Thermochimica Acta 659 (2018) 222–231

Contents lists available at ScienceDirect

Thermochimica Acta

journal homepage: www.elsevier.com/locate/tca

Artificial neural networks as a supporting tool for compatibility study based on thermogravimetric data

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ARTICLE INFO

Keywords:
Caffeine
Compatibility/incompatibility
Thermogravimetry
Multivariate statistical analysis
Artificial neural networks
Self-organizing maps

ABSTRACT

This paper focuses on applying of artificial neural networks (ANNs) for the incompatibility detection between an active pharmaceutical ingredient (API) and excipients on the basis of thermogravimetric data. In binary model mixtures, caffeine was used as API mixed with selected excipients. The interpretation of ANN results was based on the assumption that the model mixtures with relatively high content of API (70 and 90%), should undergo similar course of thermal decomposition and be placed in nearby neurons, as opposed to mixtures where excipient predominated. When different behaviour of model mixtures was observed, the incompatibility between mixture ingredients was determined. The results indicate ANNs combined with thermogravimetry to be a simple diagnostic tool that visualizes the behaviour of ingredients in binary mixtures by placing them in different neurons of the topological map so as to determine incompatibility occurrence. The findings were confirmed with complementary techniques − DSC, FTIR and XRPD.

1. Introduction

Preformulation is a critical stage in drug development where the physicochemical profiling of an active pharmaceutical ingredient (API) and excipients are determined and model formulation is prepared. The choice of excipients is associated with an exhaustive evaluation of drug-excipient compatibility or interaction [1]. Thus, compatibility screening of an API with excipients or other active ingredients is recognized as one of the mandatory factors that is at the forefront of drug product research and technology. In addition, a complete understanding of the physicochemical interactions in dosage forms is expected under quality by design prototype of drug development and is encouraged by various regulatory bodies worldwide. The introduction of thermoanalytical methods into the initial steps of pre-formulation studies have contributed significantly to early prediction, monitoring and characterization of the API incompatibility to avoid costly material wastage and considerably reduce the time required to arrive at an appropriate product formulation [2,3].

The most frequently used thermal methods for prospective compatibility screening studies include differential scanning calorimetry (DSC), differential thermal analysis (DTA), and thermogravimetry (TG) [2,4]. Since no generally accepted procedures to evaluate compatibility/incompatibility between drug and excipients exist, there is still ongoing search for more effective methods for incompatibility detection.

The TG by its nature is a quantitative technique and can frequently be used to determine the amount of a substance in a mixture or a purity of a substance. TG has been particularly fruitful in determination of reaction rates. Data obtained by this method are often more accurate than those from other techniques but usually require the support of complementary chemical and structural characterizations to identify and confirm the reaction stoichiometry [5]. To detect incompatibility in drug-excipient mixtures, the TG profiles of API and excipients are being compared with those of their mixtures. Unfortunately, these comparisons provide equivocal data, because crucial information that can be extracted from the shape of TG traces is the change of mass (loss or gain) during thermal decomposition and the temperature range within which this process occurs. Hence, full information about the character of thermal processes cannot be derived from the TG traces and a plain detection of incompatibility of API with excipients can be deceptive [6]. In addition, TG by itself is not a distinctive technique and the identification of incompatibility solely on TG data may lead to misinterpretation and unreliable conclusions. Therefore, TG data may require the application of multivariate methods [7,8].

Among multivariate methods, special meaning has been given to artificial neural networks (ANNs) [9,10]. The most characteristic feature of ANNs is the ability to learn complex nonlinear input-output relationships, use sequential training procedures, and adapt themselves to the data. The most commonly used ANNs for pattern classification tasks are feed-forward networks, i.e. multilayer perceptron and radial-

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https://doi.org/10.1016/j.tca.2017.12.015
Received 17 October 2017; Received in revised form 7 December 2017; Accepted 8 December 2017
Available online 11 December 2017

basis function. Another popular networks are self-organizing maps (SOMs), also called Kohonen networks, used mainly for data clustering and feature mapping [11].

The SOMs are probably the best known of the unsupervised neural network methods and has been used in varied applications [9]. The SOM is often chosen because of its suitability to visualize data, otherwise difficult to interpret [12]. These ANNs are composed of only two layers: the input and the output layer of radial neurons. Accordingly, the formation of SOM is determined by the size of the output layer, where the samples are to be mapped and by the size of the neighbourhood (the distance between neurons where the samples are to be considered similar). SOM leads to clustering of data and relating similar classes to each other [13].

However, it must be noted that if the number of neurons is too small, the samples will be placed in the same or adjacent neuron regardless of their characteristics. If the number is too big, the samples will be scattered all over the map making identification of any vital similarities (differences) impossible to discern. Additionally, when two or more input variables are highly correlated, the SOM model can depend entirely either on one variable or on the other or on some arbitrary combination of them. In such situation it is advisable to eliminate some variables, because ANN will not recognize the data structure properly.

The above mentioned properties of SOM underlay the search for effective and fast method for detecting drug-excipient incompatibility based on the data from TG traces. The additional incentive was also the fact that up to now, the use of ANNs as a solution to the problem of thermoanalytical results has rarely been reported [14–17].

As the study material the binary mixtures of caffeine and some excipients were used. The findings of ANN studies were to be confirmed by complementary techniques – DSC, Fourier transform infrared spectroscopy (FTIR) and powder X-ray diffraction (PXRD).

2. Material and methods

2.1. Materials

Caffeine, ($C_8H_{10}N_4O_2$); HPLC purity ≥ 99%, m.p. 232–236 °C, was supplied by Fluka (Siegen, Germany). Glicocol, ($C_2H_5NO_2$); sorbitol, ($C_6H_{14}O_6$); sucrose, ($C_{12}H_{22}O_{11}$); and arabic gum were purchased from POCh (Gliwice, Poland). Glucose, ($C_6H_{12}O_6$) was provided by Centro-Chem (Lublin, Poland), whereas microcrystalline cellulose (Avicel PH-101), $(C_6H_{10}O_5)_n$ was obtained from the FMC Corp. Europe NV (Brussels, Belgium). Caffeine and excipients were used as obtained without further purification.

Binary physical mixtures of caffeine with selected excipient at molar or mass ratios of 9:1, 7:3, 1:1, 3:7 and 1:9 were prepared by gentle mixing of both ingredients in agate mortal for 5 min. Ingredients with similar molar masses were mixed at the molar ratios (caffeine with glicocol, glucose, sorbitol and sucrose), whereas those that differed significantly in molar masses were mixed at mass ratios (caffeine with arabic gum and microcrystalline cellulose).

2.2. Thermogravimetry

The TG measurements were carried out with TGA Discovery device (TA Instruments, New Castle, DE, USA). The samples of approximately 10 mg were placed in platinum pans and heated from 25 to 700 °C at the heating rate 10 °C/min. The investigations were realized in air atmosphere (purity 99,999%, Air Products, Warsaw, Poland) with a flow rate of 25 mL/min. Mass-temperature diagrams were analysed using Trios software.

The interpretation of TG traces was based on the determination of the temperatures of mass loss taken as an arithmetic mean of three measurements, starting with the temperature of 5% mass loss (T_5) and ending on the temperature of 75% mass loss (T_{75}). The temperatures were measured every 5% of mass loss, giving 16 variables (T_5, T_{10}, T_{15}, T_{20}, T_{25}, T_{30}, T_{35}, T_{40}, T_{45}, T_{50}, T_{55}, T_{60}, T_{65}, T_{70}, T_{75}) in all. Through correlation analysis, only some temperature values were selected as input variables for ANN calculations.

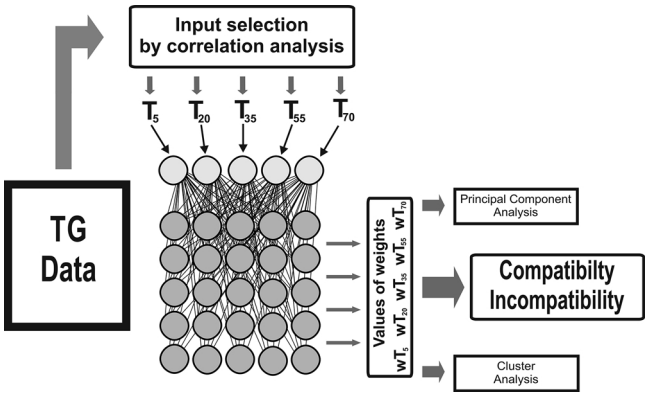

Fig. 1. Scheme of neural and pattern recognition techniques employed in the study.

2.3. Calculations

Chemometric calculations were performed using Statistica 10 software (StatSoft Inc., Tulsa, OK, USA). A schematic of the computational procedure is shown in Fig. 1. Firstly, the correlation matrix between temperatures of particular mass loss was computed to identify strong linear correlations between variables.

The SOM is made up of numerous processing units called neurons placed in two different layers – input and output (Fig. 2). The input layer is built of linear neurons, and the output layer of radial ones, which are arranged in two-dimensional grid often referred to as topological map. Each neuron uses an aggregation function to collect the weighted input values, which is passed through a transfer function to give their output. In linear neuron it is a weighted sum of its inputs, while in radial ones it is a scaled squared distance of weight vector from input vector. It must be also noted that the transfer functions differ in both types of neurons. In linear neurons the transfer function is typically sigmoidal, but in radial neurons it is Gaussian.

The SOM operates using unsupervised training, in which the weights of neurons (w_1, w_2, …, w_k) in the topological map are entirely adjusted in response to the input pattern (x_1, x_2, …, x_m). A single pass through the entire input pattern to update the weights of neurons is called an epoch. The network forces the neurons to compete against each other to determine which one is to be activated. The result of the

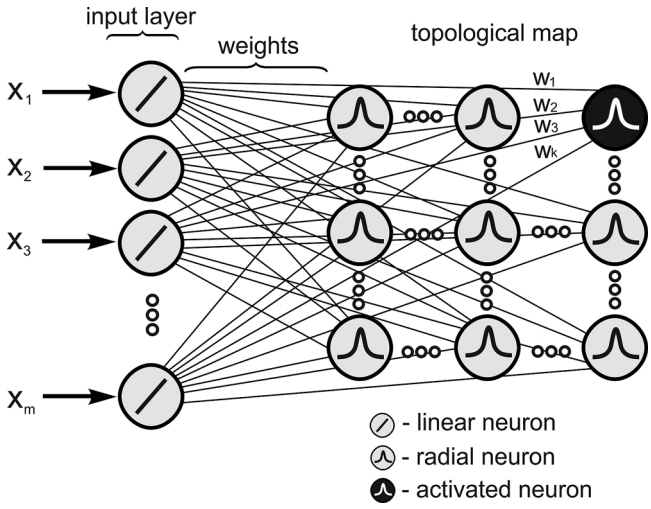

Fig. 2. The general architecture of SOM.