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ARTICLE

Prediction of Optimum Compositions of Parenteral Nanoemulsion System Loaded Low Solubility Drug for Treatment of Schizophrenia by Artificial Neural Networks

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Aripiprazole was encapsulated in the palm kernel oil esters nanoemulsion for the purpose of brain delivery via intravenous administration. High shear and high pressure homogenizers were applied for formulating low solubility drug in the nanoemulsion system and stabilized by different emulsifiers; lecithin, Tween 80 and glycerol. The artificial neural networks (ANNs) modeling of nanoemulsion formulation was carried out to achieve the minimum particle size. The effects of palm kernel oil ester (PKOE) (3-6%, w/w), lecithin (2-3%, w/w), Tween 80 (0.5-1%, w/w), glycerol (1.5-3%, w/w), and water (87-93%, w/w) amounts on the particle size were considered as inputs of the network trained. The particle size of samples in various compositions was measured as output. To obtain the optimum topologies, ANNs were trained by Incremental Back Propagation (IBP), Genetic Algorithm (GA), Batch Back Propagation (BBP), Quick Propagation (QP), and Levenberg-Marquardt (LM) algorithms for testing data set. The topologies were determined by the indicator of minimized root mean squared error (RMSE) for each algorithm. According to the results, the QP-5-4-1, GA-5-12-1, IBP-5-11-1, BBP-5-10-1, and LM-5-9-1 were selected as the optimized topologies. It was found that the optimal algorithm and topology were the quick propagation and the configuration with 5 inputs, 4 hidden and 1 output nodes, respectively. Conclusively, ANN models were developed for the prediction of particle size of nanoemulsions loaded with aripiprazole and stable nanoemulsion system which could be used effectively for intravenous administration.

Introduction

Schizophrenia is a serious, chronic and debilitating mental illness for which most patients require long term treatment with antipsychotic treatment.[1] This mental illness is characterized by positive symptoms (e.g., hallucinations, delusions and deranged thoughts), negative symptoms (e.g., loss of motivation, restricted emotional experience, poverty of speech) and cognitive impairment. The first hypothesis formulated that could explain the pathophysiology of this mental illness, is namely the "dopamine theory", which attributed prominent role to dopamine system dysregulation. In recent years, a medication (aripiprazole) has received a growing attention to treatment of schizophrenia.[2-5]

Schizophrenia disease is mostly related to Central Nervous System (CNS) in the body. All organisms with a well-developed CNS have a blood–brain barrier (BBB) [6]. BBB acts as a barrier to prevent any macromolecules from entering the brain cell.[7]

Aripiprazole is regarded as a third generation antipsychotic drugs (APD) with excellent therapeutic efficacy in controlling schizophrenia symptoms and a low incidence of extra-pyramidal side effects (EPS) and weight gain side effects.[8-11]

Aripiprazole possessed poorly-water soluble characteristics in the form of salt. To ensure that it can reach the target cell effectively, a higher dosage of aripiprazole is needed. But, in some clinical practice, higher dosage of aripiprazole can cause some side effects.[12] A nanoemulsion-based aripiprazole carrier could improve the solubility of the drug in the dispersed phase and drug penetration into blood–brain barrier (BBB) and target cells due to its extremely small size. Thus, a smaller dosage of aripiprazole is preferred to reduce its side effects. For enhancing the poorly-water soluble molecule's dissolution rate, the surface area is purposely increased by reducing the particle size of drug molecule. The performance can extremely affected by increasing the surface area.[13] In this context, the development of new drug nanodelivery systems to increase drug bioavailability and reduce adverse effects has been claimed as a good option.

An emulsion is consisting of a mixture of two immiscible liquids which is dispersed throughout the others. Water and oils is considered as its basic component which is

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required a surfactant to decrease the interfacial tension and maintain the stability of the emulsion. An emulsion can be prepared in the form of oil-in-water or water-in-oil.[14] Palm kernel oil esters (PKOEs) consist of higher amount of short chain esters compared to other oils. In pharmaceutical industry, palm kernel oil esters are used in the formulation because they can be a good carrier for active components. Due to its lower slip melting point and higher saponification value, palm kernel oil esters have unique properties for nanoemulsions and can be used in many applications such as cosmetics [15] and pharmaceutics.[16]

A nanoemulsion is thermodynamically stable transparent (or translucent) systems of oil, water, and surfactants, having a droplet size usually in the range of 20-200 nm.[17-18] It was proven that a very small particle size of emulsion can provide an effective encapsulation for delivery in system of the body.[19] Nanoemulsion represent as a good drug delivery and parenteral delivery due to their small nanometer size particles, biocompatibility, relative stability, ability to solubilize high quantities of hydrophobic compounds, ability to reduce the toxicity of drugs, and ability to protect drugs from hydrolysis and enzymatic degradation under physiological conditions.[20]

Nanoemulsions are classified as non-equilibrium systems. To form the nanoemulsion, the energy input from mechanical devices or from the chemical potential of the components is needed.[21] There are two emulsification methods that been used to make nanoemulsions. The first emulsification method is called dispersion or high energy emulsification method that used mechanical energy (such as high-pressure homogenization).[22] This method is widely used in industries to produce small and uniform droplet size of emulsions. The second emulsification method is low energy emulsification technique. This method consists on stepwise addition of one component to a mixture of the other components at constant temperature.[23]

In recent years, the artificial neural network (ANN) was introduced in pharmaceutical applications as an effective tool to solve complex multivariate non-linear relationships.[24-25] ANNs are artificial neurons to simulate the method which the biological neurons process information.[26] It consists of an interconnected group of neurons in modeling process to give prediction about the behavior of a given system, designing a new process and analyze existing processes. Moreover, this process can be done in a short period computing with high potential for adaptive performance of adequate quality.[27-30] In pharmaceutical research, ANN has been used successfully in the analysis and modeling such as forming the controlled release drug delivery systems, enhancing the understanding of the formation nanoemulsions and evaluation of the stability of nanoemulsions.[31]

In this work, optimization of the composition of nanoemulsion containing aripiprazole with respect to the amount of oil, lecithin, Tween 80, glycerol and water was carried out. The response which is particle size was studied to find the best model in ANN.

Methodology

Materials

Palm kernel oil esters (PKOEs) were synthesized in our laboratory through enzymatic transesterification of palm kernel oil and oleyl alcohol.[15] Pure soy bean lecithin (Lipoid S75) was purchased from Lipoid GmbH, Ludwigshafen, Germany. Glycerol was purchased from JT Baker, USA. Polysorbate 80 (Tween 80) was obtained from Fluka, Sigma–Aldrich Chemie GmbH, Germany. Aripiprazole was purchased from Laboratory & Scientific Enterprise, Malaysia. Water was deionized using a Milli-Q filtration system, Milipore, USA.

Determination of the solubility of aripiprazole in oil

The solubility of aripiprazole in the PKOEs was determined. Different amounts of drug were added into the oil containing lecithin (3%). The solutions were kept under moderate magnetic stirring for 24 h to reach equilibrium. The samples were then centrifuged at 4500 rpm for 15 min. The best amount of drug was observed 0.1% in the composition formulation.

Preparation of formulation of the emulsion using low shear rate emulsification

Emulsions were prepared via low shear rate stirring emulsification using an overhead stirrer (IKA® RW20 Digital, Nara, Japan) at 300-305 rpm. Aripiprazole (0.1%) was dissolved in the oil phase which is PKOEs (3.0-6.0%) containing lecithin (2.0-3.0%) as the surfactant. Tween 80 (0.5-1.0%) was then added into the oil phase as a co-surfactant after the aripiprazole was completely dissolved. The oil phase was added drop wise into the aqueous phase consisting of glycerol and was continuously stirred to form a coarse emulsion. The mixing of emulsions was carried out with a shear rate of 300-305 rpm for 3 hours.

Preparation of nanoemulsion by using high shear and high pressure homogenization

The prepared emulsion by low shear rate emulsification is homogenized using a high shear homogenizer (Kinematic Switzerland) at high speed (3500 rpm) for 15 minutes. The samples were further homogenized using a high-pressure homogenizer 1000 psi for 14 cycles. The final products were put into sample bottles.

Stability study

Freshly prepared samples were put in a container and it was stored in the refrigerator at ±5oC for nine months. To test the stability of the samples, the samples were centrifuged at 4500 rpm for 15 min. The samples were then observed to see if there were any precipitates formed.

Particle size measurement

The particle size distribution was measured by a diffusion method using dynamic light scattering (DLS) particle analyzer (Zetasizer Nano ZS, Malvern Instruments, Malvern, UK). The size distribution using a diffusion of scattered laser light by the

particles was measured. The measurement conducted using Photon Correlation Spectroscopy (PCS) principle.[32-33]

Transmission electron microscopy (TEM)

The particle size was also measured by transmission electron microscopy (Hitachi H7100, Japan). A formvar coated copper grid was placed on top of a drop of sample and leave in room temperature (25 ±0.5°C) for 5 minutes. The filled copper grid was stained for 2 minutes by using 2% phosphotungstic acid and air dried for measurement.

Experimental design

The modeling and optimizing of the nanoemulsions containing aripiprazole were carried out by NeuralPower software version 2.5.[28-29] In a mixture design where the composition is the factor of interest, the levels cannot be chosen arbitrarily. All fractions of the components must sum to unity.[34] As Table 1 shows, the total of 27 experiment points have been randomly divided into two data sets of training (20 experiments), testing (4 experiments), and validation set (3 experiments). The software facilitated the option of the randomization. The training and testing data sets were used to compare and ensure robustness of the network parameters, respectively. Moreover, the testing set was utilized to avoid over fitting by controlling errors.[35]

Table 1

The ANN description

Artificial Neural Networks (ANNs) are computer programs which are for stimulation of some roles in the human brain by using dissimilar learning algorithms. ANN possess the extraordinary information processing attribute of human brain such as nonlinearity, high parallelism, robustness, fault and failure tolerance, learning, capability to manage imprecise and distorted information, and their ability to generalize. ANN is able to manage multiple independent and dependent variables simultaneously in one model.[36] The effectiveness of the ANN model is shown when modeling non linear relationships between dependent and independent variables by using an approach which is similar to a 'black box'.[37] It is because the performance of the ANN model is not needed for the end user to have extended understanding. ANN model can predict and formulate optimization capabilities and also can update with new raw data. After the models are trained, the response for new experimental conditions can be predicted by using the ANN models.[31]

ANNs that contain input, hidden and output layers are mathematic free functionalization of the complicated practical process.[38] The layers which consist of several nodes, are connected by multilayer normal feed-forward or feed-back connection formula.[39] The hidden layer could be more than one parallel layer however the single hidden layer is universally suggested. The connection is that the nodes of particular layer are connected to the nodes of the next layer. The nodes are simple artificial neurons which simulate the behavior of biological neural networks.[40] The nodes of input layer are qualify by sending data via the special weights to the nodes of hidden layer and then to the output layer.[39, 41] The qualification is carried out by associated weights during learning process by well known learning algorithms.

The learning process

In the learning process, the weights are calculated by the weighted summation of received data from the former layer and transfer to next layer.[42] The number of hidden nodes is obtained by trial and error training calculation which is examined from one to n nodes. In the process, the output of the hidden nodes in turn, acts as input to final (output) layer's nodes which undergoes similar or different transformation. The universal learning algorithms are QP, IBP, GA, BBP and LM while the multilayer is the nodes' connection type.[43] The usual transfer function is the logarithmic sigmoid for both hidden and output layers that is bounded from (0–1).[29, 44] The sigmoid bounded area is used to normalize the input and output data that is provided by the software scaling. The scaled data are passed into the first layer, propagated to hidden layer and finally meet the output layer of the network. Each node in hidden layer or in output layer firstly acts as a summing junction which modifies the inputs from the previous layer using the following equation:

$$y_i = \sum_{j=1}^{i} x_i w_{ij} + b_j \quad (1)$$

where y_i is the input of the network to j node in hidden layer, i is number of nodes, x_i are the output of previous layer while w_{ij} are the weights of connection between the ith node and jth node. The bias associates with node j that is presented by b_j. The main aim of the process is to find the weights for minimizing the error of RMSE which is obtained from difference between network prediction and actual responses.

$$\mathrm{RMSE} = \left(\frac{1}{n}\sum_{i=1}^{n}(y_i - y_{di})^2\right)^{\frac{1}{2}} \quad (2)$$

where n is number of the points, y_i is the predicted values and y_{di} is the actual values. Therefore, the learning process with an algorithm is continued until finding the minimum RMSE which is called topology. To avoid random correlation due to the random initialization of the weights, learning of a topology is repeated several times. As a result, the topology with the lowest RMSE is selected to compare with other nodes' topologies.[45] Therefore, the topologies for the n numbers of hidden layer for the considered algorithms are obtained in same way. Finally the topologies of the algorithms are compared to select the provisional model by maximum R^2 (Eq.

(3)), minimum RMSE and average absolute deviation (AAD) (Eq. (4)),

$$R^2 = 1 - \frac{\sum_{i=1}^{n}(y_i - y_{di})^2}{\sum_{i=1}^{n}(y_{di} - y_m)^2} \quad (3)$$

$$AAD = (\frac{1}{n}\sum_{i=1}^{n}\frac{|y_i - y_{di}|}{y_{di}}) \times 100 \quad (4)$$

where n is the number of points, y_i is the predicted value, y_{di} is the actual value and y_m is the average of the actual values.

Results and Discussion

The topologies of the algorithms

The hidden layers are in between the input and output layers to provide a link between the input and output layers. The structure of the hidden layer was constructed by examining a series of topologies with varied node number from 1 to 15 for each algorithm which were QP, IBP, BBP, GA, and LM algorithms. In order to determine minimum value of RMSE as error function, the model learning was performed for testing data set. However, to obtain a best model, it was done by repeating 10 times for each node to avoid random correlation due to the random initialization of the weight.

To determine the optimized topology for each algorithm, the training was going through with the same steps for QP, IBP, BBP, GA and LM algorithms. The minimum value of RMSE was chosen among the 10 time learning repetition data for each node and plotted in graphs of minimum value of RMSE *versus* the nodes of the algorithms' hidden layer that shown in Figure 1.

Figure 1

In comparison of the best topology, one node of 15 topologies in each algorithm has been selected as the lowest RMSE. The selected topologies were 5-4-1, 5-11-1, 5-12-1, 5-10-1 and 5-9-1 for QP, IBP, GA, BBP and LM algorithms, respectively. As shown in Figure 2, the topology of QP-5-4-1 presented the lowest RMSE among the other topologies that chosen as the provisional model for the nanoemulsion containing aripiprazole composition.

The model selection

To train the neural networks in the multivariate optimization of reaction, gradient descent backpropagation algorithm in QP version was applied. The experimental data of mixture experimental design were divided into two sets: 20 of the data experiments were used as the training set, 4 of the data experiments were used as the test set and the remaining 3 data experiments were used as the validation set (Table 1).

ANN modeled the raw data and the best model is created to provide better quality predictions for particle size of nanoemulsions. RMSE, R^2, and AAD of the model for training and testing for particle size are shown in Table 2. To select the final model for the particle size of nanoemulsions, the values of RMSE, R^2 and AAD were relatively studied for the topologies of QP-5-4-1, BBP-5-10-1, IBP-5-11-1, GA-5-12-1 and LM-5-9-1. The best value of RMSE was chosen based on 10 repeated runs. As shown in Table 2, QP was at minimum of RMSE value which is 2.614 in comparison with the other algorithms. Therefore, the performance of QP with 5-4-1 topology was more effective than IBP, BBP, GA and LM algorithms.

Table 2

As the scatter plots depicted, in the comparison with other topologies, the topology of QP-5-4-1 has presented the R^2, 0.972 which is the best performance with minimum RMSE. Then, the performed results of the topologies were used to calculate RMSE, R^2 and AAD. To calculate the R^2, the prediction of the topologies and actual values of particle size were plotted for testing and training data set in Figure 2 and 3.

Figure 2
Figure 3

The network of QP-5-4-1

Figure 4 shown the schematic representation of a multilayer perceptron feedforward network of ANN based on QP consisting of 5 inputs, one hidden layer with 4 nodes and one output. It illustrated the structure of QP-5-4-1 topology as final model for nanoemulsion containing aripiprazole. The input layer with 5 nodes (PKOEs, lecithin, Tween 80, glycerol and water) is the distributor for the hidden layer with 4 nodes which were determined by learning process. The input data of hidden nodes are calculated by weighted summation (Eq. (5)). Then the output data of hidden layer are transferred to output layer (particle size) by using log-sigmoid function (Eq. (6)).

$$S = \sum_{i=1}^{nh}(b - W_i I_i) \quad (5)$$

where S is summation, b is a bias, I_i is the ith input to hidden neuron and W_i is the weight associated with I_i. The bias shifts the space of the nonlinearity properties.

$$f(x) = \frac{1}{1 + \exp(-x)} \quad (6)$$

where f(x) is the hidden output neuron. As a result, QP-5-4-1 topology was the best result used to determine the optimum and importance values of the input variables of the

composition of nanoemulsion containing aripiprazole to obtain the smallest particle size.

Figure 4

Model verification

Table 3 showed that three random formulations were prepared to validate the final model. Verification of the model was carried out to examine the adequacy of the predicted particle size. This result indicated good agreement between actual and predicted values.

Table 3

Optimization of compositions

Table 4 suggested the optimum formulation of nanoemulsion containing aripiprazole by the final ANN model. The smallest particle size (62.23 nm) was obtained by nanoemulsion composition of 3% of PKOEs, 2% of lecithin, 1% of Tween 80, 2.25% of glycerol, and 91.75% of water.

Table 4

Importance of the effective variables

Figure 5 showed that the importance percentage of input variables on particle size of nanoemulsions. Tween 80 content at 29.45% is the most important factor controlling the particle size, followed by water at 19.34%, glycerol at 18.57%, lecithin at 17.39%, and PKOE at 15.25%, respectively. The presence of Tween 80 was appeared to be most influential on the particle size. In the other hand, the effects of other variables such as water, glycerol, lecithin, and palm kernel oil esters were very strong on the particle size. As a result, none of the variables is neglect able in this work.

Figure 5

Morphological studies

Since the range of size normally expand over the capacity of any advanced instrument, the measurement of particle size must be taken at least with two corresponding techniques. Dynamic light scattering and transmission electron microscopy are the most recommended tools to measure the particle size which is lower than 1µm. Transmission electron microscopy was implemented to obtain confirmation about the DLS data and to gain more information about the shape and size of nanoemulsion oil globules. Figure 6 shows the particle size of nanoemulsion containing aripiprazole as determined by TEM. It was found that the average of particle size is smaller than 100 nm (between 65 nm - 80 nm) with almost spherical shape oil globules. It is shown that the particle shape is most likely corresponding to the results measured by dynamic light scattering (DLS).

Figure 6

Conclusion

The compositions of nanoemulsions containing aripiprazole such as PKOEs, Tween 80, lecithin, glycerol, and water as effective variables were modeled at different compositions by ANN to define the desirable particle size of nanoemulsion containing aripiprazole. In order to obtain the qualified network, the different five algorithms including QP, IBP, BBP, GA and LM were learned by using training and testing data sets. The results of the learning program were 5 topologies: QP-5-4-1, BBP-5-10-1, IBP-5-11-1, GA-5-12-1 and LM-5-9-1. The performance of the topologies was optimized by RMSE, AAD and R^2. The topology (QP-5-4-1) with the lowest RMSE was selected as provisional network of the composition of nanoemulsion containing aripiprazole. The importance of the variables was included Tween 80 content at 29.45% is the most important factor controlling the particle size, followed by water at 19.34%, glycerol at 18.57%, lecithin at 17.39%, and PKOE at 15.25%, respectively which show none of the variables is neglect able in this work. As conclusion, the ANN is efficient quantitative tool that is able to model the effective input variables to predict the desirable particle size of nanoemulsion containing aripiprazole.

Conflict of interest statement

The authors have declared no conflict of interest.

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Table Caption

Table 1. The experimental design that consists of training and testing data sets.

Table 2. The performance results of the optimized topologies.

Table 3. Validation set for nanoemulsion containing aripiprazole.

Table 4. Optimum compositions derived by ANN based on QP model for particle size of nanoemulsion.

Table 1.

Run No.	PKOEs (%)	Lecithin (%)	Tween 80 (%)	Glycerol (%)	Water (%)	Particle size (nm)	
						Actual	Predicted
Training Set							
1	6.00	3.00	0.50	1.50	89.00	124.97	127.67
2	6.00	2.00	1.00	3.00	88.00	87.62	87.62
3	4.50	2.00	0.75	2.25	90.50	86.55	86.56
4	5.25	2.50	0.63	1.88	89.75	103.43	103.44
5	6.00	2.00	1.00	1.50	89.50	86.18	88.34
6	3.00	2.50	0.50	1.50	92.50	81.35	81.35
7	3.00	2.00	0.50	3.00	91.50	84.43	84.43
8	6.00	3.00	0.50	1.50	89.00	130.37	127.67
9	6.00	2.00	1.00	1.50	89.50	90.48	88.34
10	3.00	2.00	1.00	2.25	91.75	66.20	64.22
11	6.00	3.00	1.00	2.25	87.75	89.59	89.59
12	3.00	3.00	0.50	2.25	91.25	81.39	81.39
13	3.00	2.00	0.75	1.50	92.75	71.56	71.56
14	6.00	2.00	0.50	2.25	89.25	124.57	124.57
15	3.00	3.00	1.00	1.50	91.50	65.25	65.25
16	5.25	2.75	0.88	2.63	88.50	89.07	89.07
17	4.50	2.50	0.75	3.00	89.25	87.12	87.12
18	4.50	3.00	1.00	1.50	90.00	80.26	80.26
19	3.00	3.00	1.00	3.00	90.00	65.55	65.55
20	4.50	2.00	0.50	1.50	91.50	106.13	106.14
Testing Set							
1	5.50	2.50	0.50	1.50	89.25	120.40	121.78
2	4.00	2.50	1.00	1.50	90.00	72.66	73.74
3	4.50	2.00	0.75	2.50	91.00	92.53	87.02
4	4.25	2.75	0.60	2.10	90.25	92.64	93.78

Table 2.

Learning algorithms	Architecture	Training Data			Testing Data		
		RMSE	R^2	AAD	RMSE	R^2	AAD
GA	5-12-1	4.639	0.940	4.114	2.822	0.993	2.631
LM	5-9-1	1.228	0.996	0.728	2.801	0.982	2.350
BBP	5-10-1	1.244	0.996	0.744	2.712	0.979	2.182
IBP	5-11-1	1.327	0.996	1.095	2.706	0.984	2.203
QP	5-4-1	1.228	0.996	0.730	2.614	0.972	2.402

Table 3.

Run No.	PKOEs (%)	Lecithin (%)	Tween 80 (%)	Glycerol (%)	Water (%)	Particle size (nm)	
						Actual	Predicted
1	3.75	2.00	0.75	2.50	91.00	76.73	78.76
2	4.25	2.25	0.50	2.25	90.75	96.18	98.49
3	4.50	2.50	0.60	2.10	90.30	98.04	96.13

Table 4

Methods	Optimal Compositions					Particle size (nm)		
	PKOEs (%)	Lecithin (%)	Tween 80 (%)	Glycerol (%)	Water (%)	Actual	Predicted	RSE%
ANN (QP)	3.00	2.00	1.00	2.25	91.75	62.23	64.38	3.34

Figure Captions

Figure 1. The selected RMSE *vs*. node number of the composition of nanoemulsion containing aripiprazole network's hidden layer for QP, IBP, BBP, GA and LM.

Figure 2. The scatter plots of the predicted particle size versus actual particle size for testing data set that show the performed R^2 of optimized topologies, QP-5-4-1, BBP-5-10-1, IBP-5-11-1, GA-5-12-1 and LM-5-9-1.

Figure 3. The scatter plots of the predicted particle size versus actual particle size for training data set that show the performed R^2 of optimized topologies, QP-5-4-1, BBP-5-10-1, IBP-5-11-1, GA-5-12-1 and LM-5-9-1.

Figure 4. The network architecture (5-4-1) of the multilayer normal feed-forward connection type for Quick Propagation algorithm which consists of 5, 4 and 1 nodes in input, hidden and output layer, respectively.

Figure 5. The relative importance of the particle size of nanoemulsion containing aripiprazole input variables of Tween 80, water, glycerol, lecithin and PKOEs.

Figure 6. TEM photomicrographs of freshly prepared aripiprazole loaded nanoemulsion. The scale bar represents 200 nm.

Fig.1

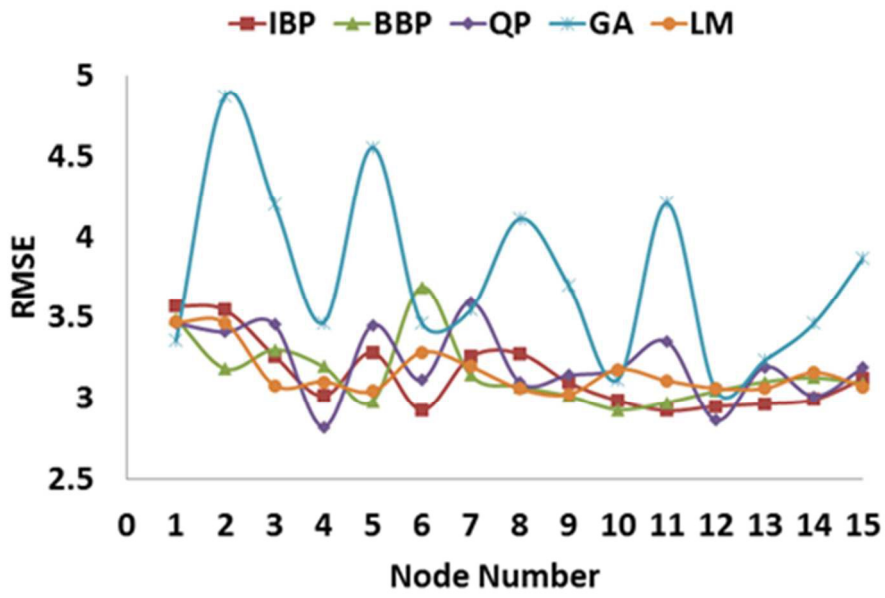


Fig. 2

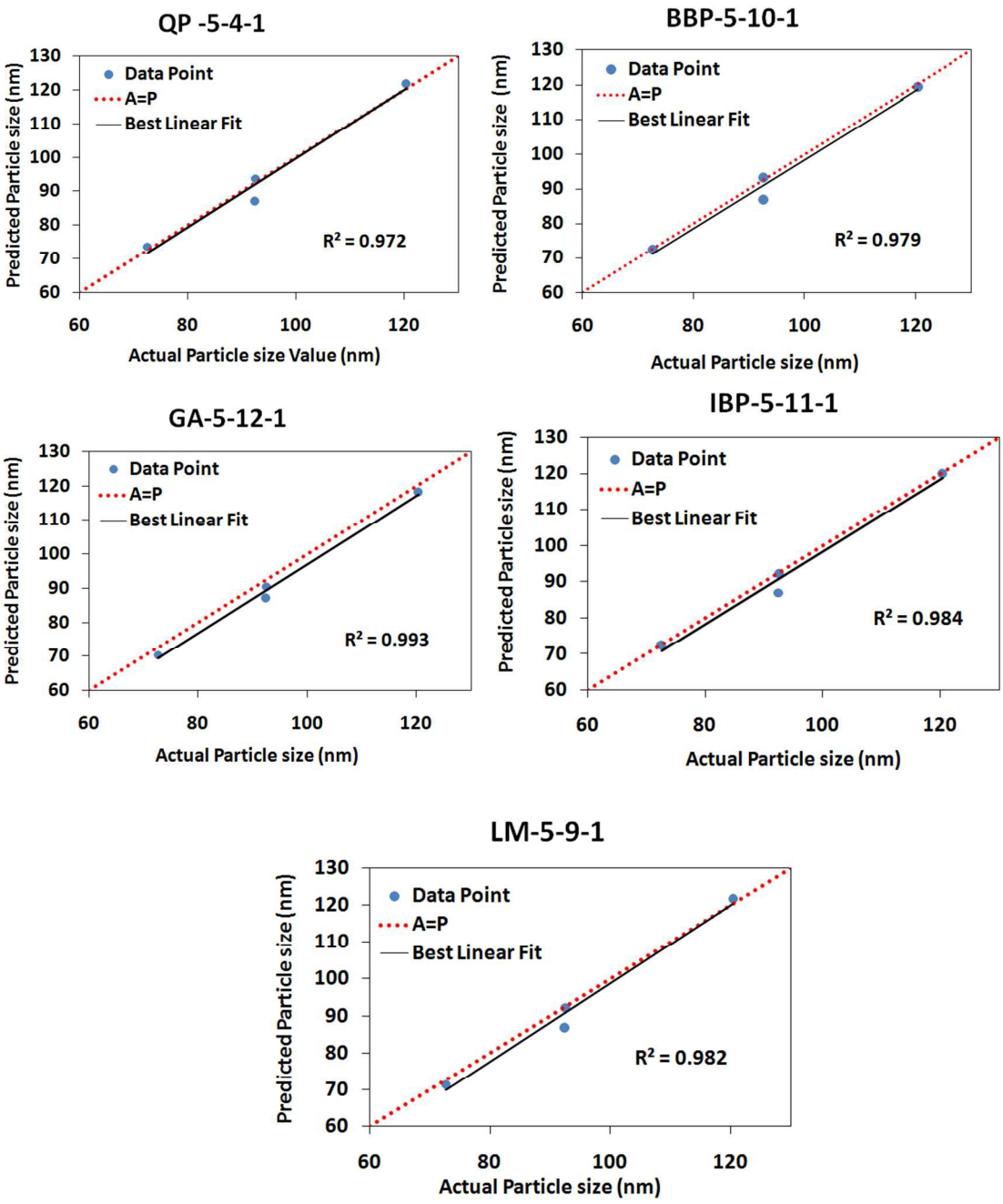


Fig.3

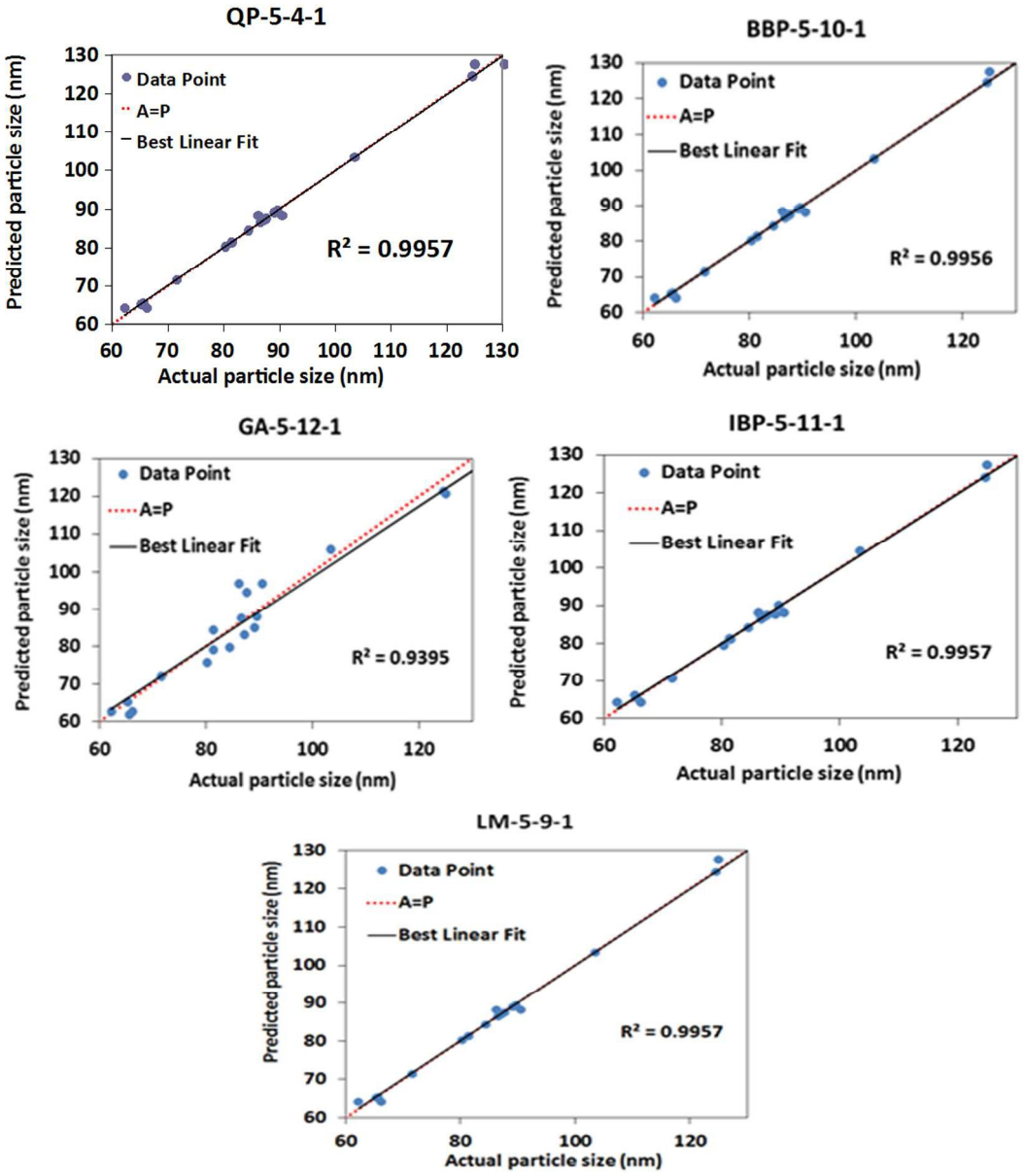


Fig. 4

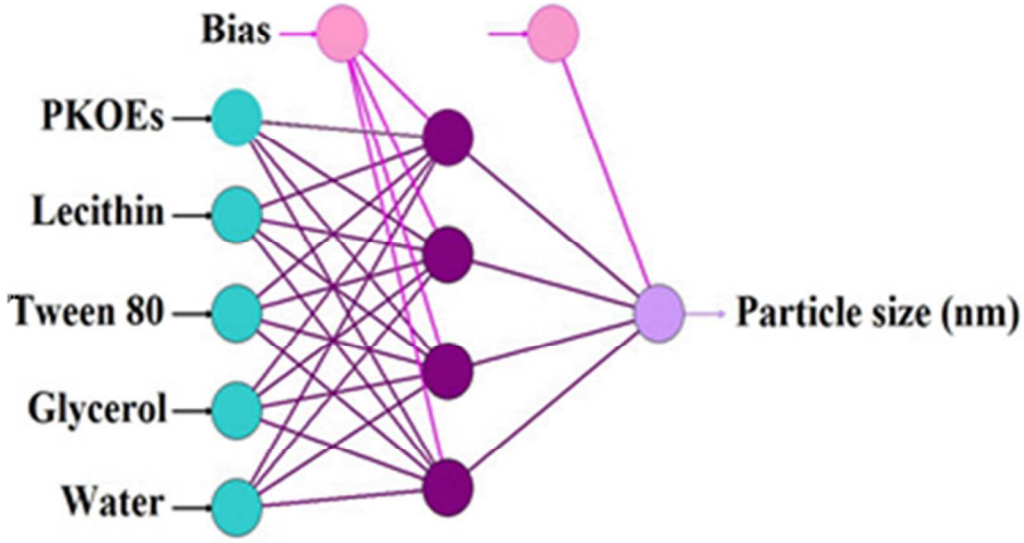


Fig. 5

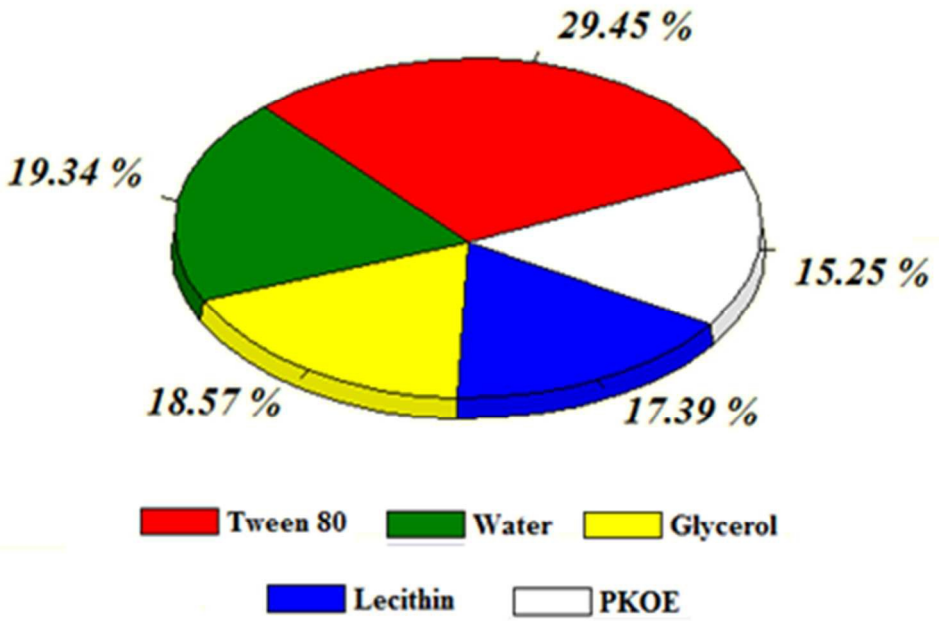
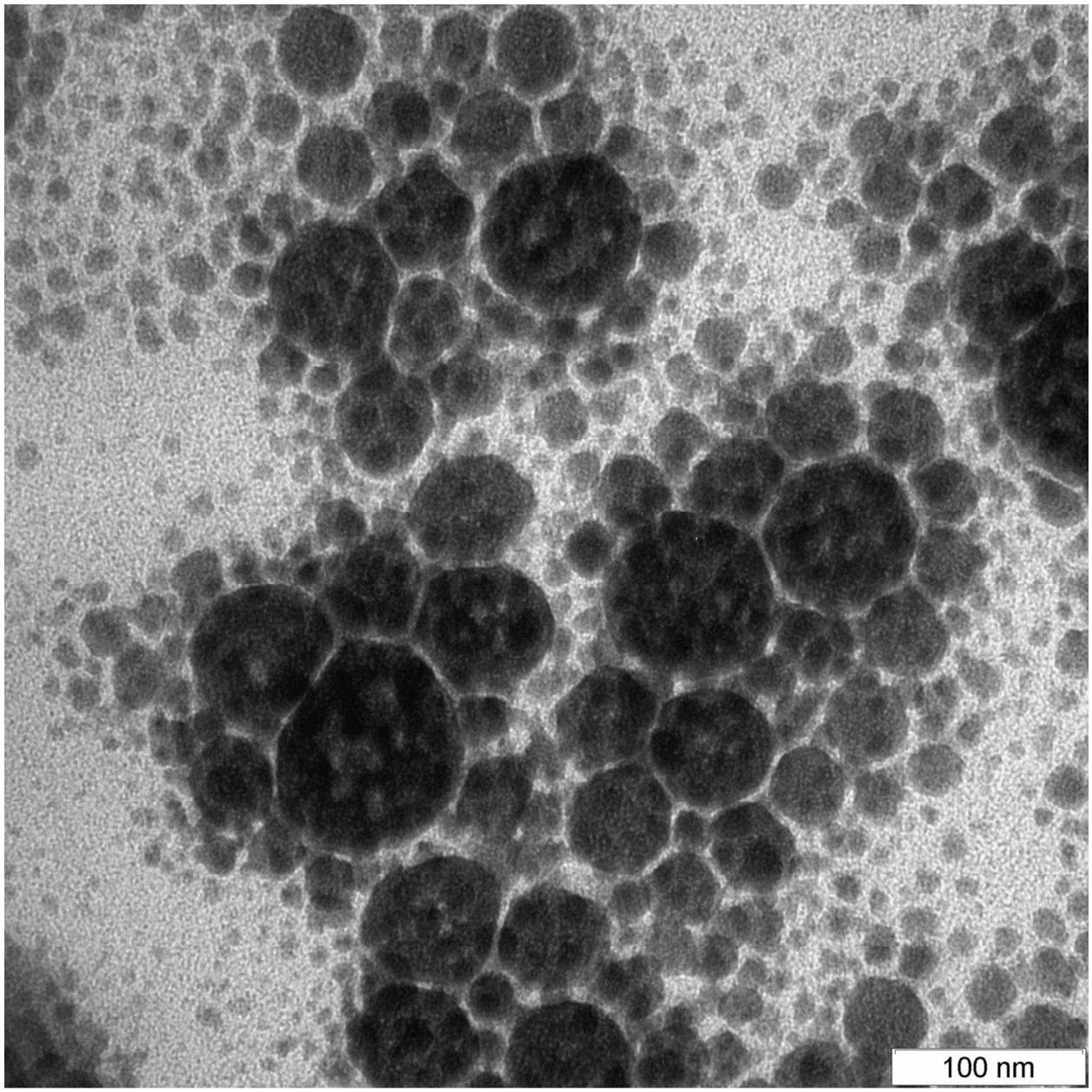


Fig. 6



Graphical Abstract