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The application of artificial neural networks and support vector regression for simultaneous spectrophotometric determination of commercial eye drop contents

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ABSTRACT

In the present study, artificial neural networks (ANNs) and support vector regression (SVR) as intelligent methods coupled with UV spectroscopy for simultaneous quantitative determination of Dorzolamide (DOR) and Timolol (TIM) in eye drop. Several synthetic mixtures were analyzed for validating the proposed methods. At first, neural network time series, which one type of network from the artificial neural network was employed and its efficiency was evaluated. Afterwards, the radial basis network was applied as another neural network. Results showed that the performance of this method is suitable for predicting. Finally, support vector regression was proposed to construct the Zilomole prediction model. Also, root mean square error (RMSE) and mean recovery (%) were calculated for SVR method. Moreover, the proposed methods were compared to the high-performance liquid chromatography (HPLC) as a reference method. One way analysis of variance (ANOVA) test at the 95% confidence level applied to the comparison results of suggested and reference methods that there were no significant differences between them. Also, the effect of interferences was investigated in spike solutions.

1. Introduction

Regression analysis is a common approach for evaluating relationships between variables and from the simple shape of linear regression to complex machine learning methods has been widely studied in the literature. One of the specific types of machine learning algorithm is artificial neural network (ANN) which, inspired by the biological neural system in the human brain [1]. ANN has different applications such as pattern recognition [2], hybrid recommender system [3], forensic age prediction [4] and other various applications. The other machine learning algorithm is support vector machine (SVM) which, introduced by Vladimir Vapnik as a maximum margin model and it was developed based on statistical learning theory [5,6]. The SVM has the stronger generalization ability and commonly performs better than neural networks because of the principle of structural risk minimization [7]. Support Vector Regression (SVR) is the algorithm derived from SVM, which linear and non-linear regression problems can be solved in high dimensional feature space [8]. The SVR has already been applied in many subjects like global sensitivity analysis [9], predicting the sorption capacity of lead (II) [10], modelling permeability prediction of hydrocarbon reservoir [11], regional flood frequency analysis [12], modelling of heat transfer in a thermosyphon reboiler [13] and etc. SVR finds the best model, no local optimal, unlike in neural networks. Also, despite having large dimensions, prevent from overfitting due to the algorithm optimization.

In the following, Zilomole is presented as a multiple component eye drop. Dorzolamide hydrochloride (DOR), used in eye drop as a powerful and selective inhibitor in order to decrease elevated intraocular pressure [14,15]. The chemical name of DOR is (4Strance)-4-(Ethylamino)-5,6-dihydro-6-methyl-4Hthieno [2,3 b] thiopyran-2-sulphonamide 7,7-dioxide hydrochloride [16]. On the other hand, Timolol maleate (TIM), is the first-blocker that use as an antiglaucoma agent and it can be said that TIM more effective than the newer-blockers. The chemical name of it is (*S*)-1-tert-Butylamino-3-(4-morphilino-1,2,5-thiadiazol-3-yloxy) propan-2-ol maleate. DOR and TIM are combined in eye drops for treatment of glaucoma [17]. The chemical structures of these two drugs are shown in Fig. 1.

In the literature, very few analytical methods reported for simultaneous determination of DOR and TIM such as reverse high-performance liquid chromatography (RP-HPLC) [18,19], High-Performance Liquid Chromatography (HPLC) [20] and Tin layer chromatography (TLC) [21].

These methods need prior separation of DOR and TIM before analysis. In addition, these methods are time-consuming, expensive and want very pure solvents which are harmful to the environment. On the other hand, spectral overlapping in pharmaceutical mixtures is a limiting

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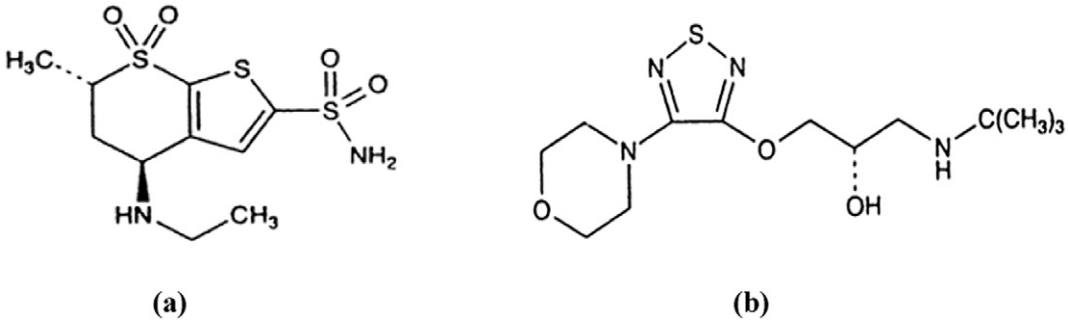

Fig. 1. Chemical structures of (a) dorzolamide hydrochloride, (b) timolol maleate.

factor for spectrophotometry technique. This paper reports a simple and rapid method for the simultaneous determination of DOR and TIM in eye drop by artificial neural network (time series neural network, radial basis function neural network) and support vector regression with spectrophotometry technique. Hence, the spectral overlapping problem of components in the pharmaceutical mixture can be resolved. Moreover, spectral resolution is increased and signal to noise ratio (S/N) is improved. The proposed methods were tested by analyzing synthetic mixtures consist of DOR and TIM. Also, the results obtained from analyzing the commercial sample by proposed methods were compared to the HPLC method by one-way analysis of variance (ANOVA) test. Comparison between investigated approaches indicates a good agreement between the results. Also, the effect of interferences was investigated in spike solutions.

2. Methodology

2.1. Neural Network Architecture

The fundamental architecture of an artificial neural network composed of three layers: an input layer, an output layer and hidden layer. Measured molecular descriptors expressed by neurons in the input layer and the engineering properties investigated by neurons of the output layer. Input neurons are divided into subsequent hidden layers and eventually to the output layer through weighted connections. Each node in the network works by taking the sum of its weighted inputs and then the result transmit via a nonlinear activation function [1,22]. The architecture of the artificial neural network model is shown in Fig. 2. In this study, time series network and radial basis function neural network are used for predicting.

2.2. Neural Network Time Series

A time series is a set of observations, which each of them is extracted at a specified time. In general, the goal is to find a predictive machine that can predict future values by observing the values of a series of times. This algorithm is able to predict their sample after examining steps, by observing the (i) sample of the time series, it can predict (o) sample of them. For training, a training set with p member and a test set with q members is used for testing and validating.

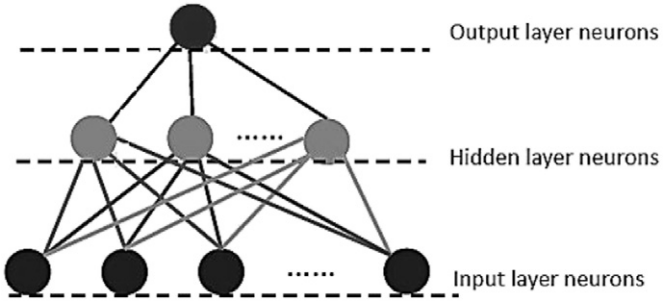

Fig. 2. Artificial neural network architecture with one hidden layer.

2.3. Radial Basis Function Neural Network Algorithm

The radial basis function (RBF) is a feed-forward network, which has three layers consist of an input layer, hidden layer and output layer. The hidden layer takes the RBF function as the activation function, not a gaussian function which is commonly used. This network can evaluate any continuous function with optional precision. RBF has an adaptive structure that output values are independent of the initial values and so on. Also, it has a simple architecture, simple training process and extensive application [23]. Fig. 3 shows the common structure of radial basis function neural network.

2.4. Support Vector Regression

The input x is first mapped into a l-dimensional feature space using some non-linear function and then linear function is built in this feature space. For linear regression problem, the training data are shown as (x_i, y_i), $(i = 1\ldots, m)$ where x is a l-dimensional input such that $x \in R^l$ and $\in R$. The SVR linear regression model can be demonstrated by Eq. (1).

$$f(x) = (\omega, x) + b \tag{1}$$

where f (x) is the output of linear SVR, (ω, x) represent dot product between ω and x, $\omega \in \mathcal{R}^m$ is the weight vector and $b \in \mathcal{R}$ is the threshold [24,25]. Constant C which will optimize an objective function given in Eqs. (2) and (3).

$$Min\ \frac{1}{2}||\omega||^2 + C\sum_{i=1}^{N}\left(\xi_i^2 + \xi_i^*\right) \tag{2}$$

$$\text{Subject to} \begin{cases} Y_i - (\omega, x_i) - b \le \varepsilon + \xi_i \\ (\omega, x_i) + b - Y_i \le \varepsilon + \xi_i^* \\ \xi_i^*, \xi_i \ge 0 \end{cases} \tag{3}$$

The constant C is a regularization factor and ξ_i^*, ξ_i are slack variables. The value of epsilon (ε) specifies the number of support vectors [26,27]. By using Lagrange multipliers, the constrained optimization function of Eq. (3) can be transformed into dual space and the solution obtained is represented in Eq. (4).

$$f(x) = \sum_{k}^{K}(a_k, a_k^*)\varphi(x_k, x) + b \tag{4}$$

where α *and* a_k^* are dual variables and the kernel function is $\varphi(x_k, x)$ which, maps the input data to feature space [28,29].