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Research Paper

Adaptive Neuro-Fuzzy Modeling of Poorly Soluble Drug Formulations

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Purpose. The purpose of this study was to evaluate the efficiency of a neuro-fuzzy logic-based methodology to model poorly soluble drug formulations and predict the development of the particle size that has been proven to be an important factor for long-term stability.
Methods. An adaptive neuro-fuzzy inference system was used to model the natural structures within the data and construct a set of fuzzy rules that can subsequently used as a predictive tool. The model was implemented in Matlab 6.5 and trained using 75% of an experimental data set. Subsequently, the model was evaluated and tested using the remaining 25%, and the predicted values of the particle size were compared to the ones from the experimental data. The produced adaptive neuro-fuzzy inference system-based model consisted of four inputs, i.e., acetone, propylene glycol, POE-5 phytosterol (BPS-5), and hydroxypropylmethylcellulose 90SH-50, with four membership functions each. Moreover, 256 fuzzy rules were employed in the model structure.
Results. Model training resulted in a root mean square error of 4.5×10^{-3}, whereas model testing proved its highly predictive efficiency, achieving a correlation coefficient of 0.99 between the actual and the predicted values of the particle size (mean diameter).
Conclusions. Neuro-fuzzy modeling has been proven to be a realistic and promising tool for predicting the particle size of drug formulations with an easy and fast way, after proper training and testing.

KEY WORDS: adaptive neuro-fuzzy inference system (ANFIS); formulation development; neuro-fuzzy modeling; particle size; poorly soluble drugs.

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ABBREVIATIONS: ANFIS, adaptive neuro-fuzzy inference system; ANN, artificial neural network; BPS-5, PEG-5 soy sterol; EDM, empirical-data-based model; FD, factorial design; FL, fuzzy logic; HPMC, hydroxypropylmethylcellulose; $In_j^i(k), j = 1, 2, \ldots, N_i; k = 1, \ldots, M_i, i = 1, 2$, denotes the experimental phase, i.e., FD ($i = 1$) or RSM ($i = 2$), M_i is the number of available data per causal factor, N_i is the number of causal factors per experimental phase i, $In_j^i(k)$ denotes the value of the causal factor j for the ith experimental phase and the kth experiment; IT, infusion technique; $M_{25\%}$, the 25% of the available samples per causal factor denoting the size of the testing vector; $M_{75\%}$, the 75% of the available samples per causal factor denoting the size of the training vector; OXC, oxcarbazepine; PIDS, polarization intensity differential scattering; $PS^i(k)$, $k = 1, \ldots, M_i$, the particle size estimated at the ith experimental phase and the kth experiment; $PS_{ANFIS}(k)$, $k = 1, \ldots, M_{25\%}$, the particle size estimated by ANFIS for the kth experiment that belongs to the testing vector; $PS_{ANN}(k)$, $k = 1, ..., M_{25\%}$, the particle size estimated by ANN for the kth experiment that belongs to the testing vector; RMSE, root mean-square error; RSM, response surface methodology.

INTRODUCTION

The development of pharmaceutical formulations depends on several factors and process parameters. The response variables relating to effectiveness, safety, and usefulness must be optimized through a factorial relationship by combining the causal factors. However, this effort addresses a multiobjective optimization problem since it has to circumvent many difficulties in the quantitative approach, like the understanding of the actual relationship between causal factors and individual pharmaceutical responses or the prediction of those formulations that are desirable for as many as possible drug properties.

Due to the complex nature of the development of pharmaceutical formulations, some computer-based optimization techniques have been proposed in the literature. Among them, factorial design (FD) and response surface methodology (RSM) are the most widely used, and several research efforts have adopted either FD followed by an RSM (1–3) or solely RSM (4–7). FD is a technique that contributes to the structure of the data collection process. Through a designed experiment, FD is capable of characterizing the relationships between process factors and responses and of distinguishing between important and unimportant factors. Nevertheless, it is obvious that FD has no prediction possibilities of the best formulation. Regarding the RSM procedure, it consists of (a)

composite statistical experimental designs that prepare systemic model formulations, (b) modeling among factors and response variables of these formulations, (c) parameter prediction by predicting the final responses (8–11) or by keeping them in the desired ranges needed to be obtained (12) using a polynomial multiple regression analysis, and (d) mathematical optimization algorithms for deciding the best formulation under a set of constrained equations. However, the prediction effectiveness of RSM is often restricted to low levels since it is based on second-order polynomial equations and one dependent variable (13–15), and thus, it frequently results in poor estimation of optimal formulations. As a result, a multiobjective simultaneous optimization technique, which incorporates an artificial neural network (ANN), has been proposed to overcome the shortcomings in RSM (13–15). ANN is a learning system that simulates the neurological processing ability of the human brain (16), and it has successfully been applied to address various pharmaceutical research problems (16), achieving more accurate predictions than those predicted by polynomial equations (14).

In this work, an extension to the ANN-based optimization technique is introduced based on neuro-fuzzy modeling. The concept of neuro-fuzzy models has emerged in recent years as researchers have tried to combine the transparent, linguistic representation of a nonlinear system with the learning ability of ANNs. The adopted neuro-fuzzy model consists of an adaptive neuro-fuzzy inference system (ANFIS) (17), which combines ANNs with fuzzy logic (FL) (18) to model nonlinear complex problems such as the optimization of pharmaceutical formulations. FL is a powerful tool that has been successfully used in many signal processing fields like system modeling and control, pattern recognition, detection, denoising, and prediction (19,20). Unlike the Boolean logic, FL allows the input and output values to a fuzzy inference model to belong to multiple sets, with different degrees of membership in each set defined by a particular membership function (18). This facilitates the idea that a nonlinear system can be approximated by softly merging locally linear systems, avoiding discontinuities if the system state moves from one local model to another (21). This fuzzy transition is achieved using the membership functions to calculate the validity of the different local models for a certain state (22). The resulting structure of the fuzzy system has the appearance of a network; hence, the learning methods of an ANN can be easily applied to form a neuro-fuzzy model with favorable characteristics.

The usefulness and reliability of the proposed neuro-fuzzy approach are examined through the drug formulation optimization with respect to its particle size. It is estimated that about 40% of active substances during formulation development by the pharmaceutical industry are poorly water soluble (23–25). For substances like oxcarbazepine (OXC), which are classified by the Biopharmaceutics Classification System as a class II active pharmaceutical ingredient (high permeability, low solubility), the dissolution of the drug substance is the rate-limiting factor to absorption. It is of importance for such substances to increase the dissolution rate and, thus, enhance absorption and bioavailability. This can be achieved when the poorly soluble drugs are formulated as nanoparticles. A broadly based technology applicable to this class of molecule is applied to improve the performance of the formulations by decreasing the particle size. A method based on infusion technique (IT) (26) is mainly used to produce nanoparticles. However, particle sizes below 500 nm are difficult to obtain. Thus, the introduction of a method for formulation optimization with respect to particle size is required. The objectives of this paper were to prepare nanoparticle formulations using the IT and then to develop a neuro-fuzzy model to accurately predict the particle size.

Experimental results proved the efficiency of the proposed neuro-fuzzy model to accurately predict the particle size since it exhibited a high correlation coefficient between its predicted values and the experimental ones. By using a limited number of inputs and with increased implementation simplicity, the proposed neuro-fuzzy model can provide rapid identification of the optimum formulation, contributing to the enhancement of the understanding of the phenomenon and the accurate assessment of the excipients in pharmaceutical industry.

MATERIALS AND METHODS

Chemicals

Acetone [puriss pro analysis American Chemical Society (p.a. ACS) > 99.5%] and propylene glycol were purchased from Sigma-Aldrich Chemie (Steinheim, Germany). PEG-5 soy sterol (BPS-5) and hydroxypropylmethylcellulose (HPMC), under the brand name Metolose 90SH-50, were purchased from Nikko Chemical Co., Ltd. (Tokyo, Japan) and Shin-Etsu Chemical Co., Ltd. (Tokyo, Japan), respectively. OXC as a model compound for a BCS class II substance was donated by Novartis Pharma A.G. (Basel, Switzerland).

Nanoparticle Formulations

The increase in bioavailability of poorly water-soluble drugs occurs when they are formulated as nanometer-sized drug particles with high surface area in accordance with the Noyes–Whitney equation (27):

$$\frac{\mathrm{d}Q}{\mathrm{d}t} = \frac{D}{h} S\left(\mathrm{C}_s - \mathrm{C}_g\right), \tag{1}$$

where the dissolution rate $\mathrm{d}Q/\mathrm{d}t$ expressed in terms of the change of drug concentration, Q, as a function of time, t, is directly proportional to the diffusion coefficient of the drug (D), the available surface area (S), and the difference between saturation solubility of the drug in the boundary layer (C_s) and concentration of drug in the bulk fluid (C_g).

Polymers, such as HPMC, were found to not only decrease the particle size by adsorption (28,29) on the hydrophobic drug surface but also inhibit crystallization (30) of several drugs. The control of crystal growth of the obtained particle size ensures formulation stability. HPMC shows high surface activity because of the high degree of saturation (DS) of the methoxyl and hydroxyprolyl groups. For these reasons, HPMC was chosen as the stabilizing agent combined with the surfactant BPS-5, which acts as an emulsifier.

The nanoparticle formulations were prepared by using the IT (26) based on a precipitation step. According to this

technique, a drug solution A precipitates with a polymeric solution B in which the drug is insoluble. The precipitation step took place under controlled conditions of infusion rate, stirring rate, and temperature. The methodology for obtaining nanoparticle formulations presents the following procedure:

1. Preparation of the homogeneous solution (A) composed of OXC and BPS-5 in the water-miscible solvents acetone and propylene glycol. The amount of HPMC 90SH-50 was dissolved in distilled water, forming a homogeneous polymeric solution (B).
2. By adding solution A to solution B, a dispersion was formed instantaneously. The drug solution (A) was infused rapidly (infusion rate, 250 mL/min) into the polymeric solution (B), assisted by a Millipore peristaltic pump (Millipore Corporation, Dedford, MA, USA). The temperatures of the drug and polymeric solutions were 50 and 20°C, respectively, whereas the stirring rate of the solution B was 1000 rpm. The obtained particle size distribution was dependent on a number of factors, including the choice of the solvents and the polymer.
3. Acetone was removed from the produced formulations using a Büchi rotavapor R-114 and a Büchi Vacobox B-177 (BÜCHI, Switzerland). Acetone removal occurred at 25°C and 200 mbar for 1 h.

Preparation of Nanoparticle Formulations Based on Experimental Design

A four-factor, two-level full FD was used for the optimization study. The model study consisted of 17 experiments (see Table I) and one center point. Analysis of the experimental data estimated linear effects and various combinations of interaction effects. The amounts of acetone, propylene glycol, PEG-5 soy sterol (BPS-5), and HPMC 90SH-50 were selected as the causal factors with ranges 3–5 mL, 1.5–2 mL, 0.3–0.5 g, and 50–100 mg, respectively, whereas OXC was kept stable (100 mg). The mean volume diameter of the drug substance particles was selected as the response variable.

Experimental Particle Size Analysis

The particle size was experimentally determined using diffraction of laser light. Sizing measurements were routinely performed using a Coulter LS 230 (Coulter Corporation, Miami, FL, USA). Size distribution and mean volume diameters were calculated using the Mie theory (31) in connection with polarization intensity differential scattering (PIDS; Beckman Coulter exclusive).

PIDS uses three wavelengths of light, filtered for polarization in the vertical and the horizontal planes. The combination of multiple wavelengths and two polarizations provides information that differentiates between submicron particle sizes and dramatically increases resolution. In particular, the PIDS assembly measures the particle size within the range of 0.04–0.4 μm. Each measurement consists of eight runs with 90 s run length.

Table I. Experimental Design of Oxcarbazepine (100 mg)

Formulation number	Acetone (3–5 mL)	PG (1.5–2 mL)	BPS-5 (0.3–0.5 g)	HPMC 90SH-50 (50–100 mg)	Size (mean diameter, μm)
1	3	1.5	0.3	50	0.540
2	5	2.0	0.5	50	0.599
3	3	2.0	0.3	100	0.478
4	3	1.5	0.5	100	0.681
5	3	2.0	0.5	50	0.876
6	3	1.5	0.5	50	0.975
7	5	2.0	0.3	50	0.625
8	3	2.0	0.5	100	0.648
9	5	2.0	0.3	100	1.054
10	5	1.5	0.5	50	0.932
11	4	1.75	0.4	80	0.616
12	5	1.5	0.5	100	1.176
13	5	1.5	0.3	100	0.828
14	5	1.5	0.3	50	0.945
15	3	2.0	0.3	50	0.515
16	3	1.5	0.3	100	0.594
17	5	2.0	0.5	100	1.052

Factors: acetone (3–5 mL), propylene glycol (1.5–2 mL), BPS-5 (0.3–0.5 g), HPMC 90SH-100 (50–100 mg). Response: particle size (mean volume diameter, in microns). Total volume: 13 mL; infusion rate$_{(org)}$: 250 mL/min; $T_{(aq)}$: 25°C; $T_{(org)}$: 50°C; pH: 7.

Neuro-Fuzzy Modeling

Neuro-fuzzy models belong to the category of empirical-data-based models (EDMs). These models rely on the fact that the intrinsic features of the observed interactions of a complex system and their mutual interrelations can be learned from the data using a great number of simultaneously cooperating simple processing units or operations. This approach allows the extraction of information (knowledge) from these low-level data into other forms that might be more abstract (32). EDMs that make use of fuzzy inference system (FIS), combined with adaptive networks, provide a neuro-fuzzy network that consists of nodes and directional links through which the nodes are connected. Part or all of the nodes are adaptive; hence, each output of these nodes depends on the parameters pertaining to this node. The learning rule specifies how these parameters should be changed to minimize a prescribed error measure (33). In a neuro-fuzzy network, the synergism of ANNs and FL manages to model the structure of complex systems by extracting the necessary knowledge from pairs of crisp input–output data. On the basis of the FL technology, the model can be linguistically described by means of input–output parameterized variables and well-defined IF/THEN rules. This human-perceived information is all encoded, at the mathematical level, by means of "fuzzy" representations, which do not pursuit precision. On the other hand, the ANN technology, by means of the precise input–output values, identifies the parameters involved in the model by training a generic model to adaptively approximate the relationship between the input–output data (34). Thus, by means of its structure, a neuro-fuzzy network manages to not only deal with the uncertainties of complex systems but also provide their model with a transparent and

interpretable structure. Furthermore, based upon this modeling, a neuro-fuzzy network manages to generalize; hence, it produces predictive outputs when presented with new "proper" input. The theoretical details of the neuro-fuzzy modeling can be found in (33,34). Moreover, a simplified introduction regarding the general issues of FL modeling, fuzzy sets, membership functions, and fuzzy clustering is provided in (19). However, relevant features and context that refer to the adopted means of neuro-fuzzy modeling, i.e., ANFIS (17), are described below.

ANFIS Structure and Implementation

The adaptive neuro-fuzzy inference system is expected to estimate the particle size (mean volume diameter) when presented with values of the four causal factors. To infer this response value, ANFIS is trained to evaluate the relation between the particle size and the four causal factors. However, this initially unknown relation is hidden within the empirical data that are obtained from the experimental particle size analysis (see previous section and Table I). Therefore, ANFIS training is an equivalent procedure to learning from empirical data. ANFIS adopts a five-layer, feed-forward network structure (17), as depicted in Fig. 1. During training, at each level, the parameterized nodes perform specific functions of the incoming signal, as follows.

Suppose, for simplicity, that ANFIS rule base contains two rules of Sugeno type (17) and is fed by two causal factors only:

R1: IF X is A_1 AND Y is B_1, THEN $f_1 = p_1X + q_1Y + r_1$; ELSE,
R2: IF X is A_2 OR Y is B_2, THEN $f_2 = p_2X + q_2Y + r_2$,

where X,Y correspond to any two of the four causal factors and A_i, B_i and p_i, q_i, and r_i, with $i = 1, 2$, are linguistic variables (such as "very low," "low," "medium," and "high") and constants, respectively (35). The ith node function of the first layer performs fuzzification of the incoming signal as follows (see also Fig. 1):

$$O^1_{X_i} = \mu_{A_i}(X), O^1_{Y_i} = \mu_{B_i}(Y), i = 1, 2, \tag{2}$$

where μ_{A_i}, μ_{B_i} denote the membership functions that specify the degree to which X and Y belong to the corresponding linguistic variables A_i and B_i, respectively. $O^1_{X_i}$ and $O^1_{Y_i}$ describe the X and Y causal factors, respectively, using fuzzy values (e.g., low or medium X; very low or high Y). The shape of the continuous and piecewise differentiable membership functions is described by parameters. These are the premise parameters and are adjusted by using the learning algorithm. Each node of the second layer O^2_i presents the firing strength of a rule, estimated by multiplying the incoming membership values of the previous layer:

$$O^2_i = w_i = O^1_{X_i} \cdot O^1_{Y_i}, i = 1, 2. \tag{3}$$

The ith node of the third layer O^3_i normalizes the firing strength of the rules:

$$O^3_i = \overline{w}_i = \frac{w_i}{w_1 + w_2}, i = 1, 2. \tag{4}$$

The node function at the fourth level is of the form:

$$O^4_i = \overline{w}_i f_i = \overline{w}_i (\, p_i X + q_i Y + r_i), i = 1, 2, \tag{5}$$

where $\{p_i,q_i,r_i\}$ are the consequent parameters. A single node constitutes the fifth layer, which computes the overall crisp output:

$$O^5_1 = \sum_i \overline{w}_i f_i = \frac{\sum_i w_i f_i}{\sum_i w_i}. \tag{6}$$

The overall development of ANFIS requires the following primary procedures:

1. *Data acquisition*. The experimental procedure provides the data of interest (both for the four inputs and the one output) as presented in Table I. In the cases of limited number of available data, the performance of ANFIS is enhanced by interpolating the experimental data.
2. *Definition of the training and testing data set*. From the overall input–output data, 75% are normally used for the

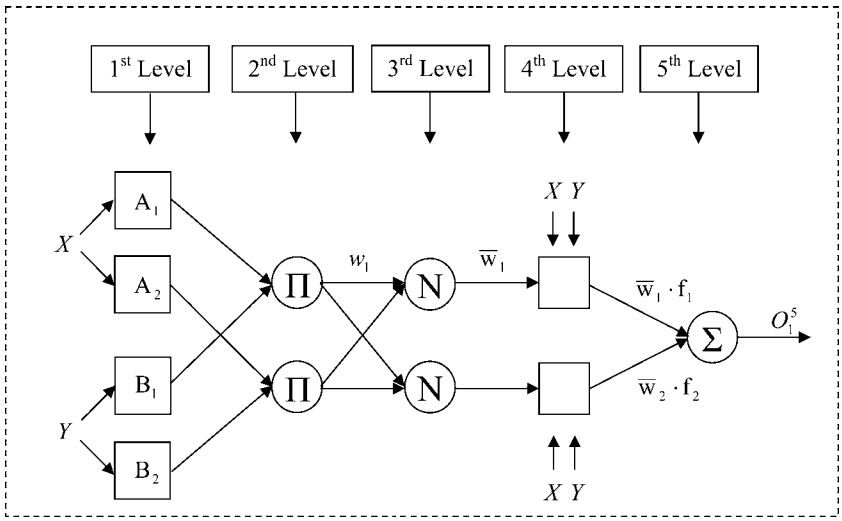

Fig. 1. The five-level organization of the ANFIS architecture (17).

training procedure, whereas the remaining 25% are used for model testing, as described below.

3. *Training procedure*. The input–output pairs are all presented to the system during ANFIS training. Learning is implemented in epochs to define the values of the premise and consequent parameters by minimizing the root mean square error (RMSE) (17). Each epoch foresees two passes: a forward pass of the signal, where the premise parameters are kept fixed and the consequent parameters are calculated by the least squares method, and a backward pass, where the consequent parameters are kept fixed and the premise parameters are updated by the gradient descent method (17).

4. *Testing procedure*. The testing data set is presented to the model, and the equivalent RMSE is calculated. When this value is within a predefined accuracy, the generalization ability of the model is verified. Such generalization is equal to prediction of the particle size that corresponds to a predefined set of values of the causal factors.

Figure 2 depicts the procedures followed for the particle size estimation when using FD followed by RSM (Fig. 2a) and ANFIS (Fig. 2b). From this figure, it is clear that ANFIS involves an iterative procedure to refine the membership functions and the fuzzy rules that better describe the mapping from the input space to the output space, without, however, requiring any new experimental phase. Once ANFIS is trained, it can immediately estimate the response for any value of the input pairs (Fig. 2b). On the other hand, FD usually requires the follow-up with the RSM experimental phase (Fig. 2a) to achieve an estimation of the optimized response. Moreover, the whole procedure should be restarted every time new values of the input pairs appear.

ANFIS was implemented using Matlab (Version 6.5, Release 13, 2003, The Mathworks, Inc., Natick, MA, USA). In particular, the Matlab Fuzzy Toolbox (35) was adopted as the means for building ANFIS. To this end, the data matrix was structured in the form of five columns, with the first four corresponding to the input vectors (the four causal factors) and the fifth one to the output vector (response). Before the analysis, the size of the training data set of Table I (12 samples per causal factor, corresponding approximately to 75% of the total 17 samples per causal factor) was increased up to 750 samples per causal factor, using cubic–spline interpolation (36). For each of the causal factor, four membership functions of a Gaussian-bell shape (35), uniformly distributed in their universe of discourse, and four linguistic variables, i.e., very low, low, medium, and high, were defined as the initial conditions of ANFIS, i.e., before the training procedure. The target RMSE for the training procedure was set to 0.005.

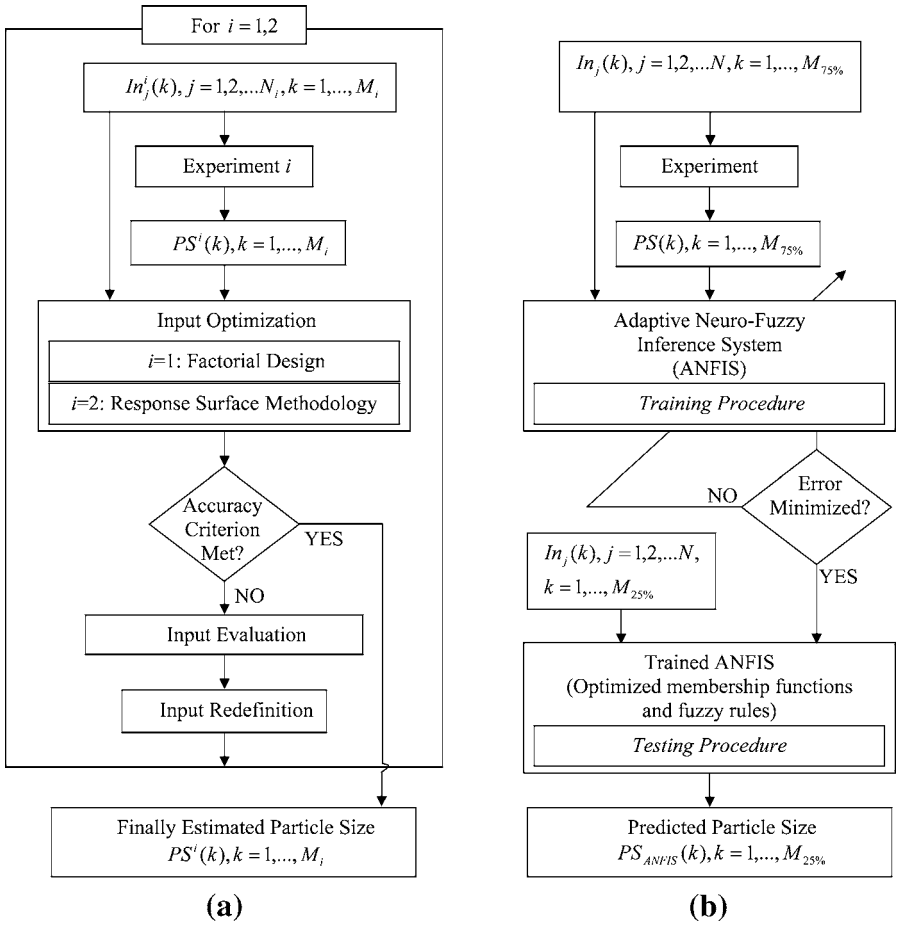

Fig. 2. A block diagram of the procedures followed for the particle size estimation when using (a) FD followed by RSM and (b) ANFIS (training and testing phases).

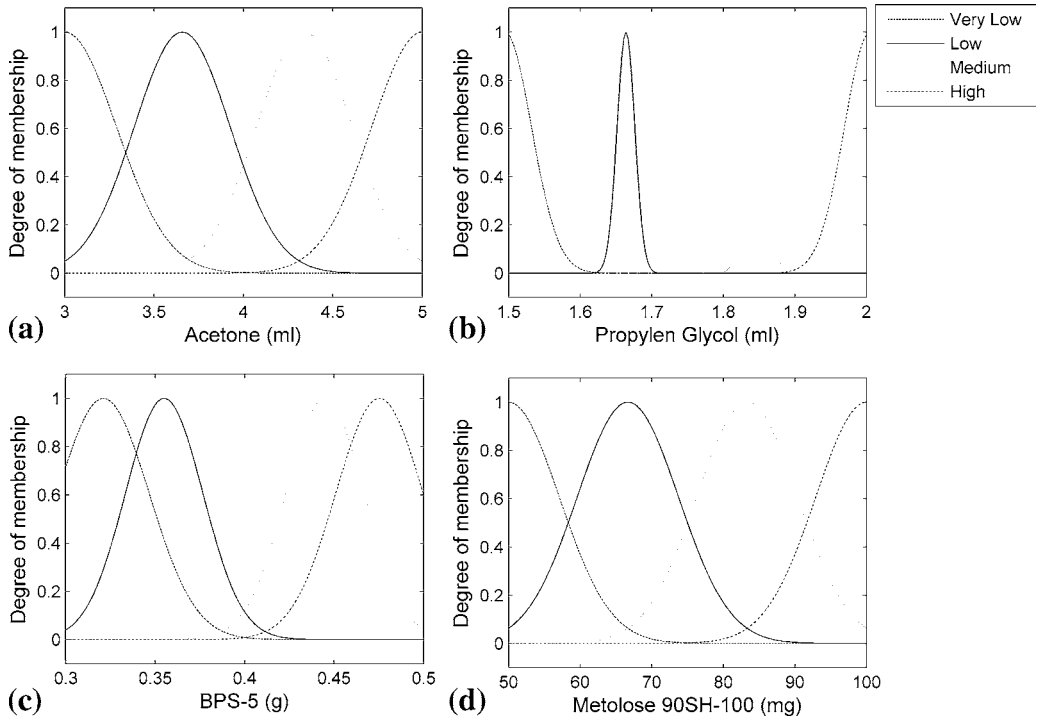

Fig. 3. The estimated membership functions of the trained ANFIS for each of the four causal factors, i.e., (a) acetone, (b) propylene glycol, (c) BPS-5, and (d) HPMC 90SH-100. In all cases, the solid, dashed, dotted, and dashed-dotted lines denote the linguistic variables very low, low, medium, and high, respectively.

RESULTS AND DISCUSSION

The experimentally derived particle sizes (mean volume diameter values) for a series of 17 experiments with different setting of the input pairs are presented in Table I (last column). Based on these data, the trained ANFIS has resulted in 256 fuzzy rules, exhibiting a training RMSE equal to 0.0045 (<0.005) with fast convergence (<250 epochs). The estimated membership functions for each of the four causal factors are illustrated in Fig. 3. From this figure, it is evident that the bell shape of the membership functions was preserved after training; however, the input–output relations have affected the uniformity of the membership functions across their universe of discourse, mainly for the case of propylene glycol (Fig. 3b) and BPS-5 (Fig. 3c).

For testing the efficiency of the trained ANFIS to accurately predict the particle size of unknown values of the four causal factors, the testing data set (5 samples per causal factor, corresponding approximately to 25% of the total 17 samples per causal factor) was presented to the model. The results of this testing procedure are presented in Fig. 4. From this figure, it is clear that ANFIS predicts the values of the particle size, i.e., $PS_{ANFIS}(k)$, $k = 1, ..., 5$, with high accuracy, when compared to the experimentally derived ones, i.e., $PS(k)$, $k = 1, ..., 5$. This is further justified by the excellent correlation coefficient, $r^2 = 0.99$, resulting from the comparison between the ANFIS output and the corresponding experimental data. These results denote that neuro-fuzzy modeling of pharmaceutical formulations could successfully be used to predict the particle size. In a similar optimization problem (14) that, however, did not involve the same factors and response variable, ANNs showed smaller prediction efficiency than the one exhibited by ANFIS here.

To directly compare the performance of ANNs with the one from ANFIS, an ANN was set up, trained, and tested with the same data sets used for the ANFIS training and testing procedures, respectively. Similar to (4), an ANN with four causal factors (acetone, propylene glycol, BPS-5, and HPMC 90SH-50), one hidden layer with 12 neurons (three times the input number), and one response variable (mean volume diameter of the drug substance particles) was structured; a sigmoid

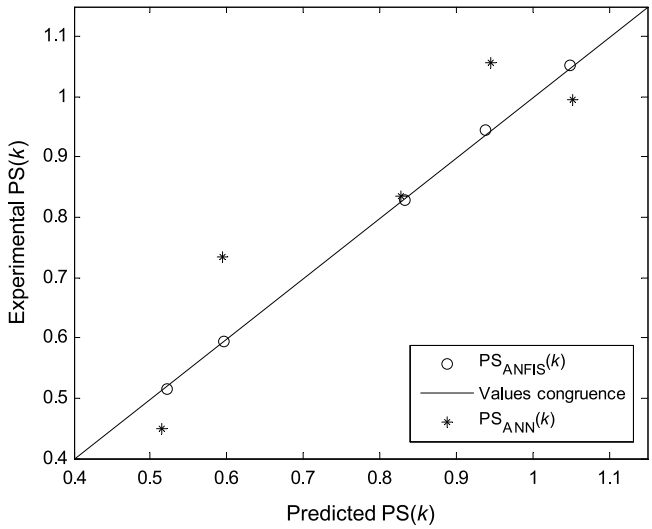

Fig. 4. Testing procedure results. The circles denote the plotting of the experimentally produced particle size values, i.e., $PS(k)$ with the ones predicted by the trained ANFIS, i.e., $PS_{ANFIS}(k)$, whereas the stars denote the plotting of $PS(k)$ with the particle size values predicted by the trained ANN, i.e., $PS_{ANN}(k)$. The solid line denotes the position of the congruence of the values ($x = y$).

function was used as the nonlinear function employed in the hidden layer, whereas a back-propagation training algorithm was applied for training the ANN. The latter refers to the Levenberg–Marquardt algorithm (37), which is a fast training algorithm for networks of moderate size (i.e., trains neural networks at a rate 10 to 100 times faster than the usual gradient descent back-propagation method) and has memory reduction feature for use when the training set is large (38). The target RMSE for the training procedure was set to 0.005, which was reached in 573 epochs. The ANN was built using the Matlab Neural Networks Toolbox (38).

After training, the ANN was tested for its prediction efficiency, resulting in the predicted values of the mean particle size, i.e., $PS_{ANN}(k)$, $k = 1, ..., 5$, superimposed on the plot of Fig. 4 (denoted with stars). From this figure, it is clear that ANN predicted less accurate (over-/underestimated) values of the mean particle size when compared both with the experimental ones (distance from the diagonal line) and those predicted with ANFIS (circles). This is further justified by the correlation coefficient, $r^2 = 0.84$, resulting from the comparison between the $PS_{ANN}(k)$ and $PS(k)$, $k = 1, ..., 5$.

The above results indicate that ANFIS, as a combination of ANNs with FL, increases the generalization efficiency of ANNs and could provide better prediction ability in many case-study optimization of pharmaceutical formulations.

Apart from its prediction efficiency, ANFIS reveals information about the system being modeled. This is evidenced by the three-dimensional diagrams of the response variable as a function of the causal factors (in pairs of two), as presented in Fig. 5. From this figure, it is apparent that nonlinear relationships between the causal factors and the response variable were well represented with response surface predicted by ANFIS. This complies with the general notion that the quantitative relationships between causal factors and response variables *in vitro* are thought to be complex and nonlinear (14). From the results of Fig. 5, it appears that ANFIS captures such relationships and could be used as a tool where approximations of such relationships are required.

Clearly, ANFIS structure allows the elimination of many experimental phases (see Fig. 2). Even with a few inputs, ANFIS has resulted in successfully predicting the particle size. Consequently, the repetition of the experiments involved in FD and RSM and the low efficiency due to the weak optimization procedures based on second-order polynomial equations could be waived by adopting a properly trained ANFIS. In this vein, future studies would include efforts to increase the number of compounds for which all input descriptors are available, to create a larger training data set that might better represent the data space; hence, an improved model, in terms of its generalization capability,

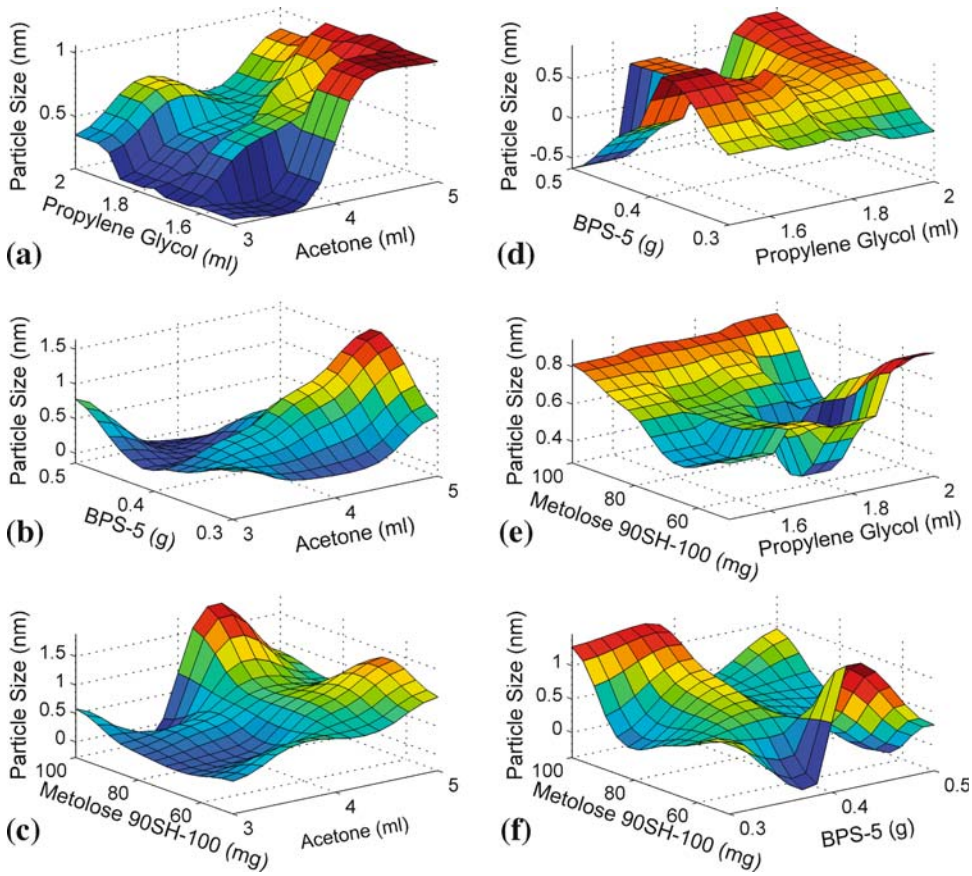

Fig. 5. Response surfaces of the response variable (particle size) predicted by ANFIS as a function of the four causal factors, i.e., acetone, propylene glycol, BPS-5, and HPMC 90SH-100, in pairs of two. The values of the two other causal factors remaining constant for a given surface response are the following: (a) BPS-5 = 0.4, HPMC 90SH-100 = 75; (b) propylene glycol = 1.75, HPMC 90SH-100 = 75; (c) propylene glycol = 1.75, BPS-5 = 0.4; (d) acetone = 4, HPMC 90SH-100 = 75; (e) acetone = 4, BPS-5 = 4; (f) acetone = 4, propylene glycol = 1.75.

could be achieved. Moreover, modifications in the input vectors of ANFIS will be considered toward the integration of experts' insight into the data structure. This is facilitated by the linguistic character of the fuzzy values of its variables. In this way, the neuro-fuzzy model will boost its ability to gain better understanding of the essential components of particle size, which could contribute to ideally model such drug formulations.

CONCLUSION

A neuro-fuzzy model, namely, ANFIS, has been proposed for the prediction of the drug particle size using four causal factors. The proposed scheme combines ANNs with FL, thereby increasing their generalization efficiency. After proper training and testing using experimental data, ANFIS results in a prediction of the particle size of higher accuracy than that of an ANN. Furthermore, ANFIS sheds light on the intrinsic relationships between the causal factors and the response variable, identifying their underlying complex and nonlinear aspects. With proper training and due to its feasible implementation, ANFIS can be used as a reliable tool for the prediction of the particle size and can contribute to the accurate evaluation of the excipients in pharmaceutical industry.

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