European Journal of Pharmaceutical Sciences 44 (2011) 321–331

Contents lists available at SciVerse ScienceDirect

European Journal of Pharmaceutical Sciences

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

Drug release control and system understanding of sucrose esters matrix tablets by artificial neural networks

Krisanin Chansanroj [a,*], Jelena Petrović [b], Svetlana Ibrić [b], Gabriele Betz [a]

[a] Industrial Pharmacy Research Group, Department of Pharmaceutical Sciences, University of Basel, Mülhauserstrasse 51, 4056 Basel, Switzerland
[b] Institute of Pharmaceutical Technology, Faculty of Pharmacy, University of Belgrade, Vojvode Stepe 450, 11221 Belgrade, Serbia

ARTICLE INFO

Article history:
Received 15 December 2010
Received in revised form 16 July 2011
Accepted 15 August 2011
Available online 23 August 2011

Keywords:
Controlled release
Matrix tablet
Sucrose esters
Neural network
Swelling
Hydrophilic–lipophilic property

ABSTRACT

Artificial neural networks (ANNs) were applied for system understanding and prediction of drug release properties from direct compacted matrix tablets using sucrose esters (SEs) as matrix-forming agents for controlled release of a highly water soluble drug, metoprolol tartrate. Complexity of the system was presented through the effects of SE concentration and tablet porosity at various hydrophilic–lipophilic balance (HLB) values of SEs ranging from 0 to 16. Both effects contributed to release behaviors especially in the system containing hydrophilic SEs where swelling phenomena occurred. A self-organizing map neural network (SOM) was applied for visualizing interrelation among the variables and multilayer perceptron neural networks (MLPs) were employed to generalize the system and predict the drug release properties based on HLB value and concentration of SEs and tablet properties, i.e., tablet porosity, volume and tensile strength. Accurate prediction was obtained after systematically optimizing network performance based on learning algorithm of MLP. Drug release was mainly attributed to the effects of SEs, tablet volume and tensile strength in multi-dimensional interrelation whereas tablet porosity gave a small impact. Ability of system generalization and accurate prediction of the drug release properties proves the validity of SOM and MLPs for the formulation modeling of direct compacted matrix tablets containing controlled release agents of different material properties.

1. Introduction

Direct compacted matrix tablet formulations have gained more interest in controlled release drug delivery systems due to simplicity of formulation developments and manufacturing processes. Success of the formulations relies on selection of an appropriate matrix-forming agent that gives a desirable drug release rate (Colombo et al., 2000). Sucrose esters (SEs) have been recently presented a promising controlled release property for matrix tablet systems (Chansanroj and Betz, 2010; Ntawukulilyayo et al., 1995). They are classified as biodegradable non-ionic surfactants composed of mono- and polyesters of sucrose and fatty acids. SEs possess a wide range of material properties with hydrophilic–lipophilic balance (HLB) values ranging from 0 to 16 based on monoester proportions. A combination of their lipophilicity and hydrophilicity in the composition affects the drug release where hydrophilicity of the material accelerates swelling phenomena and sustains the drug release rate (Chansanroj and Betz, 2010).

Despite the impact of controlled release agents, influence of tablet properties, including tablet shape, dimension, surface area (Ford et al., 1987; Siepmann et al., 2010), porosity and pore networks (Castellanos Gil et al., 2009; Mäki et al., 2006; Petrone et al., 2008; van Veen et al., 2005), also contribute to the release behavior which may lead to inconsistency in the drug release rate of the final products. To date, the concept of quality by design (QbD) guided by US FDA invokes comprehensive understanding of product and manufacturing processes in order to assure the consistence of product performance (US FDA, 2009). In the development of multivariate systems such as controlled release matrix tablet formulations, this approach urges formulators to find a powerful computational module that enables to generalize the system complexity and gain insight into the relationships among formulation and process variables.

Artificial neural networks (ANNs) are computational algorithms implemented by software programs that analyzes data in the same way as human brain functions to learn, generalize and solve the problems based on experience. Similar to the brain structure, the network composes of several processing elements or nodes which are capable to extract non-linear relationships from the data and use this knowledge to interpolate the results from desirable conditions. These abilities encourage their implementation in pharmaceutical developments where multivariate systems are generally contributed (Agatonovic-Kustrin and Beresford, 2000; Bourquin et al., 1997a; Hussain et al., 1991; Sun et al., 2003; Takayama

* Corresponding author. Tel.: +41 61 381 0723; fax: +41 61 381 0430.
E-mail addresses: Krisanin.chansanroj@unibas.ch, krisanin@yahoo.com (K. Chansanroj).

0928-0987/$ - see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.ejps.2011.08.012

et al., 2003). ANNs present superiority over a commonly used multi-linear regression methodology in many complex systems, including particle distribution of fluid bed granules (Laitinen et al., 2002), powder flow during mixing (Kachrimanis et al., 2003), tableting processes (Bourquin et al., 1997b, 1998), dissolution behavior of poorly soluble drugs (Wilson et al., 2005) and controlled release matrix tablets (Barmpalexis et al., 2010; Ibric et al., 2002; Takahara et al., 1997; Takayama et al., 2000).

Several topologies of ANNs have been tested for the modeling of controlled release matrix tablets mainly based on the formulation basis. Multilayer perceptron neural networks (MLPs) are the most commonly used networks due to the ability of data generalization and accurate prediction regarding their supervised learning (Barmpalexis et al., 2010; Takahara et al., 1997; Zupani Bozi et al., 1997). Besides, generalized regression neural networks provide faster computation speed and less data treatment due to their unsupervised learning (Ibric et al., 2002) whereas dynamic neural networks interpolate the drug release with a consideration of time-series influence (Petrovic et al., 2009). Selection of an appropriate network is problem- and objective-dependent and the efficiency of the analysis can be improved with a combination of different network topologies.

We investigated in a previous study the effect of hydrophilic–lipophilic properties of SEs on the drug release from direct compacted matrix tablets (Chansanroj and Betz, 2010). In this study, two objectives are further assigned; (i) to evaluate the effects of SE concentration and tablet porosity on the release behavior and (ii) to employ ANNs for the system understanding and prediction of drug release properties from the complex system of SE matrix tablets based on SE and tablet property variables. Data of drug release, including the results from the previous study, are used for the ANNs analysis. A self-organizing map neural network (SOM) is applied for visualizing interrelation among the data whereas MLPs are employed for the prediction of drug release properties. Optimization of MLPs performance based on network learning algorithm is performed in order to achieve the best prediction. Importance of the variables is verified in multi-dimensional relation by sensitivity analysis. Ability of SOM and MLPs to simplify the systems and estimate the drug release for controlled release approaches is discussed.

2. Materials and methods

2.1. Materials

Sucrose stearates with HLB values 0, 1, 3, 5, 9, 11, 15 and 16 (Ryoto Sucrose Esters®) were kindly provided by Mitsubishi-Kagaku Foods Corporation, Tokyo, Japan. Materials were in a food grade and contained monoesters in the proportions of <1%, 1%, 20%, 30%, 50%, 55%, 70%, 75%, respectively (Mitsubishi-Kagaku Foods Corporation, 2003). Metoprolol tartrate (Batch number MT-20/00, Karinco, Milan, Italy) was used as a highly water soluble model drug, sieved through a 200 μm standard sieve. Dibasic calcium phosphate dihydrate (Edward Mendell, New York, US) and magnesium stearate (Hänseler AG, Herisau, Switzerland) were used as tablet filler and lubricant, respectively.

2.2. Compaction of matrix tablets

Drug powder and SEs were weighed in a 100 ml amber glass bottle and mixed with a Turbula mixer (Willy A. Bachofen AG, Switzerland) at 50 rpm for 5 min. Tablet filler was added to the powder blend and mixed for further 5 min. Before compaction, 0.5 wt.% magnesium stearate was added and mixed for 3 min. A formulation without SEs was prepared for comparison in which the proportion of SEs was replaced by tablet filler. Matrix tablets were prepared by a tablet press replicator, Presster™ (Metropolitan Computing Co., US), equipped with 10 mm flat-faced punch at the linear speed of 0.408 m/s, simulating the production of a rotary tablet press, Korsch PH336, at 10800 tablets/h. Powder blend of 400 mg, comprising 100 mg of the drug, was accurately weighed and compacted by manual feed at different compaction force. At least 10 tablets were prepared for each formulation and stored in an airtight container at ambient condition before analysis.

2.3. Determination of physical properties of tablets

Tablet mass was examined immediately after the compaction using an analytical balance (AX204 DeltaRange, Mettler Toledo, Switzerland). Tablet dimensions and tensile strength were measured after 24 h storage in order to assure the completion of tablet relaxation. Tablet dimensions were measured by a digital calliper (Mauser International, Germany) and calculated tablet volume. Tablet porosity (ε) was calculated according to apparent density (ρ_A), derived from tablet dimensions, and true density (ρ_T), calculated from the density of the components measured by a helium pycnometer (AccuPyc 1330, Micromeritics, US). Porosity was reported in percentage according to the following equation:

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

Five tablets were subject to a diametral load with a hardness tester (Pharmatron, Dr. Schleuniger, Switzerland) and tensile strength (σ_x) was calculated from the following equation (Fell and Newton, 1970):

$$\sigma_x = \frac{2 \times F}{\pi d h} \quad (2)$$

where F is the diametral crushing force, d the tablet diameter and h the tablet thickness.

2.4. In vitro dissolution test

In vitro dissolution test was performed by a USP Apparatus II (AT 7 smart, Sotax, Switzerland) in 500 ml phosphate buffer (pH 6.8, 37 ± 0.5 °C) at 50 rpm for 12 h (n = 6). Drug content was analyzed using a UV spectrophotometer (Lambda 25, PerkinElmer, Switzerland) at 273 nm. Three release properties, i.e., burst release at 10 min, mean dissolution time and release exponent were determined. Mean dissolution time was calculated using the following equation (Costa and Lobo, 2001):

$$MDT = \frac{\sum_{i=1}^{n} \hat{t}_i \Delta M_i}{\sum_{i=1}^{n} \Delta M_i} \quad (3)$$

where i is the sample number, the midpoint of the time period between t_i and t_{i-1} and ΔM_i the amount of drug released between t_i and t_{i-1}.

Release mechanism was interpreted using an exponential relation; $M_t/M_\infty = kt^n$, proposed by Peppas (1985). The equation was expanded by Lindner and Lippold (1995) with the addition of an intercept (b), referring to a burst effect, for the better correlation. The equation is presented as follows:

$$\frac{M_t}{M_\infty} = kt^n + b \quad (4)$$

where M_t is the amount of drug release at time t, M_∞ the total amount of drug release, k the constant and n the release exponent.