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Unified methodology of neural analysis in decision support systems built for pharmaceutical technology

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Abstract

The objective of this study was to create universal methodology of artificial neural networks (ANNs) application in construction of decision support systems designed for various dosage forms. Two different dosage forms (solid dispersions and microemulsions) were modeled with use of the same methodology, software and hardware environments. Completely different models prepared confirmed their generalization ability both for solid dosage forms (solid dispersions) and liquid dosage forms (microemulsions). *ME_expert* and *SD_expert* systems basing on the neural expert committees were created. In the pilot study their application allowed for appropriate choice of qualitative and quantitative composition of particular pharmaceutical formulation. It was also proposed that *ME_expert* and *SD_expert* might provide in silico formulation procedures. Unified methodology of neural modeling in pharmaceutical technology was confirmed to be effective in providing valuable tools for pharmaceutical product development.

Keywords: Artificial neural networks; Decision support systems; Pharmaceutical technology; Unified methodology; Solid dispersions; Microemulsions

1. Introduction

The objective of pharmaceutical technology is to design drug formulations chemically and physically stable on over prolonged period of time. Several dosage forms, (i.e. tablets, capsules, etc.), each having selected pharmaceutical properties, are developed to maximize drugs therapeutic response, thus ensuring maximum effectiveness of administered drug (Hulton, 2002). In order to achieve good quality of the dosage form, preparation must be done under carefully controlled conditions of production. It involves appropriate selection from numerous excipients and preparation technologies, which are key factors in drug formulation. In terms of more quantified approach, an optimization of qualitative and quantitative composition of the dosage form is performed. Classical algorithmic approach requires gathering of knowledge derived from various disciplines, in purpose to understand every aspect of drug action and interactions between drugs and excipients. Having such ultimate knowledge it is possible to ensure an effective optimization of dosage form. One major drawback is when the large number of governing variables is to be processed or in the worst scenario not all governing variables are fully identified. Thus, the analysis suffers from "curse of dimensionality" or, in the opposite, of lack of appropriate data. In another case, when there is not available mathematic formula describing relationships between characteristics of formulation and previously collected information, algorithmic reasoning is substituted by employing experience and rule-of-thumb approaches. Quantification of dosage form development process requires new tools for data analysis capable of handling complicated relationships, characterized by substantial predictive performance and easy in the management. Regarding this, artificial neural networks seem to be promising technique to be explored.

Artificial neural networks (ANNs) are well-established tools of computational intelligence, which were proved to

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be reliable and flexible in many applications in real life and science as well (Żurada, 1992). Although it is impossible to present all applications of neural networks, there might be named major areas of their usage:

- signal processing (noise reduction, compression),
- pattern recognition and feature extraction (handwriting, facial recognition, medical imaging, fraud detection),
- forecasting (financial, medical, weather).

Successful implementations of ANNs are the result of automatic mode of model form selection which derives from their learning ability. Recently, pharmaceutical technology applications of ANNs have been also considered. Regarding ANNs applications they could be grouped in two main classes: (1) optimization of dosage form composition and (2) optimization of preparation technology of particular dosage form. Main research areas were dedicated to solid dosage forms like tablets, capsules, pellets (Bourquin, Shmidli, van Hoogevest, & Leuenberger, 1998; Chen, McCall, Baichwal, & Meyer, 1999; Goh, Lim, & Peh, 2003; Rocksloh et al., 1999; Takahara, Takayama, & Nagai, 1997; Türkoğlu, Özarslan, & Sakr, 1995). There were also other applications: emulsions (Gašperlin, Tušar, Tušar, Kristl, & Šmid-Korbar, 1998; Gašperlin et al., 2000), microemulsions (Agatonovic-Kustrin & Alany, 2001), transdermal therapeutic systems (Kandimalla, Kanikkannan, & Singh, 1999), preformulation studies (Ebube, Owusu-Ababio, & Adeyeye, 2000) and in vitro–in vivo correlation (Dowell, Hussain, Devane, & Young, 1999).

Hussain, Yu, and Johnson (1991) as one of the first pointed that ANNs could be beneficial in the development of dosage forms. In the pilot study the proof was provided that ANNs allowed for accurate prediction of kinetics of chlorpheniramine maleate release from hydrophilic matrix-loaded capsules. Neural network inputs consisted of qualitative and quantitative composition of matrix. Higher accuracy of ANNs models was demonstrated in comparison to the RSM method. Numerous researchers followed the matter of ANNs application in pharmaceutical technology.

Goh et al. (2003) used neural networks of Jordan–Elman type to predict release characteristics of theophylline from pellets basing on their qualitative and quantitative composition. They found ANNs superior to classical regression analysis and confirmed superior predictive abilities of ANNs. In order to achieve these results, a sophisticated AdaBoost technique of expert committees preparation was applied, where specific training procedure for particular members of committee was used. The dataset for this problem counted only six formulations.

Bourquin et al. (1998) carried out neural analysis with substantially larger database counting 205 formulations. The task was to optimize composition and technology of preparation of tablets produced by direct compression method. Following input variables were chosen: amounts of excipients (silica aerogel, microcrystalline cellulose, carboxymethyl cellulose, magnesium stearate), time and compression force of tablet press. Several output variables were selected: tablets hardness, friability, ejection force and drug release characteristics. Specific neural network architecture was chosen for modeling purposes – a generalized feed forward multilayer perceptron network with extra connections between inputs and outputs and single hidden layer. The results have shown that ANNs were more precise than classical response surface method (RSM) in modeling relationships for direct compression tablets. Identification of non-linear relationships was easier and more effective in case of ANNs, however outliers presence in the learning dataset undermined substantially ANNs performance. Application of ANNs allowed to identify key factors for tablets ejection force which were amounts of silica aerogel and magnesium stearate. In conclusions authors recommend use of ANNs in the direct compression tablets development.

There were also other applications of ANNs apart from being only standalone data-modeling systems. Such an approach was presented by Chen et al. (1999) where ANNs were integrated with statistical tools to create hybrid system designed to develop optimal formulation of tablets characterized by controlled release of drug. ANN was trained to predict in vitro release characteristics of drug basing on the quantitative and qualitative composition of the tablet. Stella simulation software was applied to predict in vivo time–concentration profile of model drug basing on the drug dissolution characteristics. Therefore, it was created the chain of relationships: (1) tablet composition $\rightarrow$ {ANN} $\rightarrow$ (2) in vitro dissolution profile $\rightarrow$ {Stella} $\rightarrow$ (3) in vivo time–concentration profile, connected by two modeling tools: ANN and statistical system Stella. By a priori establishing optimal in vivo time–concentration profile and reversing the original relationships chain, it was possible to apply neural model in order to find optimal composition of tablet providing controlled release of drug.

In general, recent studies were focused on single, selected dosage form, thus providing specialized solutions adjusted to specific applications (Mendyk & Jachowicz, 2005). A logical consequence would be to create more general framework in order to establish a guideline of ANNs' use in pharmaceutical technology regardless of particular dosage form researched.

The aim of this study was to provide single methodology, which could be universal for application of ANNs for various dosage forms modeling. Two completely different dosage forms: solid dispersions and microemulsions were chosen to be modeled by ANNs in order to create decision support systems providing an aid in the prospective formulation of abovementioned dosage forms.

2. Materials and methods

In order to unify methodology of neural modeling for various dosage forms there was made assumption of expert-systems-like construction and function of such