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Research paper

Artificial neural networks in the optimization of a nimodipine controlled release tablet formulation

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ABSTRACT

Artificial neural networks (ANNs) were employed in the optimization of a nimodipine zero-order release matrix tablet formulation, and their efficiency was compared to that of multiple linear regression (MLR) on an external validation set. The amounts of PEG-4000, PVP K30, HPMC K100 and HPMC E50LV were used as independent variables following a statistical experimental design, and three dissolution parameters (time at which the 90% of the drug was dissolved, $t_{90\%}$, percentage of nimodipine released in 2 and 8 h, Y_{2h}, and Y_{8h}, respectively) were chosen as response variables. It was found that a feed-forward back-propagation ANN with eight hidden units showed better fit for all responses (R^2 of 0.96, 0.90 and 0.98 for $t_{90\%}$, Y_{2h} and Y_{8h}, respectively) compared to the MLR models (0.92, 0.87 and 0.92 for $t_{90\%}$, Y_{2h} and Y_{8h}, respectively). The ANN was further simplified by pruning, which preserved only PEG-4000 and HPMC K100 as inputs. Optimal formulations based on ANN and MLR predictions were identified by minimizing the standardized Euclidian distance between measured and theoretical (zero order) release parameters. The estimation of the similarity factor, f_2, confirmed ANNs increased prediction efficiency (81.98 and 79.46 for the original and pruned ANN, respectively, and 76.25 for the MLR).

1. Introduction

Nimodipine (NIM) is an active pharmaceutical ingredient (API) that belongs to the class of pharmacological agents known as calcium channel blockers [1]. It has cerebrovasodilatory and neuronal affects and is mainly used in the treatment of subarachnoid haemorrhage (SAH), focal or global ischemia, as well as epilepsy [2]. Oral administration of NIM is associated with certain problems such as frequent dosing (30–60 mg every 4–8 h) varying half life and fluctuating plasma concentrations [1]. The preparation of a NIM-controlled release formulation could be an appealing solution to these problems, and until now, attempts for the preparation of a controlled release formulation include the development of floating-sustained release tablets [3] and soft gelatine capsules [4].

Development of a controlled release tablet formulation is commonly achieved by the use of hydrophilic polymer blends. Hydrophilic matrices are widely accepted because of their biopharmaceutical and pharmacokinetics advantages over conventional dosage forms [5], offering precise modulation of drug release as a result of hydration and swelling. Commonly used polymers for the preparation of hydrophilic matrices include substituted celluloses such as hydroxypropylmethylcellulose (HPMC) and hydroxypropylcellulose (HPC) [6], different grades of polyvinylpyrrolidone (PVP) and polyethylene glycol (PEG).

Furthermore, the preparation of controlled release formulations involves handling and optimizing a large number of factors, such as polymer matrix composition and drug to matrix ratio. Conventional trial-and-error methods require increased amounts of experiments in order to identify an acceptable solution. As the number of factors increases, these types of methods become highly inefficient. Therefore, they have been merely superseded by statistical experimental design methodology known as Design of Experiments (DoE). DoE usually includes a screening and an optimization phase [7]. Screening designs involve experimentation at two extreme factor levels (high and low), in order to identify factor's significance (the insignificant factors are excluded from the next step of optimization). Response surface methodology has been widely used as an optimization technique for drug delivery systems [8–10], and it is proven to be efficient in terms of cost, time and effort. This methodology involves the use of various types of experimental designs involving three or more factor levels, thus enabling the fitting of not only just linear (as is the case for two-level screening designs), but also quadratic or cubic polynomial equations. Mapping of response(s) over the experimental domain allows for the determination of optimum solution(s) [8,9].

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Despite the advantages of DoE-based polynomial model fitting, often the developed models show bad fit resulting to a poor optimum estimation. An alternative approach that has been successfully applied in cases where conventional DoE methods prove inadequate is the use of feed-forward artificial neural networks (ANNs) [11–15]. ANNs are biologically inspired computer algorithms that act as universal function approximators, having the ability to model highly complex relationships where the response variables are non-linearly related to the independent variables. Two of the main advantages of the ANN are [16] (a) there is no need to assume an underlying data distribution and (b) ANNs are applicable to highly non-linear multivariate problems. However, a critical evaluation of the ANN can reveal several disadvantages including [16] (a) minimizing over-fitting requires a great deal of computational effort and (b) it is not so straightforward to investigate the individual relations between the input variables and the output variables, as the ANN models lack a sound theoretical background.

Therefore, the present work investigates the use of ANNs in the development of a NIM-controlled release matrix tablet formulation typically releasing 90% of the drug in 12 h that follows a zero-order profile. Hydrophilic polymers (HPMC, PVP and PEG) are used as matrix formers. Screening of significant formulation factors (amounts of various hydrophilic polymers) is performed according to a two-level full factorial design, and the levels of the identified significant factors are subsequently optimized by fitting feed-forward ANN models to experimental drug release data obtained according to a circumscribed central composite design (CCD). In order to simplify ANNs' structure, different pruning techniques are applied, and the efficiency of the ANNs is compared to that of conventional polynomial multi-linear regression (MLR) models.

2. Materials and methods

2.1. Materials

Micronized NIM, with mean particle size of 18.2 (±11.2) μm, measured as circle equivalent diameter by digital imaging analysis using a Quantimet 500 system (Leica, Cambridge UK) supplied by Union Quimico Farmaceutica S.A. (UQUIFA, Barcelona, Spain) was used as an API.

Polyethylene glycol (PEG-4000, CLARIANT, Sulzbach, Germany), polyvinylpyrrolidone (PVP K30, BASF Co, Ledgewood, NJ) and two grades of hydroxylpropylmethylcellulose (HPMC) differing in the degree of substitution and viscosity (K100M grade with methoxy content 19–24% w/w and viscosity 80,000–120,000 cps, and E50LV grade with methoxy content 28–30% w/w, and viscosity 40–60 cps), purchased from Dow Chemical Company (Midland, MI, USA), were used as hydrophilic matrix formers.

Magnesium stearate (Mg Stearate) purchased from Katayama (Osaka, Japan) was used as lubricant.

Distilled water and sodium lauryl sulfate (SLS) obtained from COGNIS (Fino Mornasco, Italy) were used for the preparation of dissolution medium.

All other materials and reagents were of analytical grade and used as received.

2.2. Preparation of NIM dispersions and tableting

Pre-weighted amounts of PEG-4000 were placed in aluminium dishes and heated in a water bath at 70 °C to complete melting. NIM and the remaining polymers were then sequentially dispersed in the PEG melt in 5 min intervals. This process leads to a dispersion of crystalline NIM microparticles in the polymer matrix, verified by the strong birefringence when observed microscopically under crossed polarizers, according to the European Pharmacopoeia method using a PriorluxPol petrological microscope (Prior, UK). The resultant dispersions were stored at −18 °C for 2 days and then pulverised using a mortar and a pestle. The 100–150 mesh size fraction was separated, and Mg Stearate (0.5% w/w) was added and mixed for 5 min with a spatula. The powders were stored in hermetically sealed dark-glass vials for further processing.

Appropriate amounts of sample containing 30 mg of NIM were compressed on a manually operated hydraulic press equipped with a 7 mm diameter flat-faced punch and die set pre-lubricated with Mg Stearate. A compression pressure of 3185 N/cm^2 was applied for 5 s (sufficient to obtain compacts of minimum attainable porosity). This procedure led to tablets of varying thickness (2.51–5.27 mm), leading to differences in the initial surface area. However, the fast and extensive swelling of the tablets leads to a rapid increase in the initial surface area, depending on the hydrophilic polymer content; therefore, these initial differences are expected to have a negligible influence on drug release.

In order to prevent the photodecomposition of NIM, all formulations were protected from light.

2.3. HPLC verification of drug content

The actual drug content of tablets was assayed using a validated HPLC method [17]. A Shimadzu Prominence HPLC system consisting of a degasser (Model DGU-20A5), a pump (Model LC-20AD), an auto sampler (Model SIL-20AC), a UV–Vis detector (Model SPD-20A) and a column oven (Model CTO-20AC) was used. Chromatographic analysis was performed on an Interchrom C8 analytical column (5 μm particle size, 250 × 4.6 mm I.D.). The mobile phase used was acetonitrile/water (67.5:32.5, v/v) with a flow rate of 0.9 ml/min, and the column temperature was 40 °C. Injection volume was set at 10 μl, and NIM was detected at 236 nm. The excipients used in this study did not interfere with the assay of NIM.

2.4. In vitro release studies

In vitro release of NIM from tablets was evaluated using apparatus II (rotating paddle method) of the USP29, on a Distek 2100C dissolution tester (Distek, North Brunswick, NJ). The dissolution medium consisted of 1000 ml of distilled water containing 0.5% w/w SLS. The test was performed at 37 ± 0.5 °C under stirring at 50 rpm. Sink conditions were maintained throughout the test. An aliquot of 4 ml of samples was collected at 5, 15, 30, 60, 120, 240, 480, 720, 960 and 1200 min using an automatic sampler (Distek Evolution 4300) and assayed for NIM content by HPLC using the apparatus and methodology described above. Each test was performed in triplicate.

The cumulative% drug release was calculated, and the drug release data were plotted using *SigmaPlot v.8.0* software package (Systat Software, Inc., San Jose, California, USA). Some common release kinetic models (first order, zero order, Higushi, Hixson–Crowell and Korsmeyer–Peppas) were fitted to the results by linear regression analysis in order to describe the release mechanism of the examined formulations.

2.5. Swelling and erosion studies

The swelling behavior of the tablets, described as water absorption capacity, was determined gravimetrically on a modified USP apparatus [18–22] consisting of a 200 mesh stainless steel basket carrying the tablet, mounted above the stirring paddle. The baskets were weighed and immersed in 1000 ml of dissolution medium, under stirring at 50 rpm, allowing the tablet to swell at 37 ± 0.5 °C. The baskets were periodically detached from the appa-