Drug Development and Industrial Pharmacy, 2011, 37(1): 80–87

ISSN 0363-9045 print/ISSN 1520-5762 online
DOI:10.3109/03639045.2010.492396

informa
healthcare

ORIGINAL ARTICLE

Optimization of extended-release hydrophilic matrix tablets by support vector regression

Nizar Al-Zoubi[1], Kyriakos Kachrimanis[2], Khaled Younis[3] and Stavros Malamataris[2]

[1]Department of Pharmaceutical Sciences and Pharmaceutics, Applied Science University, Amman, Jordan, [2]Department of Pharmaceutical Technology, Aristotle University of Thessaloniki, Thessaloniki, Greece and [3]Department of Computer Engineering, University of Jordan, Amman, Jordan

Abstract

Background: In this work, support vector regression (SVR) was applied to the optimization of extended release from swellable hydrophilic pentoxifylline matrix-tablets and compared to multiple linear regression (MLR). *Methods*: Binary mixtures comprising ethylcellulose and sodium alginate were used as the matrix-former. The matrix-former : drug weight ratio and the percentage of sodium alginate in the matrix-former were the formulation factors (independent variables) and the percentages of drug release at four different time intervals were the responses (dependent variables). Release was determined according to United States Pharmacopeia 31 for 11 pentoxifylline matrix-tablet formulations of different independent variable levels and the corresponding results were used as tutorial data for the construction of an optimized SVR model. Six additional checkpoint matrix-tablet formulations, within the experimental domain, were used to validate the external predictability of SVR and MLR models. *Results*: It was found that the constructed SVR model fitted better to the release data than the MLR model (higher coefficients of determination, R^2, lower prediction error sum of squares, narrower range of residuals, and lower mean relative error), outlining its advantages in handling complex nonlinear problems. Superimposed contour plots derived by using the SVR model and describing the effects of polymer and sodium alginate content on pentoxifylline release showed that formulation of optimal release profiles, according to United States Pharmacopeia limitations, could be located at drug : matrix ratio of 1 and sodium alginate content 25% w/w in the matrix-former. *Conclusion*: The results indicate the high potential for SVR in formulation development and Quality by Design.

Key words: Experimental design, formulation optimization, pentoxifylline, support vector regression, swellable matrix tablets

Introduction

Extended-release (ER) systems are used for improved therapy with long-term oral administration of drugs characterized by short biological half-life and by narrow therapeutic window (e.g., xanthine derivatives) because of their potential of attaining less frequent administration, relatively steady therapeutic plasma levels, and fewer side effects. For the development of ER systems, matrix tablets containing hydrophilic swellable polymers have been widely used because of their cost-effectiveness and easy manufacture by direct compression, converting powder mixtures of drugs and polymers to matrix tablets in very short one-step process[1].

The polymers hydrate forming a gel layer around the tablet, which controls drug diffusion. Particularly preferable are combinations of pH-independent dissolving polymers (e.g., ethylcellulose) with polymers whose release retarding capability is lower in intestinal than in gastric pH (e.g., sodium alginate). Such polymer combinations in different weight ratio offer the possibility of altering the in vitro drug release profiles independently of the processing variables, for example, compaction pressure, drug particle size, and incorporation of lubricant, and therefore possibly changing the in vivo release[2].

Taking into account that for the registration of ER oral dosage forms the currently suggested methodology, in

Address for correspondence: Dr. Nizar Al-Zoubi, Department of Pharmaceutical Sciences and Pharmaceutics, Faculty of Pharmacy, Applied Science University, Amman 11931, Jordan. Tel: +962 6 5609999, Fax: +962 6 5232899. E-mail: nizoubi@yahoo.com

(Received 6 Oct 2009; accepted 7 May 2010)

the Guidance for Industry issued by FDA in 1997[3], should involve (a) the development and in vivo evaluation of several formulations with different in vitro drug release rates, (b) the assessment of the hypothetical in vivo dissolution profile using an appropriate deconvolution technique, and (c) the comparison of the two sets of release data obtained (in vitro and in vivo), both the rational development of ER formulations with appropriate drug release and their in vitro evaluation become very important[4,5]. Therefore, in this work support vector regression (SVR) is applied in programming the extended drug release for swellable hydrophilic pentoxifylline matrix tablets and selection of formulations with optimal release profiles. Pentoxifylline was selected as a representative water-soluble drug of very short apparent plasma half-life (0.4–0.8 hours) administered as 400 mg ER formulation[6] and SVR was chosen as a recently introduced statistical technique in various pharmaceutical fields: quantitative structure-activity relationship (QSAR) studies[7], prediction of toxic activity[8], and quantitative analysis of polymorph mixtures[9]. Also, SVR was chosen because it possesses prominent advantages compared to conventional neural networks: high capability of generalization due to strong theoretical background and avoiding local minima; secured offer of quick solution by a standard algorithm (quadratic programming)[10]. Therefore, their use within the context of FDA's initiative for Pharmaceutical Quality by Design (QbD)[11,12], as well as ICH Q8 Pharmaceutical Development guidance[13], seems to be promising and advantageous because an essential part of the QbD approach consists of the use of statistical experimental design combined with the use of novel, highly efficient model fitting methods such as machine-learning algorithms.

Materials and methods

Materials

Pentoxifylline powder (53.8% w/w particles below 180 μm and 46.2% between 180 and 400 μm) was from Pharma International, Amman, Jordan. Ethylcellulose (41.2% w/w particles below 180 μm and 58.8% between 180 and 500 μm) and sodium alginate (90.4% w/w particles below 180 μm and 9.6% between 180 and 400 μm) were purchased from BDH, Poole, Dorset, UK. All materials were used as received.

Preparation of matrix tablets

Seventeen (11 + 6) batches of matrix tablets containing fixed amount of pentoxifylline (400 mg) and a mixture of ethylcellulose and sodium alginate at appropriate weight ratio as a matrix former were prepared by direct compression as follows. Accurately weighed pentoxifylline and polymer powders were mixed in a small mortar with a spatula for 15 minutes. Then, 1% w/w magnesium stearate was added and mixed again for 5 minutes. A 13-mm flat-faced punch and die set and a hand-operated hydraulic press (Shimadzu, Kyoto, Japan) were used to compress the powder mixture at 10 MPa pressure for 30 seconds, resulting in saturated (reaching minimum attainable near zero porosity) matrix tablets.

In vitro drug release

Percentage of pentoxifylline released from the matrix tablets was determined according to the method suggested for pentoxifylline ER tablets in USP 31 (Test 1).[14] Apparatus II paddle dissolution system (Pharma Test, PTW 2, Hainburg, Germany), at 100 rpm, with 900 mL of distilled water as dissolution medium was used. The paddle system was preferred over basket apparatus, because it did not result in disruption of the swelling and release process of the relatively large and highly swellable matrix tablets under investigation. After certain dissolution time (1, 4, 8, and 12 hours as specified in the USP 31 method, Test 1), 10-mL samples of dissolution liquid were taken and the volume was replaced with water. The samples were filtered through 0.45-μm cellulose acetate syringe filter and the concentration of dissolved pentoxifylline was determined by UV spectroscopy (Spectronic 601, Milton Roy, Ivyland, PA, USA) after suitable dilution, at a wavelength corresponding to maximum absorbance (273 nm). All tests were performed in triplicate and from the mean concentration the percentage of drug release was determined.

Experimental design

A full factorial experimental design was followed with two formulation factors as independent variables (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 (1.0, 1.5, and 2.0 for X_1 and 0, 25, and 50% for X_2) and two replicated central points[15]. The percent release at 1, 4, 8, and 12 hours (Y_1–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. The responses were related to the independent experimental variables (formulation factors) by applying multiple linear regressions (MLRs) and fitting of second-order polynomial equations including two-factor interaction terms:

$$Y = A_0 + A_1X_1 + A_2X_2 + A_3X_1^2 + A_4\ X_2^2 + A_5X_1X_2 + E, \quad (1)$$

where A_0 is an intercept, A_1–A_5 are the coefficients of the respective variables and their interaction terms, and E is an error term.

The obtained polynomial equations (full models) were simplified applying a backward elimination procedure (P to remove = 0.051) and the highest adjusted coefficient of determination, R^2_{adj} [(lowest standard error of estimates (SEE)], was selected. The MLR was performed using the MATLAB program (Mathworks

Inc., Natick, MA, USA). Response surface methodology was also applied to visualize the effects of the formulation factors on the selected release parameters.

Support vector regression

The basic idea of using support vector machines for regression (SVR) was to map data, X, into a higher-dimensional feature space, F, through a nonlinear mapping function, φ, and then to perform linear regression in this space[10,16]. The most general equation of nonlinear SVR regression resulting in a hypersurface hanging over the n-dimensional X-space is

$$f(X,W)=\sum_{i=1}^{N} w_i\varphi_i(X), \qquad (2)$$

where φ_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. A typical graph of a (nonlinear) regression problem and all the relevant mathematical variables and objects are shown in Figure 1, where ξi and ξj^* are slack variables for measurements 'above' and 'below' an ε-tube, respectively[17].

In this work, the experimental data were scaled to zero mean and standard deviation to unity, to normalize the effect of the different factors (independent variables). These normalized factors were used as inputs for the construction of the SVM model. First, the radial basis function 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.

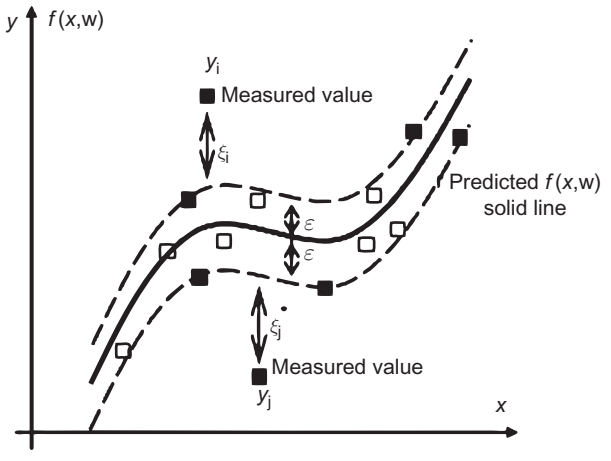

Figure 1. Typical graph of a (nonlinear) regression problem with the relevant mathematical variables and objects (ξ_i and ξ_j^* are slack variables for measurements 'above' and 'below' ε-tube, respectively, and filled square data are support vectors whereas the empty ones are not)[16].

Validation of external predictability of SVR model

The suggested SVR model and the chosen experimental design were validated for external predictability using release data of six checkpoint formulations, other than those used in the experimental design. Tablets of composition corresponding to these test points were prepared and evaluated based on the selected release parameters. Subsequently, the experimental results were compared with predicted values.

Computer programs and optimization

The LIB-SVM software package (available on http://www.csie.ntu.edu.tw/~cjlin/libsvm/) that runs on the MATLAB platform was used. Methodology of contour plots was applied using MATLAB v. 7.3.0 (MathWorks Inc.) on Pentium IV 2.4 dual core processor, to visualize the effects of the formulation factors on the dependent variables.

Results and discussion

Release programming

Release profiles of pentoxifylline from the 11 matrix tablets involved in the experimental design are shown in Figure 2. The results of the response parameters are presented in Table 1 together with the predicted values by the SVR and MLR models, respectively.

From Table 1 and Figure 2, 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, because sodium alginate is easily erodible in water, and by the reduced matrix swelling due to decreasing matrix former: drug weight ratio.

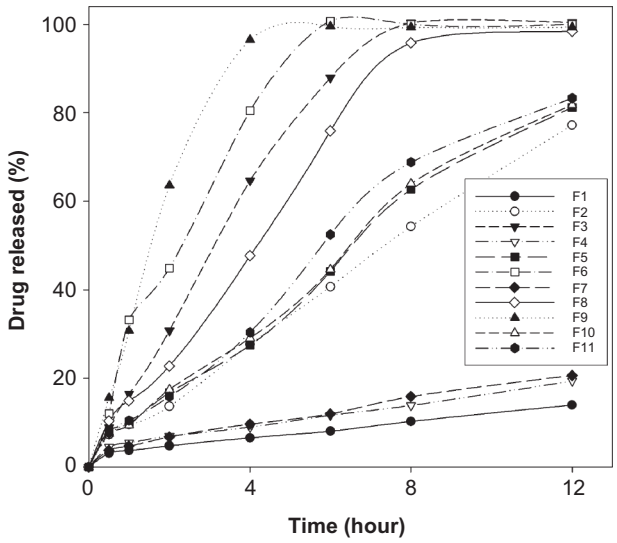

Figure 2. Pentoxifylline release profiles of the experimental matrix tablets with composition described in Table 1.

Table 1. Experimental and predicted values of drug release (responses) by support vector (P_{SVR}) and multiple linear (P_{MLR}) regression analyses.

	Formulation factors		Release responses											
			Y_1			Y_2			Y_3			Y_4		
Batch no.	X_1	X_2	E	P_{SVR}	P_{MLR}	E	P_{SVR}	P_{MLR}	E	P_{SVR}	P_{MLR}	E	P_{SVR}	P_{MLR}
1	2	0	3.8	5.7	4	6.6	8.5	7.8	10.3	12.2	5.5	14	15.9	12.3
2	2	25	9.6	11.5	6.4	27.7	29.6	25.7	54.3	56.2	64.1	77.3	75.3	81.2
3	2	50	16.5	15.2	19.5	64.7	62.8	65.5	100.3	98.4	95.3	100.4	98.5	98.1
4	1.5	0	5.5	7.4	5.8	9	10.9	5.8	13.9	15.8	10.4	19.4	21.3	16.6
5	1.5	25	9.7	11.3	11.5	27.5	29.4	30.9	62.7	64.6	67.4	81.2	81.4	83.5
6	1.5	50	33.2	31.3	28	80.5	78.6	78	100.1	98.1	96.9	100.3	98.1	98.5
7	1	0	4.7	6.6	4.2	9.7	11.6	11.7	15.9	17.8	24.2	20.7	22.6	25.2
8	1	25	15	14.8	13.3	47.7	45.8	44	95.8	93.9	79.5	98.4	96.5	90.1
9	1	50	30.8	28.9	33	96.5	94.6	98.2	99.3	97.4	107.4	99.3	97.4	103.1
10	1.5	25	9.4	11.3	11.5	29.1	29.4	30.9	64	64.6	67.4	81.8	81.4	83.5
11	1.5	25	10.5	11.3	11.5	30.4	29.4	30.9	68.8	64.6	67.4	83.3	81.4	83.5

The release rate was slowest for the formula 1 containing 800 mg of ethylcellulose only (without sodium alginate) as matrix former. The highest release rate is seen for formula 9 corresponding to 400 mg matrix former containing 50% w/w sodium alginate. The wide range of the dissolution rate, from extremely slow (14% at 12 hours, formula 1) to fast (96.5% at 4 hours for formula 9), indicates that the experimental domain is suitable for optimization.

For the SVR, it is known that the optimal value of model's error tolerance, ε, depends on the type of noise present in the data, which is usually unknown. Even if sufficient knowledge of the noise is available, to select an optimal value for ε some practical consideration of the number of resulting support vectors is important. After computing R^2 for different models, the optimal value of ε was found to be 1.9. The parameter of regularization, C, which controls the trade-off between maximizing the margin and minimizing the training error is also important. If C is too small, then insufficient stress will be placed on fitting the training data. On the contrary, if C is too large, then the SVR model will overfit on the training data. To find an optimal value of C, the R^2 of SVR models with different C values was calculated. The obtained results revealed that a suitable value of C was 191.

From Table 1, it can be seen that the predicted values by SVR (P_{SVR}) are closer to the experimental values than those predicted by MLR (P_{MLR}) with minor exceptions. The overall prediction ability was estimated based on the values of coefficient of determination (R^2) and prediction error sum of squares (PRESS) calculated on the basis of the whole set of experimental data for the constructed SVR and MLR models (11 formulations), 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 indicating better internal predictability, in the case of SVR than that of MLR for the four responses.

The high R^2 and low PRESS values, which indicate high internal predictability, do not guarantee high ability to predict external points. Therefore, six checkpoint formulations, which lie within the experimental domain but are different to those involved in the experimental design, were used to validate the external predictability of SVR and MLR models[18,19]. The compositions of the checkpoints are listed in Table 3 together with the predicted, the experimental, and the residuals values of the response variables. In general, the predicted values were in good agreement with the experimental results of the selected responses (Table 3) and the residuals varied from −5.2 to +5.6 and from −9.0 to +16.2 for SVR and MLR, respectively, indicating superiority of SVR.

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

	SVR		MLR	
Response	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 further comparison of SVR and MLR models, linear correlation of predicted versus experimental data was performed[18] and the corresponding results of R^2 and slope are shown in Table 4, together with the values of mean relative error (MRE) calculated according to the following equation[20]:

$$\mathrm{MRE} = \frac{1}{n}\sum_{i=1}^{n}\left|\frac{P_i - e_i}{e_i}\right|, \qquad (3)$$

where e_i is the experimental value of ith matrix tablet formulation, P_i is the predicted value of ith matrix tablet formulation, and n is the number of the formulations.

The results in Table 4 show that the prediction ability is better in the case of the SVR, resulting in higher R^2 values and lower MRE values. Therefore, because for the ER system under investigation (which is multi-variate) the quantitative relationship between causal factors and response variables is expected to be complex and

Table 3. Composition of the checkpoint formulations and values of experimental and predicted response variables and corresponding residuals.

Formulation no. and factors								
	X_1	X_2	Response	E	P_{SVR}	$Residuals_{SVR}$	P_{MLR}	$Residuals_{MLR}$
1	1.25	14	Y_1	9.4	8.2	1.2	11.7	−2.3
			Y_2	23.8	21.1	2.7	30.9	−7.1
			Y_3	47.4	51	−3.6	56.4	−9
			Y_4	58.5	63.7	−5.2	63.7	−5.2
2	1.7	10	Y_1	5.6	5.9	−0.3	10	−4.4
			Y_2	17.5	11.9	5.6	23.1	−5.6
			Y_3	38.2	33.7	−4.5	38.4	−0.2
			Y_4	47.5	47.7	−0.2	46.7	0.8
3	2	35	Y_1	12.3	10.3	2	13.2	−0.9
			Y_2	41.1	39	2.1	41.2	−0.1
			Y_3	82.2	79.9	2.3	69.7	12.3
			Y_4	97.8	94.2	3.6	81.6	16.2
4	1.8	50	Y_1	27.4	23.3	4.1	19.5	7.9
			Y_2	71.4	69.6	1.8	63.7	7.7
			Y_3	96.1	94.9	1.2	92.7	3.4
			Y_4	99.7	97.8	1.9	93.6	6.1
5	1.3	32	Y_1	18.7	16.5	2.2	15.5	3.2
			Y_2	49.6	47	2.6	43.2	6.4
			Y_3	82.2	82	0.2	75.4	6.8
			Y_4	98	94.9	3.1	84.4	13.6
6	1.85	37	Y_1	14.1	13.7	0.4	14.7	−0.6
			Y_2	45.1	43.9	1.2	45.5	−0.4
			Y_3	81.7	82.3	−0.6	73.5	8.2
			Y_4	93.3	95.8	−2.5	82.5	10.8

Table 4. Parameters of linear correlation between predicted and experimental data (R^2 and slope) of the checkpoint matrix tablets, together with values of mean relative error.

	SVR			MLR		
Response	R^2	Slope	MRE	R^2	Slope	MRE
Y_1	0.9884	0.8188	10.7	0.9837	0.4283	26.8
Y_2	0.997	1.055	9.8	0.974	0.7095	14.4
Y_3	0.986	1.0046	4.1	0.9145	0.771	9.4
Y_4	0.9833	0.9105	3.5	0.928	0.7104	9.8

nonlinear, we can conclude that the SVR appears to be more suitable than the polynomial equations in handling problems of ER programming like other cases of QSAR[21], prediction of toxic activity[8] or peptide mobility in capillary electrophoresis[22], and optimization of chromatographic separation[23].

Optimization (location of optimal formulation)

According to USP 31 (Dissolution Test 1), the pentoxifylline ER tablets, after 1 hour of testing, have to release not more than 30% of pentoxifylline, after 4 hours 30–55%, after 8 hours not less than 60%, and after 12 hours of testing not less than 80%[14]. The region range of formulation factor values obeying these constraints for the ER system under consideration was obtained by superposition of contour plots. Figures 3a–d and 4a–d present contour plots showing the effects of formulation factors (matrix former: drug weight ratio and sodium alginate percentage in the matrix former) on the responses (pentoxifylline release after 1, 4, 8, and 12 hours), which are based on the data derived by the proposed SVR and second-order polynomial equations, respectively. They show a nonlinear relationship between the formulation factors and the predicted release parameters by employing the SVR (Figure 3a–d), whereas using the second-order polynomial equations the contour plots are characterized by relatively plane surfaces (i.e., parallel contours) for all the responses (Figure 4a–d).

Figure 5 presents the superposition of the four contour plots derived by the SVR modeling and together with Table 1 shows that only formula 8 (low level of matrix former: drug weight ratio and medium level of sodium alginate content) agrees with these constraints, whereas 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-hour 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.

Figure 6 presents the experimental release profile and data predicted by the SVR and MLR models for the optimal formula 8 and shows higher similarity of release profiles for the case of SVR compared to MLR and therefore its superior prediction ability. This superiority

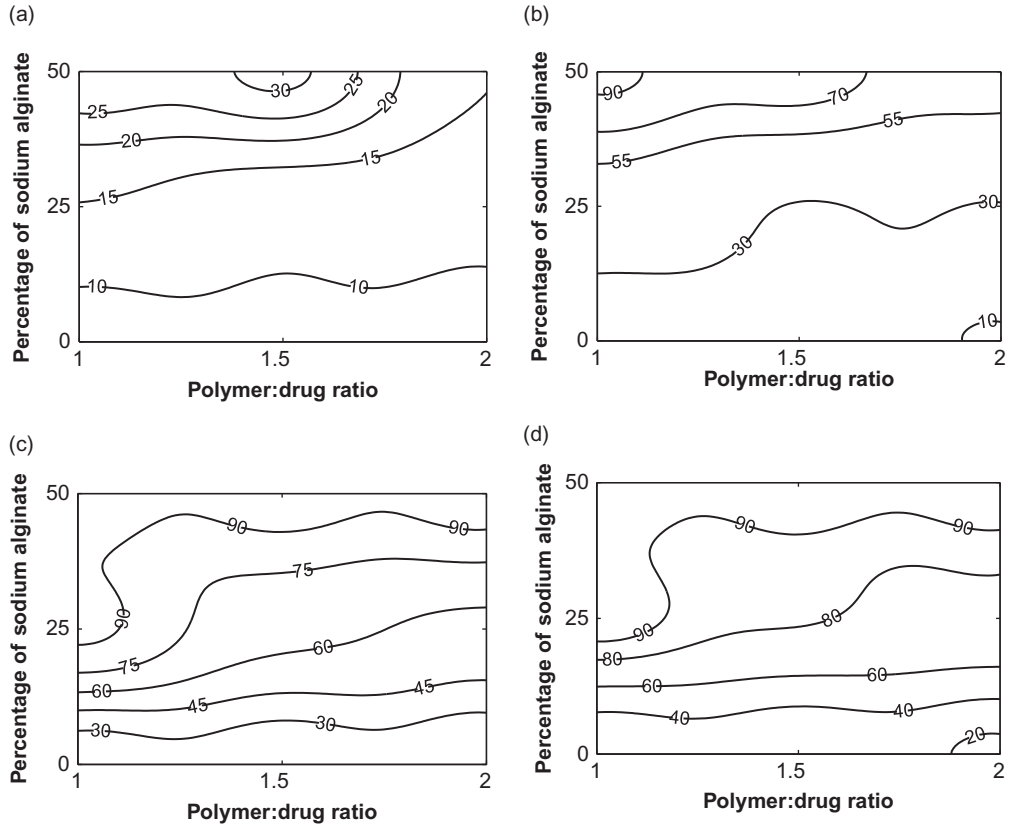

Figure 3. Contour plots showing the effects of formulation factors on percentage of pentoxifylline released after (a) 1, (b) 4, (c) 8, and (d) 12 hours, predicted by SVR.

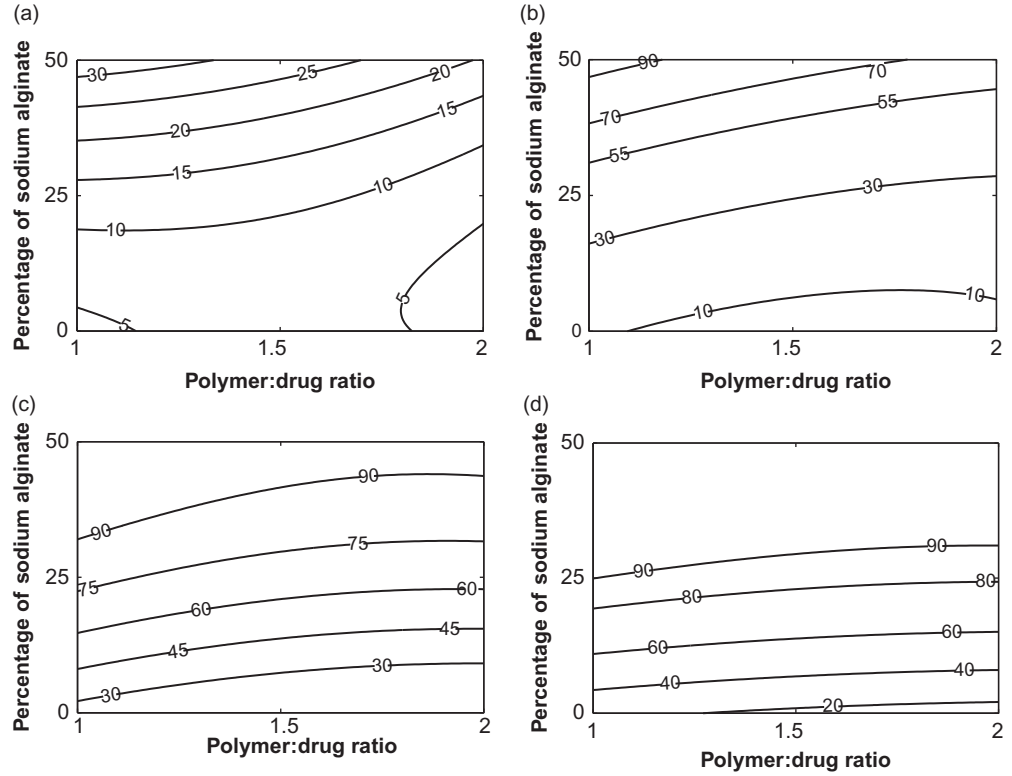

Figure 4. Contour plots showing the effects of formulation factors on percentage of pentoxifylline released after (a) 1, (b) 4, (c) 8, and (d) 12 hours, predicted by the second-order polynomial equations.

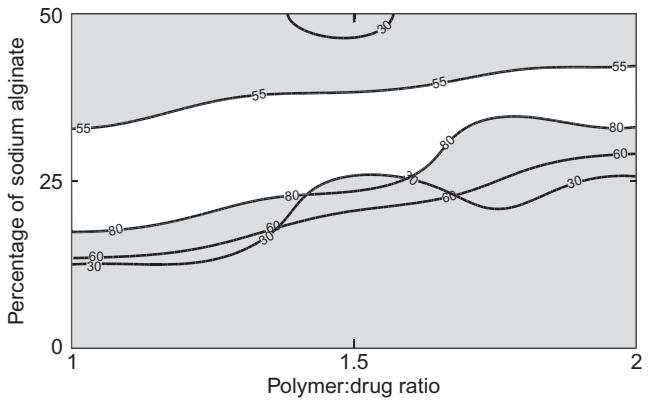

Figure 5. Superimposed contour plots derived by using SVR predicted release data (Figure 3a–d).

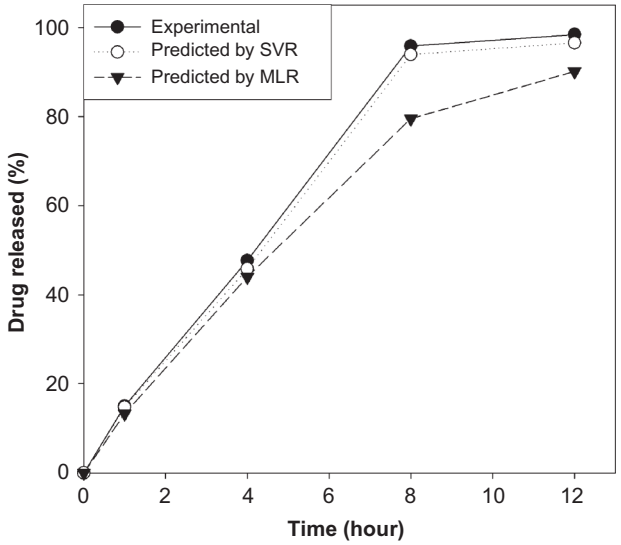

Figure 6. Experimental and predicted release data by using SVR and MLR models for the 'optimal' formulation 8.

appears clearer for Y_3 and Y_4 than for Y_1 and Y_2. However, the relative residuals (i.e., residuals divided by the experimental values) are comparable for the four responses (independent variables).

Similarity factor, f_2, was used to assess the global empiric similarity, although it does not account for the individual time point data variability. Calculation of f_2 according to the equation

$$f_2 = 50\log\left\{\left[1+\frac{1}{n}\sum_{t=1}^{n}(R_t - T_t)^2\right]^{\frac{1}{2}}100\right\}, \qquad (4)$$

where R_t and T_t are the amounts dissolved at time t, for the reference and test sample, respectively, and n is the number of samples, confirmed the superiority of the SVR model (f_2 = 86.6 compared to f_2 = 51.3 of the MLR model).

Conclusion

The superiority of SVR in handling nonlinear formulation data and in predicting formulation factors obeying Pharmacopeial constraints for ER systems clearly shows its applicability in the rational development of appropriate ER formulations and in their in vitro evaluation. The results prove the suitability of SVR models for use in formulation of optimization problems within the context of the pharmaceutical QbD initiative.

Acknowledgments

The authors thank Prof. Alexander J. Smola (Australian National University), Prof. Bernhard Schölkopf (MPI for Biological Cybernetics, Tübingen, Germany), and Dr. Asifullah Khan (Pakistan Institute of Engineering & Applied Sciences) for their helpful remarks.

Declaration of interest

This research work received financial support from the Research Council, Applied Science University, Amman, Jordan. The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

References

1. Gonzalez YM, Ghaly ES. (2010). Modified drug release of poloxamer matrix by including water-soluble and water insoluble polymer. Drug Dev Ind Pharm, 36(1):64–71.
2. Zhang G, Pinnamaraju P, Ali M. (2001). Water insoluble polymer based sustained release formulation. US Patent 6251430, 26 Jun.
3. FDA. (1997). Guidance for industry: Extended release oral dosage forms—Development, evaluation, and application of in vitro/in vivo correlations.
4. Sande SA, Dyrstad K. (2002). A formulation development strategy for multivariate kinetic responses. Drug Dev Ind Pharm, 28(5):583–91.
5. Sirisuth N, Augsburger L, Eddington N. (2002). Development and validation of a non-linear IVIVC model for diltiazem extended release formulations. Biopharm Drug Dispos, 23:1–8.
6. Reynolds J. (1996). Martindale—The extra pharmacopoeia. 31st ed. London, UK: Royal Pharmaceutical Society of Great Britain, 924.
7. Fatemi M, Gharaghani S. (2007). A novel QSAR model for prediction of apoptosis-inducing activity of 4-aryl-4-H-chromenes based on support vector machine. Bioorg Med Chem, 15:7746–54.
8. Zhao CY, Zhang HX, Zhang XY, Liu MC, Hu ZD, Fan BT. (2006). Application of support vector machine (SVM) for prediction toxic activity of different data sets. Toxicology, 217:105–19.
9. Kipouros K, Kachrimanis K, Nikolakakis I, Tserki V, Malamataris S. (2006). Simultaneous quantification of carbamazepine crystal forms in ternary mixtures (I, III, and IV) by diffuse reflectance FTIR spectroscopy (DRIFTS) and multivariate calibration. J Pharm Sci, 95:2419–31.
10. Smola AJ, Schölkopf B. (1998). A tutorial on support vector regression, NeuroCOLT technical report NC-TR-98-030, Royal Holloway College, University of London, UK. http://www.kernel-machines.org/ [accessed June 10, 2009].
11. FDA. (2004). Guidance for industry. PAT—A framework for innovative pharmaceutical development, manufacturing, and quality assurance.

12. FDA. (2006). Guidance for industry. Quality systems approach to pharmaceutical GMP regulations.
13. ICH. (2009). International conference on harmonization (ICH) proceedings, Q8(R2). Pharmaceutical Development, US FDA Federal Register, Alameda, CA.
14. USP. (2008). United States Pharmacopeia 31/National Formulary 26. Rockwell, MD: The United States Pharmaceutical Convention Inc.
15. Montgomery DC. (1996). Design and analysis of experiments. 4th ed. New York: Wiley, 436–40.
16. Burges CJ. (1998). A tutorial on support vector machines for pattern recognition. Data Min Knowl Discov, 2:121–67.
17. Kecman V. (2001). Learning and soft computing: Support vector machine, neural networks, and fuzzy logic models, Massachusetts: The MIT press.
18. Ibrić S, Jovanović M, Djurić Z, Parojčić J, Solomun L. (2002). The application of generalized regression neural network in the modeling and optimization of aspirin extended release tablets with Eudragit® RS PO as matrix substance. J Control Release, 82:213–22.
19. Sathe P, Venitz J. (2003). Comparison of neural network and multiple linear regression as dissolution predictors. Drug Dev Ind Pharm, 29:349–55.
20. Xu L, Wencong L, Shengli J, Yawei L, Nianyi C. (2006). Support vector regression applied to materials optimization of sialon ceramics. Chemom Intell Lab Syst, 82: 8–14.
21. Zhou YP, Jiang JH, Lin WQ, Zou HY, Wu HL, Shen GL, et al. (2006). Boosting support vector regression in QSAR studies of bioactivities of chemical compounds. Eur J Pharm Sci, 28:344–53.
22. Yu K, Cheng Y. (2007). Machine learning techniques for the prediction of the peptide mobility in capillary zone electrophoresis. Talanta, 71:676–82.
23. Hadjmohammadi M, Kamel K. (2008). Response surface methodology and support vector machine for the optimization of separation in linear gradient elution. J Sep Sci, 31:3864–70.