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Optimization of matrix tablets controlled drug release using *Elman* dynamic neural networks and decision trees

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ABSTRACT

The main objective of the study was to develop artificial intelligence methods for optimization of drug release from matrix tablets regardless of the matrix type. Static and dynamic artificial neural networks of the same topology were developed to model dissolution profiles of different matrix tablets types (hydrophilic/lipid) using formulation composition, compression force used for tableting and tablets porosity and tensile strength as input data. Potential application of decision trees in discovering knowledge from experimental data was also investigated.

Polyethylene oxide polymer and glyceryl palmitostearate were used as matrix forming materials for hydrophilic and lipid matrix tablets, respectively whereas selected model drugs were diclofenac sodium and caffeine. Matrix tablets were prepared by direct compression method and tested for in vitro dissolution profiles. Optimization of static and dynamic neural networks used for modeling of drug release was performed using *Monte Carlo* simulations or genetic algorithms optimizer. Decision trees were constructed following discretization of data.

Calculated difference (f_1) and similarity (f_2) factors for predicted and experimentally obtained dissolution profiles of test matrix tablets formulations indicate that *Elman* dynamic neural networks as well as decision trees are capable of accurate predictions of both hydrophilic and lipid matrix tablets dissolution profiles. *Elman* neural networks were compared to most frequently used static network, Multi-layered perceptron, and superiority of *Elman* networks have been demonstrated. Developed methods allow simple, yet very precise way of drug release predictions for both hydrophilic and lipid matrix tablets having controlled drug release.

1. Introduction

Matrix tablets are the most frequently used modified release oral dosage forms. Matrix forming material can be of hydrophilic, lipid, inert and biodegradable type; and the choice of material in dosage formulation is dependent on drug properties and desired drug release profile.

Hydrophilic matrix systems are the most commonly applied in controlled release formulations, due to their ability to provide desired release profiles for a wide range of drugs, robust formulation, cost-effective manufacture, and broad regulatory acceptance of the polymers (Tiwari and Rajabi-Siahboomi, 2008). Hydrophilic polymers commonly used for preparation of hydrophilic matrices include cellulose derivatives, various gums and polysaccharides, polyethylene oxides, homo- and copolymers of acrylic acid, etc. Polyethylene oxides (PEOs) are directly compressible hydrophilic polymers that can be used to formulate controlled release matrix tablets (Wu et al., 2005; Maggi et al., 2002). Control of the drug release is achieved by polymer swelling and formation of the compact gel layer on matrix tablet surface responsible for sustained water diffusion and subsequent drug release. Once the gel layer is formed it gradually starts to erode due to polymer dissolution, leading to zero order kinetic drug release once the swelling and erosion processes are synchronized. Diclofenac sodium is a BCS class 2 drug, with relatively short elimination half-life, therefore suitable for preparation of controlled release hydrophilic matrix tablets.

Lipid matrix systems are formulated using non-swellable lipophilic excipients, such as waxes and lipids (Özyazici et al., 2006). Biocompatible and biodegradable lipid excipients have been recommended for controlled release formulations containing highly soluble drugs. Excipients frequently used for lipid matrices formulations are carnauba and bees wax, glyceryl monostearate, cetyl and cetostearyl alcohol, stearic acid, etc. Drug diffusion from the lipid matrix is sustained, with the possibility of enhanced drug bioavailability. Lipid matrix tablets are usually produced by rather complex methods, such as melt granulation or extrusion (Pouton

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and Porter, 2008). Glyceryl palmitostearate is a lipid excipient that enables usage of direct compression method to prepare matrix tablets (Özyazici et al., 2006). It has firstly been used as tablet lubricant, whereas the potential of application in controlled release matrix tablets formulation has been recognized recently (Gökçe et al., 2009; Sudha et al., 2010). Caffeine is a BCS class 1 model drug used in the presented study to prepare controlled release lipid matrix tablets.

Mechanical properties of directly compressed matrix tablets demonstrate immense importance on drug release characteristics. Strength and porosity of matrix tablets dictate the speed of water diffusion inside the matrix tablet and subsequent release of dissolved drug from the tablet. Influence of changes in relative porosity on hydrophilic matrix tablet drug dissolution has been discussed in detail (Petrović et al., 2009a).

Usage of artificial intelligence in formulation and optimization of controlled release pharmaceutical preparations is of particular importance with the growing interest to support the establishment of the design space and quality risk management in pharmaceutical development (ICH Topic Q8, 2009). There have been various approaches to define a design space, concerning multidimensional combination of formulation factors and process parameters (Peterson, 2008; Huang et al., 2009; MacGregor and Bruwer, 2008; Kikuchi and Takayama, 2010).

Artificial neural networks (ANNs) are data analysis algorithms capable of adaptation to solve complex non-linear problems. ANNs can be classified as static and dynamic (recurrent) regarding networks architecture, i.e. interconnectedness of its elements. Architecture of dynamic neural networks allows storage and elaboration of data in time, meaning that networks outputs are integration of current inputs and previous outputs. More details on ANNs are provided in the literature (Haykin, 1999; Gupta et al., 2003; Samarasinghe, 2006).

Application of ANNs in the design of controlled release drug delivery systems has been reviewed in detail elsewhere (Sun et al., 2003). Superiority of MLP neural network over multiple regression models for prediction of dissolution profiles was demonstrated (Quek et al., 2001). ANN models were developed to optimize modified release matrix tablets dissolution profiles (Zupancic Bozic et al., 1997; Peh et al., 2000; Ibric et al., 2002; Chaibva et al., 2010; Barmpalexis et al., 2010). The importance of optimization of number of hidden layers in an ANN topology, as well as adequate selection of validation and testing data for prediction of dissolution profiles has been demonstrated (Ebube et al., 1997). Importance of influence of processing variables (processing parameters of the manufacturing method used to produce dosage form) on modified release dissolution profiles was investigated using ANNs (Leane et al., 2003; Peng et al., 2006).

Since dissolution is a time dependent process, it is assumed that dynamic (recurrent) neural networks are more appropriate tool for dissolution profile analysis, in comparison to static neural networks (such as Multi layered perceptron and Generalized regression neural network). Recurrent one layer and Gamma memory dynamic networks have been implemented in the modeling of drug release (Petrović et al., 2009b). The potential of application of *Elman* neural network (ENN) in the modeling of drug release has also been evaluated (Goh et al., 2003). ENN is considered as a special kind of feed-forward networks that has additional memory neurons and local feedback (Koker, 2006), therefore it is a simple dynamic neural network.

Decision trees are nonparametric statistical technique (Breiman et al., 1984), used for classification problems. Decision tree-based algorithms classification algorithms have tree structures consisting of nodes (or leaves), branches, etc. The tree structure is constructed following a set of decision rules applied sequentially. Each decision rule is used to form branches (i.e. splitting) at a certain level of the tree (Ren, 2003). Decision tree can be interpreted as a rule induction technique, if different scenarios are forecasted from the tree structure. Different algorithms can be used for decision trees construction: ID3, C4.5, C5.0, CART (Classification and Regression Trees), most of which were developed by Quinlan (1993). The main concern for every algorithm is to select appropriate splitting attribute in a decision node. Splitting criteria in decision nodes are goodness functions and the best splitting attribute is usually the one that results in the smallest tree. The most frequently used splitting criteria are: information gain, gain ratio and Gini index. Decision trees were used to generate an expert system for the identification of film coating (Rowe and Upjohn, 1993); as an aid in intravenous formulation development (Lee et al., 2003); for formulation selection for poorly soluble drugs (Branchu et al., 2007); to aid selection of candidate molecules for liposome loading and to optimize loading conditions (Zucker et al., 2009); for analysis of the fluidized-bed granulation process (Petrović et al., 2011), etc. Decision trees have been used to analyze dissolution profiles for immediate release tablet formulations (Shao et al., 2007), but there is no literature data on application of decision trees methodology for characterization of controlled release dissolution profiles.

The aim of the study presented here is to expand the utilization of artificial neural networks (ANNs) to prediction of controlled release matrix tablets dissolution profiles on the basis of knowledge of formulation factors (composition), processing parameters and tablets mechanical properties. ANNs of the same topology were developed to model dissolution profiles of different matrix tablets types (hydrophilic/lipid) using formulation composition, compression force used for tableting and tablets porosity and tensile strength as input data. Developed ANN models were used to construct design space in order to elucidate optimal combination of formulation factors and processing parameters to produce desired dissolution profiles. Furthermore, potential application of decision trees in discovering knowledge from experimental data was investigated.

2. Materials and methods

Compositions of matrix tablets were as follows: (a) *hydrophilic*: polyethylene oxide polymer (Sentry Polyox® WSR Coagulant-LEO NF Grade; Dow Chemical Company, Charleston, USA), diclofenac sodium (Novartis, Basel, Switzerland) and microcrystalline cellulose (Avicel® PH 102; FMC, Philadelphia, USA); (b) *lipid*: glyceryl palmitostearate (Precirol® ATO 5, Gattefossé GmbH, Weil am Rhein, Germany), caffeine (BASF, Ludwigshafen, Germany) and mannitol (Novartis, Basel, Switzerland); and magnesium stearate. The roles of the ingredients used were as follows: polyethylene oxide polymer and glyceryl palmitostearate were hydrophilic and lipid sustained release agents, respectively; microcrystalline cellulose and mannitol were used as directly compressible diluents, and magnesium stearate was used as lubricant. The content of drug in each formulation (both hydrophilic and lipid tablets) was 30% (w/w) and the content of matrix forming material and filler was varied according to Tables 1 and 2. Weight ratio of matrix forming materials was selected on the basis of results from previous experimental work (screening experimental design was performed). Prior to compression each formulation was mixed in a Turbula mixer type T2C (Willy A Bachofen AG, Basel, Switzerland) for 10 min. Matrix tablets were prepared by powder compression using compression simulator Zwick® 1478 Universal Testing Instrument (Zwick® GmbH, Ulm, Germany). Forces used for compression are represented in Tables 1 and 2, varying from 3 to 7 kN in the case of hydrophilic and from 4 to 8 kN in the case of lipid matrix tablets. The compression took place with a speed of 20 mm/min. Before

Table 1
Inputs used for training, validation and testing of artificial neural networks developed for modeling of diclofenac sodium release profiles for polyethylene oxide matrix tablets.

Formulation		% (w/w) PEO WSR coagulant[a]	Compression force (kN)	Porosity (%)	Tensile strength (MPa)
Training and validation set	C1	5	3	30.72	0.454
	C2	5	5	23.17	1.081
	C3	5	7	18.11	1.872
	C4	10	3	30.02	0.503
	C5	10	5	22.28	1.219
	C6	10	7	16.75	1.971
	C7	15	3	28.38	0.585
	C8	15	5	21.08	1.281
	C9	15	7	16.70	1.908
	C10	10	5	22.18	0.454
Test set	C11	7.5	6	19.65	1.610
	C12	12.5	4	24.64	0.827

[a] Diclofenac sodium weight ratio was 30% (w/w) for each formulation, whereas fraction of microcrystalline cellulose varied according to changes in PEO WSR Coagulant % (w/w).

Table 2
Inputs used for training, validation and testing of artificial neural networks developed for modeling of caffeine release profiles for glyceryl palmitostearate matrix tablets.

Formulation		% (w/w) Precirol[a]	Compression force (kN)	Porosity (%)	Tensile strength (MPa)
Training and validation set	P1	10	4	15.59	0.857
	P2	10	6	12.24	1.317
	P3	10	8	11.15	1.710
	P4	15	4	15.13	0.987
	P5	15	6	12.02	1.296
	P6	15	8	9.62	1.579
	P7	20	4	13.04	1.132
	P8	20	6	10.92	1.343
	P9	20	8	9.20	1.512
	P10	15	6	15.59	0.857
Test set	P11	12.5	5	13.06	1.294
	P12	17.5	5	11.75	1.346

[a] Caffeine weight ratio was 30% (w/w) for each formulation, whereas fraction of mannitol varied according to changes in Precirol % (w/w).

each compression cycle, the punches and the die wall were lubricated with magnesium stearate. The total weight of tablet matrices was kept constant at 450 mg for both hydrophilic and lipid matrix tablets.

Tablets diameters and thickness were measured using a micrometer digital caliper Digitcal (Tesa S.A., Renens, Switzerland). Knowing dimensions and tablets mass, relative density was determined as the ratio of mass to volume of the tablets, i.e. mass of the unit volume. Porosity of the tablets ε (%) was calculated using true and relative densities of drug and excipients:

$$\varepsilon = \left[1 - \left(\frac{\rho_a}{\rho_t}\right)\right] \times 100 \quad (1)$$

where ρ_a and ρ_t denote relative and true density (g/cm^3) of compressed powder compacts, respectively. True density of each component was measured by a helium pycnometer (AccuPyc 1330, Micromeritics, USA).

The hardness of tablets was measured using Dr. Schleuinger model 8M tester (Dr. Schleuinger, Pharmatron, Solothurn, Switzerland). Tensile strength σ_T (MPa) was obtained taking into account tablets diametral crushing force F (N) and dimensions R and h, radius and thickness (mm), respectively:

$$\sigma_T = \frac{2 \times F}{\pi \times R \times h} \quad (2)$$

Drug release test (Dissolution test) has been performed using paddles method (for hydrophilic matrix tablets) or rotating basket method (for lipid matrix tablets); at Erweka DT 70 (Erweka, Hausenstamm, Germany) dissolution apparatus. Phosphate buffer of pH 6.8 (USP 28) has been used as dissolution medium; for each formulation dissolution test has been conducted on 6 tablets using 900 ml of dissolution medium. Speed of rotation was 50 rpm and dissolution tests were conducted for 8 h. Samples for measurement of drug release were taken in the following time intervals: 0.5 h; 1 h, 1.5 h; 2 h, 3 h, 4 h, 5 h, 6 h, 7 h and 8 h. Samples of 4 ml were taken and each sampling was followed by addition of 4 ml of fresh medium into dissolution vessels. Prior to determination of drug concentration, samples were filtered. Determination of drug concentration has been carried out using UV spectrophotometer Evolution 300 (Thermo Fisher Scientific, Cambridge, Great Britain).

2.1. Determination of significant factors and factor interactions

In order to identify significant factors influencing dissolution profiles of diclofenac sodium and caffeine from hydrophilic and lipid matrix tablets, respectively, calculation of contrast values, Lenth t-statistics and the corresponding p values was performed. Lenth's method (1989) was used in order to reveal any statistically significant effect ($p < 0.1$) of the factors or potential interactions among factors.

2.2. Artificial neural networks

Commercially available Synapse 1.3.5 software was used on personal computer to design neural networks (Peltarion, Stockholm, Sweden). Architecture of a network consists of blocks connected with links. Blocks are information processing elements and the central element of the block is forward propagator.

Data used for development of artificial neural networks models and assessment of the models accuracy was divided into three subsets: training, validation and test data set. Data from training and validation sets have been used to build models, with 75% of data belonging to training set and 15% to validation set. Training and validation data sets were randomly selected. Test set data was

used to assess the accuracy of developed models. It is important to emphasize that test data were not represented to the network during its training.

After optimal conditions were selected (i.e. number of neurons in hidden layers, weights, signal delay), networks have been trained with simultaneous monitoring of the progress of error for training and validation data set in order to determine when the training should be stopped. When the error for training data set was not changing any more, or when the error for validation data set started to diverge, training was stopped.

Numbers of neurons in hidden layers, neurons weights and signal delay were optimized using *Monte Carlo* simulations or genetic algorithms optimizer. *Monte Carlo* simulator enables selection of number of examples and epochs used for optimization. Examples refer to the number of optimization cycles, whereas certain number of epochs constitutes one optimization cycle. Genetic optimizer algorithm enables selection of number of active populations, generations and epochs. Number of active populations is referred to as number of populations per generation (one population is one group of data). Selecting the number of trained generations as well as the number of epochs required for training of each data group basic optimizer parameters are set up. It is also possible to select the way in which selected parameters are combined in order to obtain new values of parameters (*crossover*), mutation type, i.e. the type of random change that prevents algorithm calculations to get stuck in local minimum (*mutation*) as well as the way in which single parameters are chosen from the whole population (*selection*).

2.3. Modeling of drug release profiles

To model matrix tablets drug release profiles both static and dynamic neural networks have been used. Definition of optimal artificial neural network parameters is an easier task in the case of static networks in comparison to dynamic ones, therefore data have firstly been modeled with static networks and then with dynamic networks. Since percentages of drug released in specific time points can be treated as time series, it is reasonable to expect that modeling of drug release is more adequately performed using dynamic than static neural networks.

It is important to emphasize that neural networks of the same architecture were used for both hydrophilic and lipid matrix tablets (not simultaneously but separately for data sets), in order to demonstrate modeling capabilities of ANNs regardless of the matrix tablets type.

Modeling of drug release profiles using static neural networks has been conducted by MLP network, a basic static feedforward backpropagation neural network. Each layer of a MLP network has weights and functions. Activation function selected for application in functional part of layers is *Tanh* sigmoid function. *Monte Carlo* simulator, used for optimization of number of neurons in hidden layer and neurons weights, was set up to have 1000 epochs and 100 examples. Selected number of epochs and examples in *Monte Carlo* simulations is based upon testing of the influence of optimizer parameters on networks predictive abilities. Number of epochs and examples were varied in the range of 100–1500 and 10–200, respectively.

Modeling of drug release for hydrophilic and lipid matrix tablets using dynamic neural networks has been done using ENN, optimizing the number of neurons in hidden layers, neurons weights and time delay of signals using genetic algorithms. The dynamics of the network comes from the connections among neurons, not the neurons themselves. Recurrent links are used to provide network with a dynamic memory when hidden unit patterns are fed back to themselves (Elman, 1990). The fixed back connections result in the maintenance of a copy of the previous values of the hidden units since they propagate over the connections before the learning rule is applied (Mazumdar and Harley, 2008).

In the second hidden layer (also known as the *copied* layer) a feedback connection is established, therefore the system state is memorized and integration of present and current response to activation function is possible. This type of signal recurrence is recognized as a one-step time delay (Zhang and Man, 1998). The architecture of ENN can be represented as follows:

$$y_k = f_o\left[\sum_{o=1}^{N_o} b_o + \sum_{h=1}^{N_h} w_{ho}\cdot f_h\left(b_h + \sum_{i=0}^{N_i} w_{ih}u_i + \sum_{j=0}^{N_h} w_{jh}a_h(k-1)\right)\right] \quad (3)$$

where u_k and y_k are networks primary input and output; w_{ih}, w_{jh} and w_{ho} ($i = 1, 2, \ldots, N_i$; $j,h = 1, 2, \ldots, N_h$; $o = 1, 2, \ldots, N_o$) are the weights of the connections between the input and hidden units, between the copied and the hidden units and between the hidden and the output units, respectively. b_h and b_o are biases of hidden units and output units, and $f_h(\cdot)$ and $f_o(\cdot)$ are hidden and output functions respectively (Zhang and Man, 1998). In comparison to ENN, calculation of MLP networks output is much simpler and can be represented as follows:

$$y_k = f_o\left[\sum_{o=1}^{N_o} b_o + \sum_{h=1}^{N_h} w_{ho}\cdot f_h\left(b_h + \sum_{i=0}^{N_i} w_{ih}u_i\right)\right] \quad (4)$$

Activation function of ENN in hidden layers was *Tanh* sigmoid whereas output layer had linear activation function. Key parameters of the networks that were optimized using genetic algorithms were the weights of the second (copied) hidden layer, since they determine the impact of signal recurrence on the networks output. Optimizations were carried out by selection of 20 active populations, 100 generations and 1000 epochs. Selected number of active populations, generations and epochs for genetic algorithms is based upon testing of the influence of optimizer parameters on networks predictive abilities. Number of populations, generations and epochs were varied from 10 to 25, 10 to 200 and 100 to 1500, respectively.

2.4. Decision trees

Decision tree analysis technique was performed using RapidMiner 5.0 open-source software (Mierswa et al., 2006). In order to perform classification analysis on drug release profiles, input and output parameters were discretized in bins, with each bin containing one element. Discretization transforms numerical values into categories. Decision trees are generated by recursively partitioning the training data using a splitting attribute until all the records in the partition belong to the same class (Chandra and Varghese, 2009). Split-criteria used in the study were: Gini index, gain ratio and information gain (with algorithms ID3/C4.5). Splitting criteria are actually goodness functions and the best splitting attribute is usually the one that results in the smallest tree.

Training and validation data sets were used to construct the trees and perform internal validation whereas test data set was used for external validation, i.e. testing of developed trees.

2.5. Analysis of predictions

Predicted dissolution profiles were compared to experimentally obtained profiles using *Pearson* correlation coefficient, r where n is the number of sampling points, x_i is experimentally obtained percentage of the drug released after certain time periods whereas

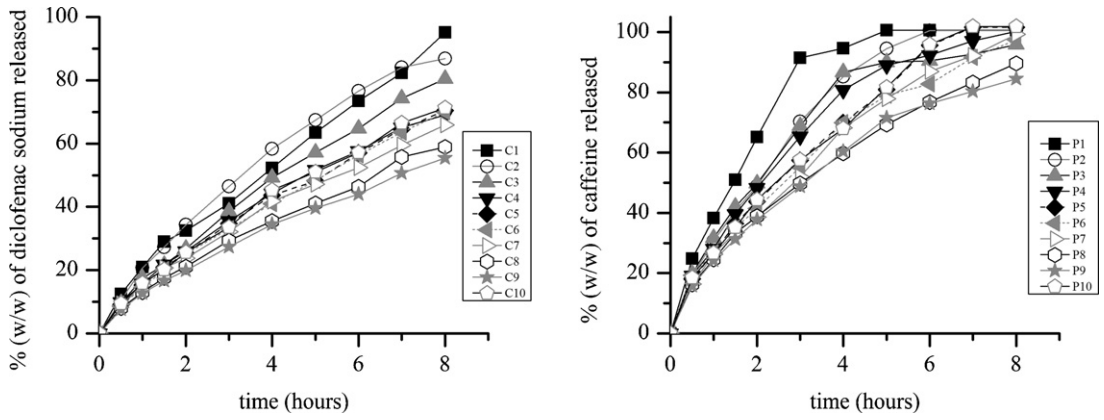

Fig. 1. Diclofenac sodium and caffeine release profiles from hydrophilic and lipid matrix tablets, respectively.

y_i denotes predicted percentages of drug released after certain time periods:

$$r = \frac{\sum_{i=1}^{n} x_i y_i - \left(\left(\sum_{i=1}^{n} x_i \sum_{i=1}^{n} y_i \right) / n \right)}{\sqrt{\left(\sum_{i=1}^{n} x_i^2 - \left(\left(\sum_{i=1}^{n} x_i \right)^2 / n \right) \right) \times \left(\sum_{i=1}^{n} y_i^2 - \left(\left(\sum_{i=1}^{n} y_i \right)^2 / n \right) \right)}} \quad (5)$$

and by calculation of difference and similarity factors, f_1 and f_2.

$$f_1 = \frac{\sum_{i=1}^{n} |x_i - y_i|}{\sum_{i=1}^{n} x_i} \times 100 \quad (6)$$

$$f_2 = 50 \log \left\{ \left[1 + \frac{1}{n} \sum_{i=1}^{n} (x_i - y_i)^2 \right]^{-0.5} \times 100 \right\} \quad (7)$$

Profiles were considered to be similar if $0 < f_1 < 15$ and $50 < f_2 < 100$.

3. Results and discussion

3.1. Determination of significant factors and factor interactions

Dissolution profiles obtained for both hydrophilic and lipid matrix tablets are represented in Fig. 1. It is evident that diclofenac sodium release from hydrophilic matrix tablets gets sustained with the increase in the weight ratio of polyethylene oxide polymer and compression force used for tablets manufacturing. Even though eight hour release was incomplete, it can be assumed that if dissolution tests were prolonged it would be confirmed that diclofenac sodium release is complete and at constant rate, approaching zero order kinetics. Caffeine release is also evidently sustained with the increase in the weight ratio of the lipid excipient, as well as with the increase in compression force used for lipid matrix tablets manufacturing. Taking into consideration high solubility of caffeine (37.2 mg/ml), obtained release profiles can be considered satisfactorily sustained since the amount of medium that was available for dissolution of caffeine from lipid formulations was sufficient for its immediate release.

The effect of significant factor and factors interactions was recognized using Lenth's method and contrast values for significant factors and factor interactions are represented in Fig. 2. *Y*-axis (in Fig. 2) denotes the drug amount (in %) released after specific time interval (from the first up to the eight hour). It can be seen that weight ratio of the matrix forming material has, as expected, the most influence on drug dissolution properties. Nevertheless, it is important to confirm that other studied factors (compression force, tablets porosity and tensile strength) are also statistically significant factors ($p < 0.1$). Furthermore, significant factors interactions are recognized, especially in the case of hydrophilic matrix tablets. Significant interactions between the hydrophilic polymer weight ratio and other three studied factors (compression force, tablets tensile strength and porosity) are confirmed. This is presumably due to complex mechanism of sustainment of drug release, as previously described (Petrović et al., 2009a). It should be emphasized that different factors can demonstrate predominating influence on drug release in different time periods; therefore careful analysis of significant factors for each point in dissolution profile should be considered.

Once it was confirmed that studied formulation and processing parameters demonstrate significant influence, as well as mutual interaction, on dissolution properties of hydrophilic and lipid matrix tablets, the study was continued in order to define design space using ANNs and decision trees.

3.2. Optimization of static and dynamic neural networks architecture

MLP neural network optimized for modeling of drug release is represented in Fig. 3. The network consists of three layers, input layer with 4 neurons, hidden layer with 6 neurons and output layer with 10 neurons. From data source input signals (information about weight ratio of matrix forming material, compression force, porosity and tablets tensile strength) go to the hidden layer and then to the output layer (10 outputs are percentages of drug released at specific time points).

Architecture of ENN optimized for modeling of drug release is represented in Fig. 4. The network consists of an input layer, two hidden layers and an output layer of neurons.

Input layer contains four neurons (information about weight ratio of matrix forming material, compression force, porosity and tablets tensile strength), first hidden layer has nineteen neurons, second hidden layer (copied layer) has eighteen neurons whereas output layer has 10 neurons (10 outputs are percentages of drug released at specific time points).

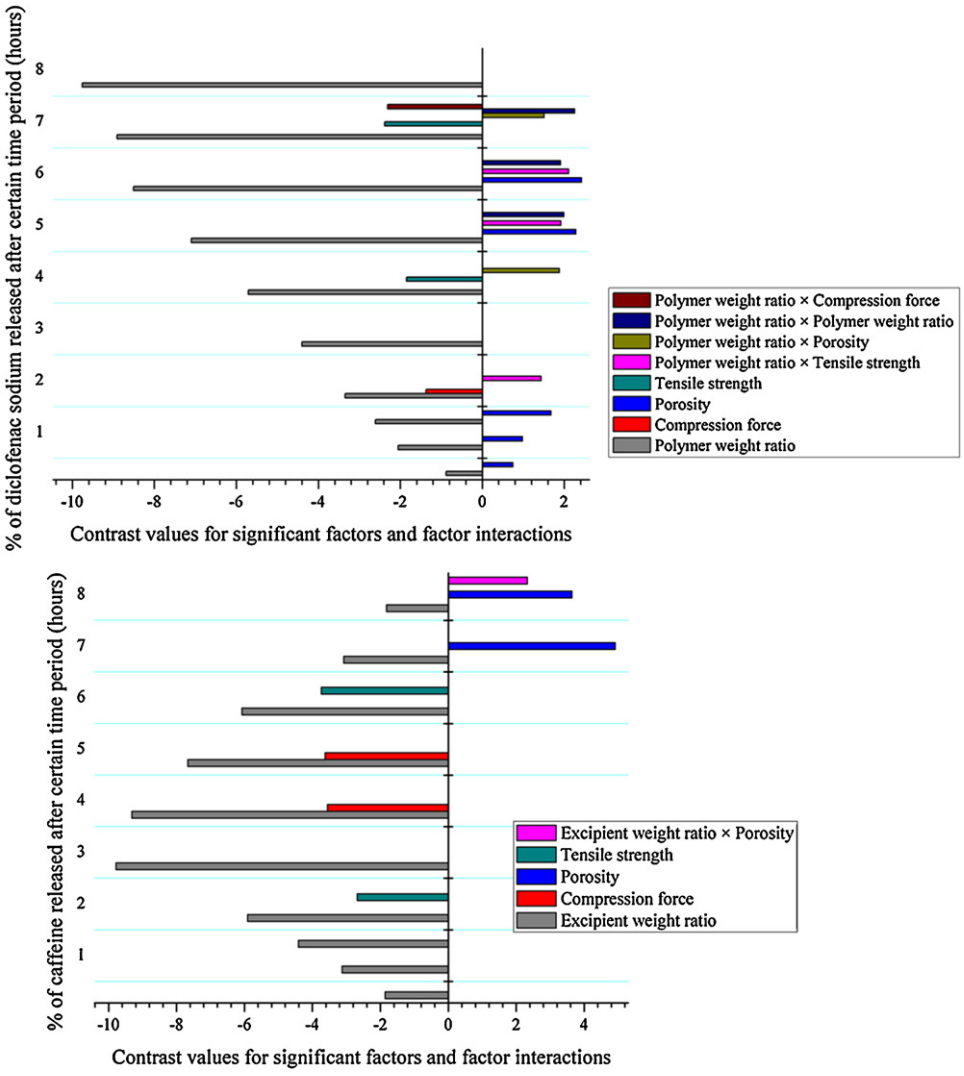

Fig. 2. Determination of significant ($p < 0.1$) factors and factor interactions influencing diclofenac sodium and caffeine release profiles.

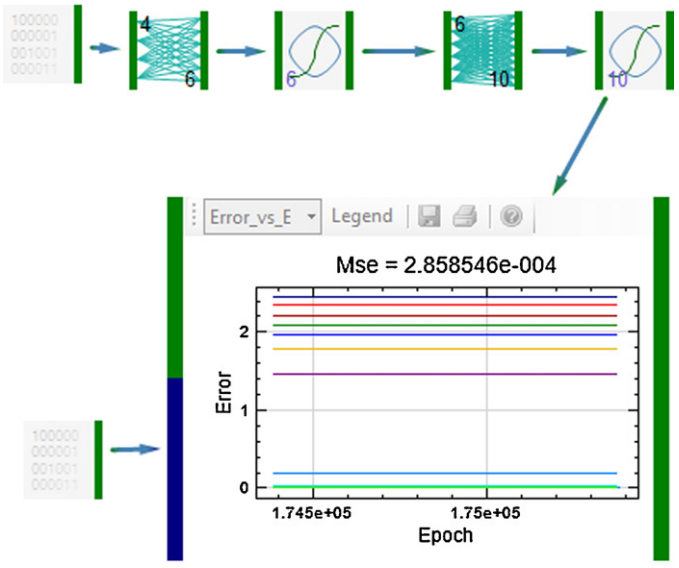

Fig. 3. Topology of Multi Layered Perceptron static network used for modeling of drug release for both hydrophilic and lipid matrix tablets.

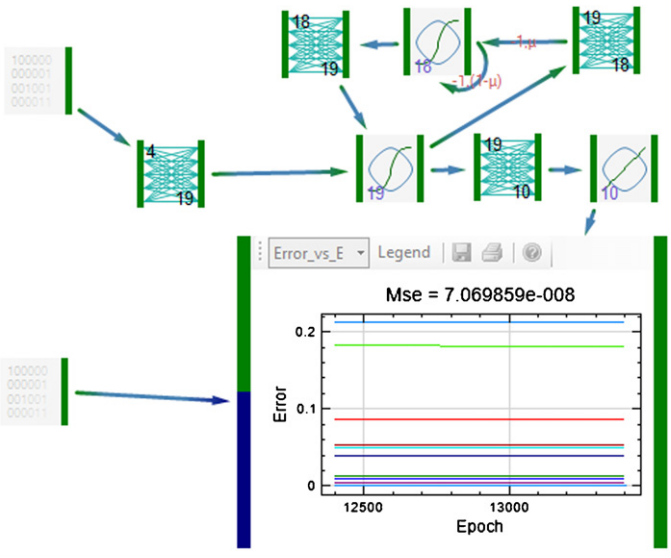

Fig. 4. Topology of *Elman*'s dynamic network used for modeling of drug release for both hydrophilic and lipid matrix tablets.

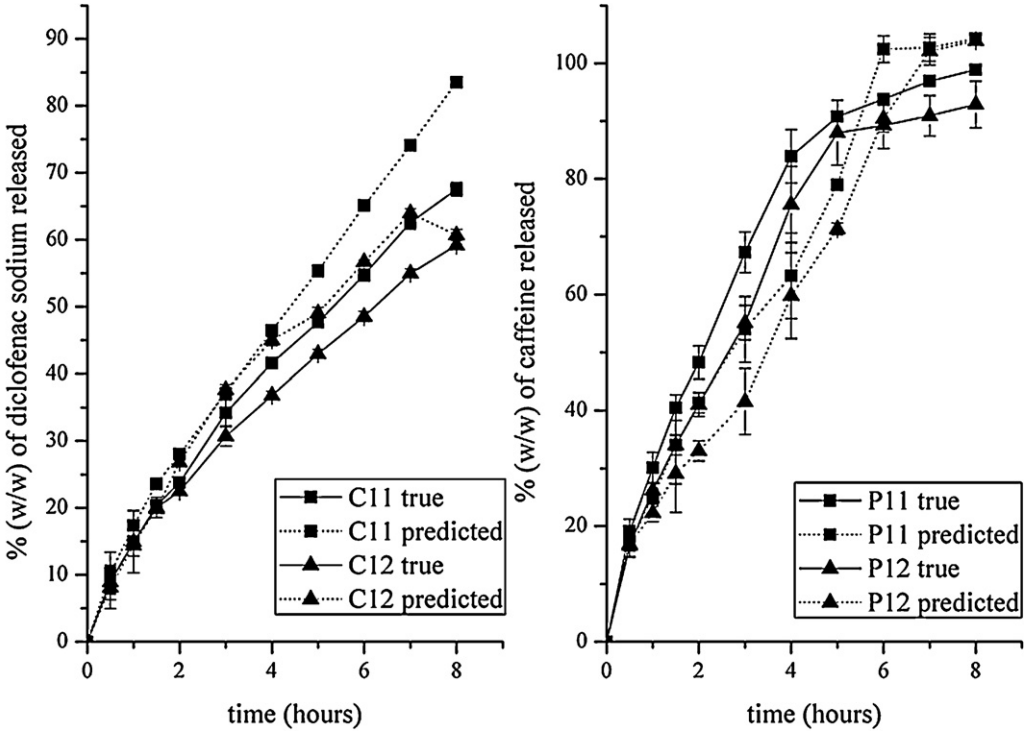

Fig. 5. Comparison of dissolution profiles experimentally obtained (true) and predicted by Multi layered perceptron neural network for hydrophilic (C11 and C12) and lipid (P11 and P12) matrix tablets test formulations.

3.3. Modeling of drug release profiles for hydrophilic matrix tablets by MLP neural network

MLP neural network was applied to model diclofenac sodium release profiles for PEO hydrophilic matrix tablets, and comparison of experimentally obtained and predicted dissolution profiles are represented in Fig. 5.

Mean error for training and validation data set during training of MLP was 4.6×10^{-4}. It is obvious that even though there is a correlation between experimentally obtained and predicted dissolution profiles (confirmed by statistically significant high values of *Pearson* correlation coefficient), predicted profile is accurate in the case of one of the test formulations but not for the other (f_2 and f_1 values are given in the Table 3). Obtained results indicate that, based on presented training data, MLP neural network predicts faster diclofenac sodium release compared to the experimentally obtained results. Difference between predicted and experimentally obtained values is especially marked after the fourth hour of the drug release study. Application of MLP in prediction of diclofenac sodium release from polyethylene oxide matrix tablets could lead to assumption of inaccurate drug release kinetics.

3.4. Modeling of drug release profiles for lipid matrix tablets by MLP neural network

MLP neural network was applied to model caffeine release for glyceryl palmitostearate matrix tablets, and comparison of experimentally obtained and predicted dissolution profiles are represented in Fig. 5. Mean error for training and validation data set during training of MLP was 7.57×10^{-3}.

In spite of the fact that similarity between the profiles is confirmed (Table 3), it is important to point out that there are some marked differences between experimental and predicted caffeine release profiles for test formulations P11 and P12, that were not taken into account when f_1 and f_2 values were calculated.

Even though the surface areas under experimental and predicted dissolution profiles are similar (leading to obtained f_1 and f_2 values), shapes of dissolution curves are very different and characteristic interlocking of dissolution curves can be observed. In the first part of the dissolution profile MLP model predicts lower and for the second part of the dissolution profile it predicts higher values of % (w/w) caffeine released in comparison to experimentally obtained values. Since caffeine is highly soluble substance it is difficult to obtain its sustained release. Important disadvantage of MLP predictions for caffeine release is that the predicted dissolution profiles are sustained to greater extent in comparison to experimentally obtained caffeine release data. This way, MLP predictions could mislead to conclusion that sustained release of caffeine is achieved.

Results obtained are indicative of necessity to carefully interpret correlation coefficients and similarity and difference factors obtained when experimental and predicted dissolution profiles are compared.

Therefore, MLP, widely used static (non recurrent) neural network, does not enable successful modeling of drug release profiles for different types of matrix tablets (hydrophilic and lipid).

3.5. Modeling of drug release profiles for hydrophilic matrix tablets by ENN

ENN was applied to model diclofenac sodium release profiles for PEO hydrophilic matrix tablets, and comparison of experimentally obtained and predicted dissolution profiles are represented in Fig. 6. Mean error for training and validation data set during training of ENN was 3.82×10^{-2}.

Results obtained are an indicator that using ENN, diclofenac sodium release profiles for PEO hydrophilic matrix tablets can be successfully predicted. Adequacy of predictions is confirmed by both Pearson correlation coefficient and similarity and difference factors (Table 3). More importantly, it is obvious that dynamic

Table 3
Characteristics of neural network models used for prediction of diclofenac sodium and caffeine release profiles for hydrophilic and lipid matrix tablets.

Formulation	Mean error for training and validation data set	*Pearson* correlation coefficient	f_2	f_1
Multi layered perceptron static neural network				
C11	4.60×10^{-4}	0.9976 ($p < 0.05$)	54.96	17.15
C12		0.9881 ($p < 0.05$)	61.99	13.46
***Elman*'s dynamic neural network**				
C11	3.82×10^{-2}	0.9939 ($p < 0.05$)	78.19	4.36
C12		0.9989 ($p < 0.05$)	74.31	6.68
Multi layered perceptron static neural network				
P11	7.57×10^{-3}	0.9620 ($p < 0.05$)	49.86	12.89
P12		0.9552 ($p < 0.05$)	49.26	14.17
***Elman*'s dynamic neural network**				
P11	5.48×10^{-2}	0.9991 ($p < 0.05$)	86.91	1.58
P12		0.9958 ($p < 0.05$)	71.34	5.24

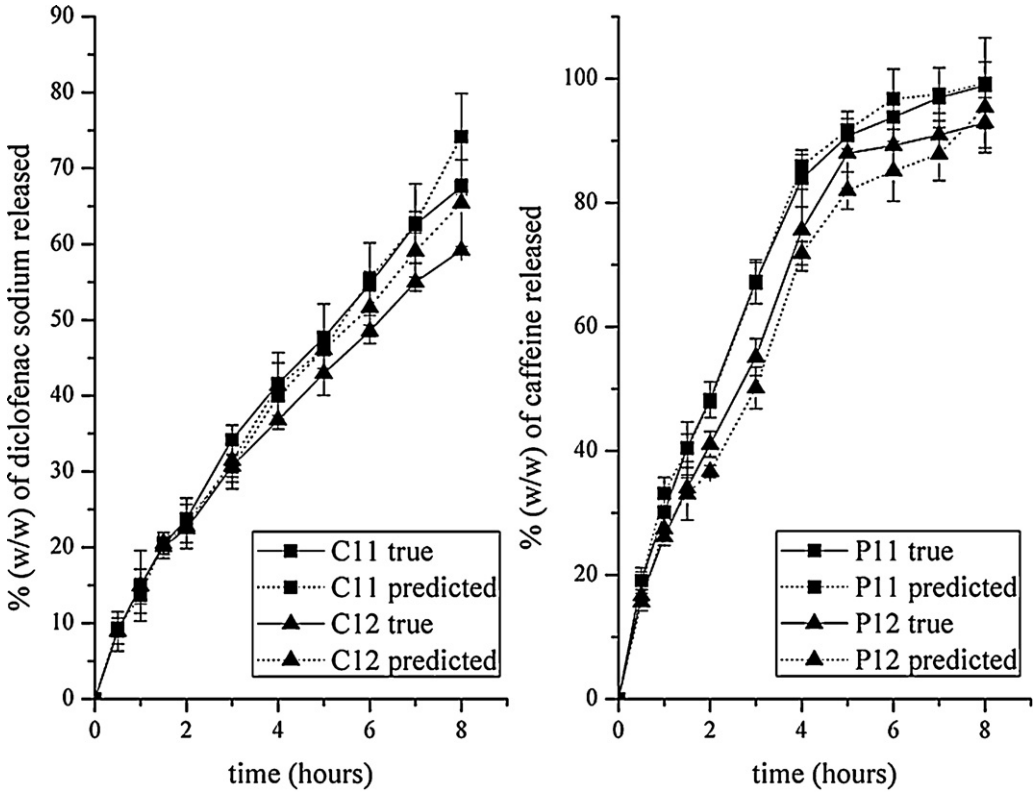

Fig. 6. Comparison of dissolution profiles experimentally obtained (true) and predicted by *Elman*'s dynamic neural network for hydrophilic (C11 and C12) and lipid (P11 and P12) matrix tablets test formulations.

network recognizes patterns of dissolution profiles, i.e. it successfully predicts changes in kinetics of drug release for test formulations which are easily recognized through shapes of release profiles as well.

High correlation obtained between experimental and predicted diclofenac sodium release profiles is improved in comparison to results obtained when diclofenac sodium release profiles for hydrophilic matrix tablets were modeled using the genetic algorithm method (Do et al., 2008), and also using Recurrent One Layer and Gamma Memory dynamic networks (Petrović et al., 2009b); bearing in mind that different software, network architecture and/or training and validation data were used in respective studies.

3.6. Modeling of drug release profiles for lipid matrix tablets by ENN

ENN was applied to model caffeine release profiles for glyceryl palmitostearate matrix tablets, and comparison of experimentally obtained and predicted dissolution profiles are represented in Fig. 6. Mean error for training and validation data set during training of ENN was 3.82×10^{-2}.

Results obtained support the fact that ENN, being dynamic network, is more appropriate for prediction of caffeine release in comparison to MLP. ENN was able not only to predict dissolution profiles of test formulations that were similar to experimentally obtained results (confirmed by f_1 and f_2 values, Table 3) but also to assume changes in caffeine release kinetics.

ENN has allowed modeling of drug release from both hydrophilic and lipid matrix tablets. It is important to emphasize that the network of the same architecture has been used to develop models for prediction of drug release from different types of matrix systems having different mechanisms controlling the drug release. Developed ENN models can be used to predict dissolution profiles of diclofenac sodium and caffeine for hydrophilic and lipid matrix tablets, respectively, on the basis of knowledge of weight ratio of matrix forming material, compression force and tablets porosity and tensile strength. Successful validation of ENNs predictions

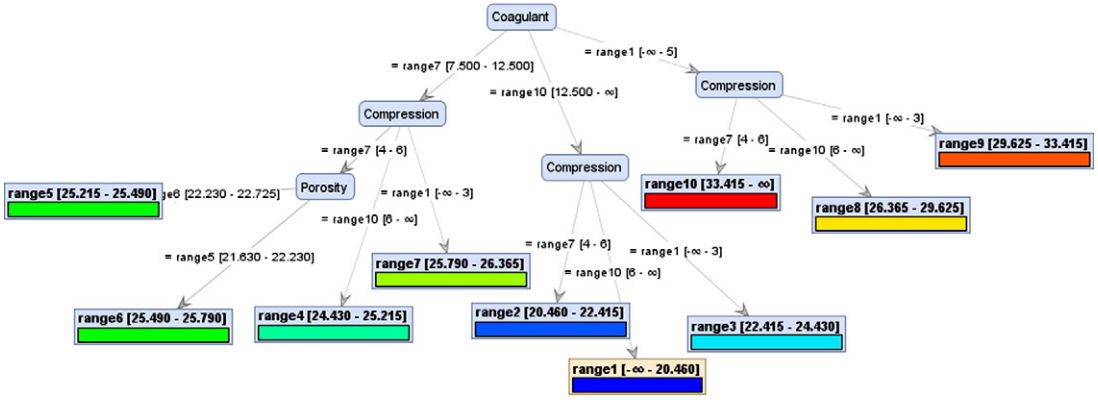

Fig. 7. Representation of decision tree developed for prediction of ranges of diclofenac sodium released after two hours from PEO hydrophilic matrix tablets.

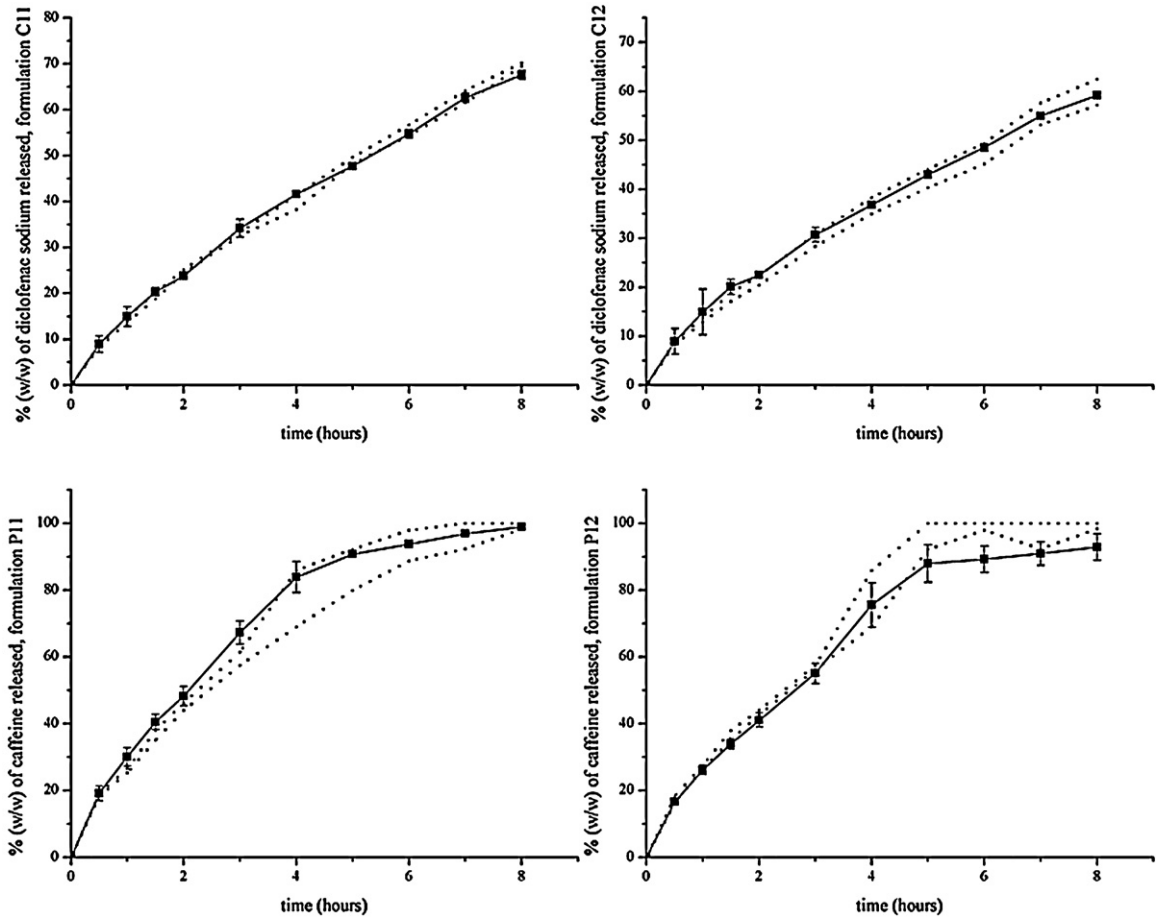

Fig. 8. Comparison of dissolution profiles experimentally obtained (■) and ranges predicted by decision trees methodology (. . .).

allows us to contend that design space for drugs dissolution rate has been identified and that dissolution properties of any matrix tablet within the design space (design space is confined by limiting values used for training and validation of ANNs) can be successfully predicted.

3.7. *Modeling of drug release profiles using decision tree methodology*

Using decision tree methodology it was possible to predict ranges of drug released in certain time periods, on the basis of data from the training and validation set. An example of developed decision tree is represented in Fig. 7. Developed decision trees have several nodes that are indicative of differences in drug release profiles in aspect to weight ratio of the matrix forming material, compression force and tablets porosity and tensile strength. Once decision trees were grown it was obvious that the main splitting criterion is weight ratio of the matrix forming material, followed by the compression force and then tablets porosity and/or tensile strength. Trees splitting can serve as the basis for creation of so called *if then* rules, e.g. if PEO as matrix forming material weight ratio is < 5% w/w and compression force is <3 kN then percentage of diclofenac sodium released after 2 h is in the range of 29.62–33.43 (as represented in Fig. 7).

Decision trees were used to predict dissolution behavior of test formulations for both hydrophilic and lipid matrix tablets and obtained results are represented in Fig. 8. It is clear from Fig. 8 that ranges predicted for diclofenac sodium release profiles are narrower in comparison to caffeine release profiles. This could be due to fact that diclofenac sodium and caffeine dissolution profiles used for tree construction differed in terms of their internal variability.

The possibility to predict ranges of drug released after certain time periods gives rise to possible application of decision tree methodology in selection of formulations meeting desired dissolution criteria (e.g. pharmacopoeial specification on amount of drug released after certain time period). Furthermore it is possible to use tree splitting as a supporting tool in risk analysis – tree node can point out to potential risk and, at the same time risk control strategies can be identified (selection of adequate values of splitting attributes).

It is important to point out that further investigation of application of decision trees in drug release modeling requires larger data sets. Inductive generalization given in the form of a decision tree is dependent on the sufficient amount of data. The amount of data required is affected by factors such as the number of properties and classes and the complexity of the classification model (Kantardzic, 2011).

4. Conclusion

Obtained results indicate the possibility of prediction of drug release profiles on the basis of key formulation factors, process parameters and tablet properties. Neural networks of different architecture were applied to study hydrophilic and lipid matrix tablets drug release profiles. It was demonstrated that dynamic neural network, ENN, is superior in drug release prediction in comparison to static neural network, MLP. In addition to successful prediction of dissolution profiles, usage of decision trees enabled generation of beneficial *if then* rules. Developed methods allow simple, yet very precise way of drug release predictions for both hydrophilic and lipid matrix tablets having controlled drug release. So far, there have been no methods in the literature that were developed for prediction of drug release regardless the type of matrix system. Therefore, it is to be expected that presented in silico tools facilitate implementation of quality by design concept, i.e. description and understanding of design space and quality risk management for formulations and processing parameters being developed.

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References

Barmpalexis, P., Kanaze, F.I., Kachrimanis, K., Georgarakis, E., 2010. Artificial neural networks in the optimization of a nimodipine controlled release tablet formulation. Eur. J. Pharm. Biopharm. 74, 316–323.

Branchu, S., Rogueda, P.G., Plumb, A.P., Cook, W.G., 2007. A decision-support tool for the formulation of orally active, poorly soluble compounds. Eur. J. Pharm. Sci. 32, 128–139.

Breiman, L., Friedman, J.H., Olshen, R.A., Stone, C.J., 1984. Classification and Regression Trees. Wadsworth International Group, Belmont, CA.

Chaibva, F., Burton, M., Walker, R.B., 2010. Optimization of salbutamol sulfate dissolution from sustained release matrix formulations using an artificial neural network. Pharmaceutics 2, 182–198.

Chandra, B., Varghese, P.P., 2009. Moving towards efficient decision tree construction. Inform. Sci. 179, 1059–1069.

Do, D.Q., Rowe, R.C., York, P., 2008. Modelling drug dissolution from controlled release products using genetic programming. Int. J. Pharm. 351, 194–200.

Ebube, N.K., McCall, T., Chen, Y., Meyer, M.C., 1997. Relating formulation variables to in vitro dissolution using an artificial neural network. Pharm. Dev. Technol. 2, 225–232.

Elman, J.L., 1990. Finding structure in time. Cogn. Sci. 14, 179–211.

Goh, W.Y., Lim, C.P., Peh, K.K., 2003. Predicting drug dissolution profiles with an ensemble of boosted neural networks: a time series approach. IEEE T. Neural Netw. 14, 459–463.

Gökçe, E.H., Özyazici, M., Gokhan, E., 2009. The effect of geometric shape on the release properties of metronidazole from lipid matrix tablets. J. Biomed. Nanotechnol. 5, 421–427.

Gupta, M.M., Jin, L., Homma, N., 2003. Static and Dynamic Neural Networks: From Fundamentals to Advanced Theory. John Wiley & Sons, Hoboken, NJ.

Haykin, S., 1999. Neural Networks—A Comprehensive Foundation. Prentice-Hall, NJ.

Huang, J., Kaul, G., Cai, C., Chatlapalli, R., Hernandez-Abad, P., Ghosh, K., Nagi, A., 2009. Quality by design case study: an integrated multivariate approach to drug product and process development. Int. J. Pharm. 382, 23–32.

Ibric, S., Jovanovic, M., Djuric, Z., Parojcic, J., Solomun, Lj., 2002. The application of generalized regression neural network in the modeling and optimization of aspirin extended release tablets with Eudragit® RS PO as matrix substance. J. Control. Release 82, 213–222.

ICH Topic Q8(R2), 2009. Guidance for Industry: Pharmaceutical Development.

Kantardzic, M., 2011. Data Mining: Concepts, Models, Methods, and Algorithms. John Wiley & Sons, Hoboken, NJ.

Kikuchi, S., Takayama, K., 2010. Multivariate statistical approach to optimizing sustained-release tablet formulations containing diltiazem hydrochloride as a model highly water-soluble drug. Int. J. Pharm. 386, 149–155.

Koker, R., 2006. Design and performance of an intelligent predictive controller for a six-degree-of-freedom robot using the Elman network. Inform. Sci. 176, 1781–1799.

Leane, M.M., Cumming, I., Corrigan, O.I., 2003. The use of artificial neural networks for the selection of the most appropriate formulation and processing variables in order to predict the in vitro dissolution of sustained release minitablets. AAPS PharmSciTech 4, 129–140.

Lee, Y.C., Zocharski, P.D., Samas, B., 2003. An intravenous formulation decision tree for discovery compound formulation development. Int. J. Pharm. 253, 111–119.

Lenth, R.V., 1989. Quick and easy analysis of unreplicated factorials. Technometrics 31, 469–473.

MacGregor, J.F., Bruwer, M.J., 2008. A framework for the development of design and control spaces. J. Pharm. Innovat. 3, 15–22.

Maggi, L., Segale, L., Torre, M.L., Machiste, E.O., Conte, U., 2002. Dissolution behaviour of hydrophilic matrix tablets containing two different polyethylene oxides (PEOs) for the controlled release of a water-soluble drug. Dimensionality study. Biomaterials 23, 1113–1119.

Mazumdar, J., Harley, R.G., 2008. Recurrent neural networks trained with backpropagation through time algorithm to estimate nonlinear load harmonic currents. IEEE T. Ind. Electron. 55, 3484–3491.

Mierswa, I., Wurst, M., Klinkenberg, R., Scholz, M., Euler, T., 2006. YALE rapid prototyping for complex data mining tasks. In: Proceedings of the 12th ACM SIGKDD International Conference on Knowledge Discovery and Data Mining (KDD-06).

Özyazici, M., Gökçe, E.H., Ertan, G., 2006. Release and diffusional modeling of metronidazole lipid matrices. Eur. J. Pharm. Biopharm. 63, 331–339.

Peh, K.K., Lim, C.P., Quek, S.S., Khoh, K.H., 2000. Use of artificial neural networks to predict drug dissolution profiles and evaluation of network performance using similarity factor. Pharm. Res. 17, 1384–1388.

Peng, Y., Geraldrajan, M., Chen, Q., Sun, Y., Johnson, J.R., Shukla, A.J., 2006. Prediction of dissolution profiles of acetaminophen beads using artificial neural networks. Pharm. Dev. Technol. 11, 337–349.

Peterson, J., 2008. A Bayesian approach to the ICH Q8 definition of design space. J. Biopharm. Stat. 18, 959–975.

Petrović, J., Ibrić, S., Jocković, J., Parojčić, J., Đurić, Z., 2009a. Determination of the percolation thresholds for polyethylene oxide and polyacrylic acid matrix tablets. J. Drug Deliv. Sci. Technol. 19, 359–364.

Petrović, J., Ibrić, S., Betz, G., Parojčić, J., Đurić, Z., 2009b. Application of dynamic neural networks in the modeling of drug release from polyethylene oxide matrix tablets. Eur. J. Pharm. Sci. 38, 172–180.

Petrović, J., Chansanroj, K., Meier, B., Ibrić, S., Betz, G., 2011. Analysis of fluidized bed granulation process using conventional and novel modeling techniques. Eur. J. Pharm. Sci. 44, 227–234.

Pouton, C.W., Porter, C.J.H., 2008. Formulation of lipid-based delivery systems for oral administration: materials, methods and strategies. Adv. Drug Deliv. Rev. 60, 625–637.

Quek, S.S., Lim, C.P., Peh, K.K., 2001. Prediction of drug dissolution profiles using artificial neural networks. Int. J. Comput. Intell Appl. 1, 187–202.

Quinlan, J.R., 1993. C4.5: Programs for Machine Learning. Morgan Kaufmann Publishers Inc, San Francisco, USA.

Ren, S., 2003. Phenol mechanism of toxic action classification and prediction: a decision tree approach. Toxicol. Lett. 144, 313–323.

Rowe, R.C., Upjohn, N.G., 1993. An expert system for the identification and solution of film coating defects. Pharm. Technol. Int. 5, 34–38.

Samarasinghe, S., 2006. Neural Networks for Applied Sciences and Engineering. Aurebach Publications, New York.

Shao, Q., Rowe, R.C., York, P., 2007. Comparison of neurofuzzy logic and decision trees in discovering knowledge from experimental data of an immediate release tablet formulation. Eur. J. Pharm. Sci. 31, 129–136.

Sudha, B.S., Sridhar, B.K., Sriantha, A., 2010. Modulation of tramadol release from a hydrophobic matrix: implications of formulation and processing variables. AAPS PharmSciTech 11, 433–440.

Sun, Y., Peng, Y., Chen, Y., Shukla, A.J., 2003. Application of artificial neural networks in the design of controlled release drug delivery systems. Adv. Drug Deliv. Rev. 55, 1201–1215.

Tiwari, S.B., Rajabi-Siahboomi, A.R., 2008. Extended-release oral drug delivery technologies: monolithic matrix systems. In: Jain, K.K. (Ed.), Drug Delivery Systems. Humana Press, Totowa, NJ, pp. 217–243.

Wu, N., Wang, L.S., Tan, D.C.W., Moochhala, S.M., Yang, Y.Y., 2005. Mathematical modeling and in vitro study of controlled drug release via a highly swellable and dissoluble polymer matrix: polyethylene oxide with high molecular weights. J. Control. Release 102, 569–581.

Zhang, J., Man, K.F., 1998. Time series prediction using recurrent neural network in multi-dimension embedding phase space. IEEE Syst. Man Cybern. 2, 11–14.

Zucker, D., Marcus, D., Barenholz, Y., Goldblum, A., 2009. Liposome drugs' loading efficiency: a working model based on loading conditions and drug's physicochemical properties. J. Control. Release 139, 73–80.

Zupancic Bozic, D., Vrecer, F., Kozjek, F., 1997. Optimization of diclofenac sodium dissolution from sustained release formulations using an artificial neural network. Eur. J. Pharm. Sci. 5, 163–169.