlation coefficient (r) of prediction; the excellent average correlation coefficient, $r = 0.9445$, resulted from the comparison of the ANN output and the corresponding experimental data. Statistical parameters of the learning performance of the neural model are summarized in Table III. The ANN--predicted (pred) particle size, conductance, zeta potential, and viscosity are shown in Fig. 1 as a function of the lauryl alcohol concentration (LA) and time in days. As can be seen from the surface plots (Fig. 1), the relationships between the inputs and the outputs of the resultant emulsion have a complex and non-linear nature which justifies the use of ANNs to identify complex relationships between causal factors and measured responses, when they cannot be expressed by any known regression equation. The validation data points and their respective predicted values IV) show good correlation, $R = 0.964–0.998$. Even with a few inputs, the ANN has resulted in successful prediction of zeta potential, particle size, conductance and viscosity. Consequently, the repetition of experiments involved in the Factorial Design and Response Surface Methodology and the low efficiency

Table III. Statistical parameters for the learning performance of the neural model

Statistical Parameters	Values
R^2	0.8425
r^2	0.8920
Mean squared error	0.016
Mean absolute error	0.093
Min. absolute error	0.003
Max. absolute error	0.328

R^2 – coefficient of multiple determination
r^2 – coefficient of determination

*Table IV. Validation data points of zeta potential (*ZP*), viscosity (*V*), conductance (*C*) particle size (*PS*) used in ANN and the corresponding predicted values*

LA (%, *m/V*)	Time (day)	*PS* (μm)		*C* (mS)		*V* (mPa s)		*ZP* (mV)	
		Actual	Predicted	Actual	Predicted	Actual	Predicted	Actual	Predicted
0.1	8	3.11	3.10	0.395	0.398	1.411	1.409	107.38	108.55
0.5	30	3.06	3.18	0.405	0.384	1.258	1.272	116.11	116.51
1.0	30	3.17	3.01	0.325	0.357	1.289	1.275	131.13	130.80
2.0	30	2.51	2.57	0.305	0.287	1.289	1.284	154.41	154.41
5.0	15	2.63	2.65	0.280	0.282	1.304	1.300	126.12	124.28
5.0	30	2.43	2.42	0.285	0.287	1.304	1.311	150.46	150.57
10.0	30	2.52	2.53	0.240	0.239	1.365	1.363	144.26	144.29
10.0	15	2.80	2.79	0.235	0.233	1.258	1.259	143.27	144.49

due to weak optimization procedures based on the second-order polynomial equations could be waived by adopting a properly trained ANN (9, 10).

Validation experiments show that the value predicted by the ANN is in good agreement with the experimental one since the absolute error is 0.003–0.328. It also justifies the lowest Mean Square Error (MSE) selected as the training endpoint for all networks and the number of hidden neurons selected.

CONCLUSIONS

Our results show that ANN modeling of pharmaceutical formulations could be successfully used to predict the particle size, zeta potential, conductance and viscosity and hence the stability of the O/W emulsions. It could provide better prediction ability in many case-study optimizations of pharmaceutical emulsions. The neuro-fuzzy model will boost its ability to gain a better understanding of the essential components of emulsifier concentration, which could contribute to ideal modeling of pharmaceutical emulsions.

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S A Ž E T A K

Primjena umjetnih neuralnih mreža u optimiranju koncentracije viših alkohola u izradi emulzije ulje/voda

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Cilj rada bio je pomoću umjetnih neuralnih mreža (ANNs) optimirati koncentraciju viših alkohola kao unutarnje faze za pripravu stabilnih emulzija ulje/voda. Rezultati ANN predviđanja su točni i omogućavaju kvantifikaciju ulaznih parametara. Nadalje, varirajući topologiju mreže i parametre moguće je dobiti izlazne vrijednosti koje su blizu eksperimentalnih vrijednosti. Usporedbom rezultata ANN predviđanja i stvarnih izlaznih vrijednosti dobiveni su visoki koeficijenti korelacije (R^2 = 0,84 i r^2 = 0,9445).

Ključne riječi: emulzija ulje/voda, emulgator, viši alkohol, mreža s povratnom propagacijom pogreške, optimizacija, stabilizacija

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