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Formula optimization based on neural networks in sustained release tablets

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Drug release from hydroxypropylmethylcelluose (HPMC) matrices is mainly affected by factors like drug character [1], polymer viscosity [2], excipient content [2–4], or HPMC particle size [5, 6]. A large spectrum of mathematical models describing drug release from HPMC matrix tablets has been developed [7]. But probably the most important aspect when developing new pharmaceutical products or elucidating drug release mechanisms is the desired/required predictive ability and accuracy of the model. In many cases, the use of simple empirical or semi-empirical models is fully sufficient. However, when reliable, detailed information is required, more complex, mechanistic theories must be applied.

In this paper, nine drugs different in solubility were selected as model drugs for the preparation of tablets. The solubility of nine drugs determined in water at 37 °C and 63 formulations of various matrix tablets used for training and optimizing the network were provided in the Table. Procedure 1 was written to construct the optimal ANN model and predict the actual dissolution of the formulation. The BP ANN model function can be described as the following:

$$T_{i,\,Predict} = f_i(P_1,\ P_2); \qquad i = 1, \ldots, 6\,. \qquad (1)$$

Two variables, the solubility (P_1) of the drug and the various ratio of HPMC : dextrin (P_2) (5 : 1, 4 : 1, 3 : 1, 2 : 1, 1 : 1, 1 : 2, 1 : 3, 1 : 4, 1 : 5) were used as input (P_1, P_2); the *in vitro* accumulate release percent of drug at different time points (T_i, $i = 1 \ldots 6$) (0.5, 1.0, 2.0, 3.0, 4.0 and 6.0 h) was used as output. Six models were constructed according to the six different time points. The accumulated release data for 63 formulations at 6 time points were made up as database. Five formulations (five HPMC : dextrin variables) were chosen randomly for each drug, therefore, $9 \times 5 \times 6$ groups of data were used as the initial training set for the model of ANN development, while the other groups of data ($9 \times 2 \times 6$) were used as test data.

As the simulation freedom must be non-minus as the superior limit, the optimum number of iterations at each specific number of hidden layer nodes (1–16) was identified that produced the minimum test error square over all predict sampling times. Then, the number of hidden layer nodes and the corresponding optimum number of iterations were used in the $9 \times 2 \times 6$ groups of test data to retrain the model of ANN. The optimum number of hidden layer nodes was determined when both the regression slopes and squared correlation coefficients (r^2) were near 1.0.

Therefore, the optimized ANN model consisted of one hidden layer, five hidden layer nodes and trained for 25 iterations. The optimal ANN model was re-confirmation through combining the initial ANN model training data and the test data (63×6 groups); predicting their dissolution profiles; comparing the profiles ANN predicted with the actual observed ones. The comparison shows the good relationship between the ANN predicted and the observed percent dissolved for all 63 formulations at each of six dissolution sampling times.

Procedure 2 has been programmed as the optimization problem based on the optimal BP ANN model decided by procedure 1 and the optimization toolbox in Matlab 5.1. The optimal problem of predicting formulation can be summarized as follows:

$$\min_{P2} \sum_{i=3,5,6} (T_{i,\,Predict} - T_{i,\,Target})^2$$

$$\text{s.t. } P_1 = \text{constant}$$

$$\text{if} \quad T_{6,\,Predict} > 75\%, \quad \text{then}, \quad T_{6,\,Predict} = 75\%$$

where $T_{i,\,Predict}$ was the accumulate release percent of drug predicted by the optimal BP ANN model from procedure 1; $T_{i,\,Target}$ was the desired target *in vitro* dissolution profiles of the optimum formulation like this: when $t = 2$ h in vitro dissolution $T_{3,\,Target} = 30\%$; when $t = 4$ h, $T_{5,\,Target} = 50\%$; when $t = 6$ h, $T_{6,\,Target} = 75\%$.The sum of squares of differences between accumulate release percent

Table: Input database used for ANN

Drugs	Solubility (P_1) (mg/ml)	HPMC : dextrin (P_2)								
		5 : 1	4 : 1	3 : 1	2 : 1	1 : 1	1 : 2	1 : 3	1 : 4	1 : 5
Diltiazem hydrochloride	1254.72	√		√	√	√	√	√		√
Ranitidine hydrochloride	592.45	√		√	√	√	√	√		√
Isoniazid	216.72	√		√	√	√	√	√		√
Ribavirin	186.15	√	√	√	√	√	√	√	√	√
Ciprofloxacin hydrochloride	74.93	√		√	√	√	√	√		√
Theophylline	16.46	√		√	√	√	√			√
Tinidazole	11.26	√	√	√	√	√	√	√		√
Propylthiouracil	2.699	√		√	√	√	√	√		
Sulfamethoxazole	1.938	√		√	√	√	√	√		

P_1 (solubility) and P_2 (various ratios of HPMC : Dextrin) were used as input in BP ANN model. The % drug dissolved at six sampling points (0.5 h, 1 h, 2 h, 3 h, 4 h, 6 h) were used as output. Among these formulations, 63 formulations (√) were used for training and optimizing the network

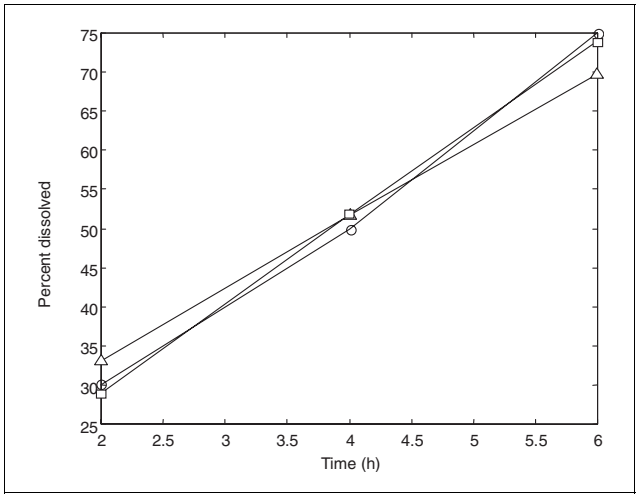

Fig.: Dissolution profiles for theophylline ($P_1 = 16.46$). Data based on: (○) target profiles; (□) ANN predicted profiles based on ANN predicted formulations; (△) observed profiles for manufactured tablets (ANN predicted $P_2 = 0.333$)

of drug predicted by the optimal BP ANN model and the desired target at the different time point (T_i, $i = 3, 5, 6$) (corresponding to 2.0, 4.0 and 6.0 h) was minimized as the optimal objective function. The P_2 (the ratio of HPMC : dextrin) was used as the optimal variable that can be varied. The following constraints were employed in using the ANN model to predict formulations. (1) The solubility of main drug in predicted formulations should be within the bounds of the nine drugs in this paper. (2) When $i = 6$, if $T_{6,\text{Predict}} > 75\%$, set $T_{6,\text{Predict}} = 75\%$, $(T_{6,\text{Target}} - T_{6,\text{Predict}})^2 = 0$. (3) Sustained release drugs are administered once every 12 h.

In this paper, theophylline was chosen as model drug to evaluate of the formulation ANN predicted. The following steps were employed to evaluate the optimal formulation that would result in desired target *in vitro* dissolution profiles: (1) According to the solubility of drug (P_1) and the desired target *in vitro* dissolution profiles, the optimum formulation (P_2) is obtained based on procedure 2. (2) Manufacture the tablets according to the optimum formulation (P_2) and determine their actual dissolution profiles, $T_{i,\text{Actual}}$. (3) According to the solubility of drug (P_1) and the optimum formulation (P_2), $T_{i,\text{Predict}}$ can be predicted by procedure 1. (4) Compare the target dissolution profiles, $T_{i,\text{Target}}$; the actual observed dissolution profiles for the manufactured formulations, $T_{i,\text{Actual}}$; with the ANN predicted profiles for the ANN generated formations, $T_{i,\text{Predict}}$ when $i = 3, 5, 6$.

By procedure 2, the optimal formulations (P_2, the ratio of HPMC : dextrin) of theophylline (corresponding to $P_1 = 16.46$) were determined ($P_2 = 0.333$). The Fig. shows the result of comparison.

Experimental

1. Tablet formulation and manufacturing

Isoniazid; robavironum; diltiazemi hydrochloridum; ranitidini hydrochloridum; ciprofloxacin hydrochloridum; theophylline; tinidazole; propylthiouracilum and sulfamethoxazolum, donated by pharmaceutical factories, were selected as model drugs. HPMC K4M (Dow company, USA), dextrin and magnesium stearate (medicinal grade) were used as matrix material, diluents and lubricant respectively. The amount of each drug in various sustained release tablets was kept constant at 100 mg while the HPMC/dextrin ratio was varied from 5 : 1 to 1 : 5. The tablet weight was kept constant at 303 mg throughout the study. The tablet manufacture was as usual way.

2. In vitro dissolution determination

The *in vitro* release studies were carried out at 37 °C for 6 h, using the USP XXIII basket apparatus. The rotation speed was 100 rpm and dissolution medium was 1000 ml purified water. At predetermined time intervals, samples were withdrawn, filtered and assayed spectrophotometrically at their corresponding wavelength

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