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An investigation into the usefulness of generalized regression neural network analysis in the development of level A in vitro–in vivo correlation

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ABSTRACT

Quantitative correlations between in vivo and in vitro data (IVIVC) reduce the number of human in vivo studies, thus decreasing the overall time and expenses necessary for the development of optimal drug product formulation. Although linear regression analysis represents the simplest relationship, it is recognized that IVIVC should not be limited to linear relationship. With regards to the implementation of non-linear IVIVC models and the ability of artificial neural network (ANN) computing to cope with non-linear relationships, the usefulness of ANN analysis in the development of IVIVC merits further evaluation. The present paper is an attempt to develop an IVIVC for model sustained release paracetamol matrix tablet formulations employing various correlation approaches based on linear and non-linear modeling of in vitro and in vivo data. Currently accepted compendial methodology was compared with the alternative approaches, involving general mixed effects model and generalized regression neural network (GRNN) analysis, in order to evaluate their usefulness for predicting the in vivo behavior of drug products. Although based on analogous approaches, data generated by GRNN were closer to those observed in vivo, leading to the higher level of IVIVC than obtained by convolution. It can be assumed that GRNN analysis was able to generalize complex relations between the output and input parameters and could account for the differences in drug release kinetics observed under various conditions in vitro, thus offering potential as a reliable and robust estimate of drug products in vivo behavior.

1. Introduction

In an attempt to reduce the burden of human in vivo studies for regulatory purposes, as well as during the development of new drug products, it was recognized that drug release kinetics in vitro should give an insight into the relevant in vivo process and may be used as a predictive tool of drug products in vivo behaviour. This is the rationale for the in vitro–in vivo correlation (IVIVC) concept in biopharmaceutics. This concept has gained increased attention both scientifically, as well as regulatory, during the past decade, resulting with the establishment and definition of relevant terms, methodology and regulatory guidelines for its development (FDA/CDER, 1997; EMEA/CPMP, 2000; USP 28). IVIVC is defined as a rational,

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quantitative relationship between a biological property or a parameter derived from a biological property produced by a dosage form, and a physicochemical property or characteristic of the same dosage form (USP 28). Currently accepted methodology for the establishment of IVIVC, involves (1) the development and in vitro and in vivo evaluation of several formulations with different drug release rates in vitro; (2) assessment of the hypothetical drug dissolution profile in vivo using an appropriate deconvolution technique and (3) comparison of the two sets of data obtained, namely in vitro and in vivo drug release profiles, in order to establish quantitative, mathematical relationship between them (FDA/CDER, 1997; EMEA/CPMP, 2000; USP 28). Although linear regression analysis which is officially recommended, represents the simplest relationship and, thus, the most appropriate to be considered first, it has been recognized that IVIVC should not be limited to only linear relationship. A number of publications emphasize the attempts to develop non-linear in vitro–in vivo correlations (Polli et al., 1996; Dunne et al., 1997, 1999; Sirisuth et al., 2002). Polli et al. (1996) proposed the model equation derived assuming first-order dissolution and permeation after oral drug administration. Dunne et al. (1997, 1999) proposed the general mixed effects models based on assumption that in vitro and in vivo distributions of time at which drug molecule enters solution could be related to one another using a proportional odds, proportional hazards or proportional reversed hazards models. Sirisuth et al. (2002) reported the use of linear and non-linear (quadratic, cubic and sigmoid) correlation models in order to develop an IVIVC for a diltiazem multiparticulate bead extended release formulation. Also, in the paper presented by Mendell-Harary et al. (1997) several non-linear functions were considered as empirical equations to describe the relationship between the in vitro and in vivo data.

With regards to the development of non-linear IVIVC models and the complexity of the relationship between in vitro and in vivo drug release kinetics, artificial neural networks (ANNs) have potential for predicting in vivo drug concentration time profiles from in vitro dissolution data in the course of IVIVC development. ANNs are machine based computational techniques which attempt to simulate some of the neurological processing ability of the human brain (Achanta et al., 1995). They represent networks of processing elements (or nodes) which through a process of learning from task examples, store experimental knowledge and make it available for use. ANNs are characterized by the arrangement of processing elements and their interconnections (i.e. the network architecture), transfer function and learning paradigm (Erb, 1993; Kustrin-Agatonović and Beresford, 2000). Two common ANN connection patterns include the feed-forward and the recurrent architectures. The feed-forward architecture allows data flow to occur in one direction and the network output is solely based on the current set of inputs. This architecture is suitable for situations when all the necessary information (inputs) is available to estimate the network response (output). The feed-forward neural networks are usually used to relate two functions, or establish an input–output relationship that is not dependent on a previous or sequential input–output relationship. Any type of non-linearity in the system must be within each input–output association, as it would be in the case of IVIVC data modeling. ANNs are trained using pre-existing data: in order to provide appropriate response it first needs to be trained to recognize underlying patterns that define functional relationships between input and output data vectors. The training process involves adjusting connection weights and methods used to accomplish this are referred to as learning rules or algorithms. A properly trained ANN can generalize to previously unseen (but within the domain of its training) input vectors. Once trained, the network can be used to predict output values for new input data.

ANN offer capabilities that are different from those offered by traditional regression/statistical approaches, however, its application in the field of pharmaceutical research and development is relatively new and gained increased interest mainly in the field of formulation and process optimization (Colbourn and Rowe, 1996; Chen et al., 1999; Takayama et al., 1999, 2003; Turkoglu et al., 1999, 2004; Faure et al., 2001; Ibrić et al., 2002; Leane et al., 2003; Behzadi et al., 2005). Hussain (1997) and Dowell et al. (1999) initiated the use of ANN analysis in the development of IVIVC. It was stressed that the self-organizational properties of ANN methods and their ability to incorporate a large number of possible variables and relationships without a predefined model structure, encourage the evaluation of ANN for determining an IVIVC. In the paper presented by Hussain (1997), it was hypothesed that a mapping network, such as the back propagation network, may be used to relate meaningful in vitro dissolution profiles directly to in vivo blood level profiles. It was concluded that inclusion of a unit impulse reference did not appear to be critical for ANN development, although this issue needs to be further evaluated (Hussain, 1997). Dowell et al. (1999) postulated that "IVIVC can be seen as an input–output relationship, while we are often not interested in the internal structure of this model as long as we have a good, validated, predictive tool". They have tested various network types and architectures in order to evaluate their applicability to recognize the pattern in the available experimental data and predict in vivo drug profile. A high level of correlation was obtained between the in vitro drug release data presented as input and plasma concentration data applied as output parameters. Although the authors discussed the "analogy" with a convolution operation, a reference drug product, which provides a measure of unit impulse kinetics in vivo, was not included in the study.

The present paper focuses on a case study of two paracetamol sustained release matrix tablet formulations based on novel carbomer polymers, Carbopol 971P and Carbopol 71G. The selected tablet samples were characterized in vivo in a group of healthy volunteers and in vitro under the range of various experimental conditions. Although chemically identical, these two polymers exhibited different drug release patterns both in vitro and in vivo (Parojčić et al., 2004a, 2005). In a separate study, poor level A correlation has been obtained for tablets based on Carbopol 71G for all the in vitro experimental conditions studied (Parojčić et al., 2004a). Consequently, various approaches to establish an IVIVC, involving convolution and deconvolution procedures followed by linear regression analysis, as well as non-linear proportional odds, proportional hazards, proportional reversed hazards models and generalized regression neural network analysis (GRNN) were applied and compared in order to evaluate their applicability and usefulness.