Optimization of extended-release hydrophilic matrix-tablets by Support Vector Regression (SVR)

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Introduction

Support Vector Regression, SVR, is a recently introduced statistical technique in various pharmaceutical fields and possesses prominent advantages comparatively to conventional neural networks [1].

In the present work Support Vector Regression, SVR, is applied in programming of extended drug release for swellable hydrophilic pentoxifylline matrix-tablets and selection of pharmaceutical formulations with optimal release profiles.

Experimental methods

- **Materials**

Pentoxifylline powder was kindly offered by Pharma International, Amman, Jordan. Ethylcellulose and sodium alginate were purchased from BDH, UK.

- **Preparation of matrix tablets**

Seventeen (11+6) batches of matrix-tablets containing fixed amount of pentoxifylline (400 mg) and mixture of ethylcellulose and sodium alginate at appropriate weight ratio as a matrix-former were prepared by direct compression on a hand-operated hydraulic press (Shimadzu, Japan), using a 13-mm flat-faced punch and die set and applying a 10 MPa pressure for 30 sec.

- **In vitro drug release**

Percentage of pentoxifylline released from the matrix tablets was determined according to the method suggested for pentoxifylline extended release tablets in USP 31, Test 1 (Apparatus II, 100 rpm, 900 ml of distilled water).

- **Experimental design**

A full factorial design was followed with two factors (the matrix-former:drug weight ratio, X_1, and the percentage of sodium alginate in the matrix-former, X_2) at three equally spaced levels and two replicated central points (Table 1). The percent release at 1, 4, 8 and 12 hours (Y_1 to Y_4) were considered as dependent variables (responses) and the USP 31 release limits ($Y_1 \leq 30$, $30<Y_2 \leq 55$, $Y_3 \geq 60$ and $Y_4 \geq 80$) were imposed as constraints for optimization.

- **Support Vector Regression (SVR)**

The most general equation of nonlinear SVR regression resulting in a hyper-surface hanging over the n-dimensional X-space is:

$$f(X,W) = \sum_{i=1}^{N} w_i \varphi_i(X) \qquad (1)$$

where $\varphi_i(X)$ is called the kernel that represents mapping from the input feature space to a higher dimensional one, and w_i is a learning adjustable coefficient.

In the present work, normalized values of the factors (independent variables) were used as inputs for the construction of the SVM model employing the LIB-SVM software package (available on http://www.csie.ntu.edu.tw/~cjlin/libsvm/) that runs on the MATLAB platform. Firstly, the Radial Basis Function (RBF) kernel was selected. Its width was set to 2, because it had good general performance. Then, the SVR model's error tolerance, ε, and regularization parameter, C, were optimized by systematically changing their values in the training step and calculating the R^2 of the model.

Multiple linear regression (MLR) was applied for comparison with the suggested SVR model, and the release data of six additional checkpoint formulations, were employed for validation of prediction ability.

Table 1. Formulation factors and experimental values (responses) of drug release

Formulation No. and Factors			Release Responses			
	X_1	X_2	Y_1	Y_2	Y_3	Y_4
1	2.0	0	3.8	6.6	10.3	14.0
2	2.0	25	9.6	27.7	54.3	77.3
3	2.0	50	16.5	64.7	100.3	100.4
4	1.5	0	5.5	9.0	13.9	19.4
5	1.5	25	9.7	27.5	62.7	81.2
6	1.5	50	33.2	80.5	100.1	100.3
7	1.0	0	4.7	9.7	15.9	20.7
8	1.0	25	15.0	47.7	95.8	98.4
9	1.0	50	30.8	96.5	99.3	99.3
10	1.5	25	9.4	29.1	64.0	81.8
11	1.5	25	10.5	30.4	68.8	83.3

Results and discussion

Release profiles of pentoxifylline from the 11 matrix-tablets involved in the experimental design are shown in Fig. 1, and the results of the response parameters are presented in Table 1.

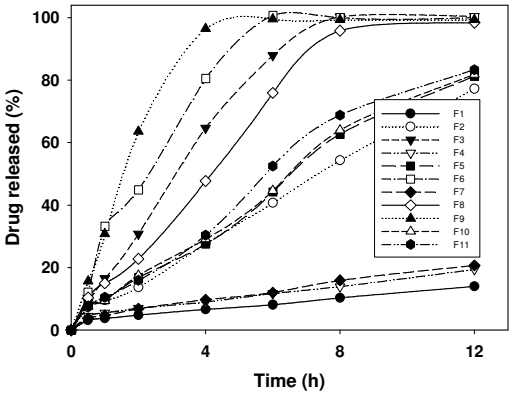

Fig. 1. Pentoxifylline release profiles of the experimental matrix-tablets (key as in Table 1).

From Table 1 and Fig. 1 it can be seen that the release rate generally increases with increasing percentage of sodium alginate (X_2) and decreasing matrix-former:drug weight ratio (X_1). This can be explained by the easier and increased erosion of the tablets, since sodium alginate is easily erodible in water, and by the reduced matrix swelling due to decreasing matrix-former: drug weight ratio.

For the support vector regression (SVR), after computing R^2 for different models in the training step, the optimal value of model's error tolerance, ε, was found to be 1.9 and for parameter of regularization, C, was 191.

The values of R^2 and PRESS calculated on the basis of the whole set of experimental data for the constructed SVR and MLR models (11 formulations) are presented in Table 2. It can be seen that the R^2 values are higher and PRESS values are lower for SVR than for MLR models for the four responses, indicating better prediction ability, in the case of SVR than that of MLR.

Table 2 Values of R^2 and PRESS for the constructed SVR and MLR models

Response	SVR		MLR	
	R^2	PRESS	R^2	PRESS
Y_1	0.9947	30.138	0.9354	64.001
Y_2	0.9988	33.576	0.9935	58.702
Y_3	0.9981	50.489	0.9525	601.073
Y_4	0.9997	32.685	0.9880	145.601

For validation of the capability of SVR models to predict release from formulas other than those used in the experimental design, the release from six additional checkpoint formulas within the experimental domain was tested. Linear correlation of predicted versus experimental data was performed for these checkpoints and the corresponding results of R^2 and slope are shown in Table 3, together with the values of mean relative error (MRE).

The linear correlation parameters listed in Table 3 show that the prediction ability is better in the case of the SVR, resulting in higher R^2 values and lower MRE values. Therefore, since for the extended release system under investigation (which is multivariate), the quantitative relationship between causal factors and response variables is expected to be complex and nonlinear, we can conclude that the SVR appears to be more suitable than the polynomial equations in handling problems such as the extended release programming.

Table 3 Parameters of linear correlation between predicted and experimental data (R^2 and slope), and mean relative error of the checkpoint matrix-tablets.

Res-	SVR			MLR		
ponse	R^2	Slope	MRE	R^2	Slope	MRE
Y_1	0.988	0.819	10.7	0.984	0.428	26.8
Y_2	0.997	1.055	9.8	0.974	0.710	14.4
Y_3	0.986	1.005	4.1	0.914	0.771	9.4
Y_4	0.983	0.911	3.5	0.928	0.710	9.8

Fig. 2 presents the superposition of the four contour plots derived by the SVR modeling and together with Table 1 show that only formula 8 (low level of matrix-former:drug weight ratio and medium level of sodium alginate content) agrees with these constraints, while formulas 5, 10, and 11 (medium levels of both factors) are almost at the border of the acceptance limits although they show better linearity over a 12 h dissolution period. The other formulas have experimental and predicted values for Y_2 outside the acceptance range (30 – 55%). Considering these constraints and taking into account that formula 8 requires minimal amount of polymer mixture as matrix-former which means reduction in tablet weight and cost, it can be considered as the ''optimal'' solution estimated on the basis of SVR.

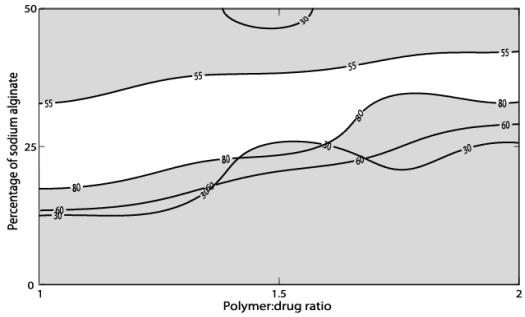

Fig. 2. Superimposed contour plots derived by using SVR predicted release data. White area corresponds to formulation factors obeying USP release limits.

Conclusion

The superiority of SVR in handling nonlinear formulation data and in prediction of formulation factors obeying Pharmacopoeial constraints clearly shows its applicability in the rational development of appropriate extended release formulations.

Reference

[1] N. Al-Zoubi et al., 2009, Drug. Dev. Ind. Pharm. Submitted.