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Optimization and characterization of controlled release multi-particulate beads formulated with a customized cellulose acetate butyrate dispersion

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Abstract

The objectives of the present investigation were: (1) to model the effect of process and formulation variables viz., coating weight gain, duration of curing, and plasticizer concentration on in-vitro release profile of verapamil HCl from multi-particulate beads formulated with a novel aqueous-based pseudolatex dispersion; (2) to optimize the formulation by response surface methodology (RSM) and artificial neural network (ANN); and (3) to characterize the optimized product by thermal and X-ray analyses. Inert beads (Nupareil®) were loaded with verapamil HCl and subsequently coated with a custom designed aqueous-based pseudolatex dispersion of cellulose acetate butyrate (CAB). Experiments were designed and data was collected according to a three factor, three level face centered central composite design. Data was analyzed for modeling and optimizing the release profile using both RSM and ANN. Model fitted the data and explained 90% of variability in response in the case of RSM and at least 70% in the case of ANN. Release profile was optimized for a zero-order model. Optimized formulations were prepared according to the factor combinations dictated by RSM and ANN. In each case, the observed drug release data of the optimized formulations was close to the predicted release pattern. However, the modeling and optimization abilities of RSM as evaluated by the R-squared values, were found to be higher than that of ANN. X-ray and drug content analysis suggested the absence of any degradation of verapamil HCl and excipients incorporated in the formulation.

Keywords: Cellulose acetate butyrate; Pseudolatex; Multi-particulate beads; Excipient compatibility; Central composite-face centered design; ANN; Mathematical modeling

1. Introduction

Multi-particulate dosage forms offer many advantages over other immediate or modified release dosage forms. Some of the commonly reported advantages of multi-particulate dosage forms are

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suitability for drug combinations, when incompatibility exist, to release the drug at different rate, individual reproducibility of gastric emptying (Amighi et al., 1998), better statistical assurance of drug release and less likelihood of dose dumping (Lordi, 1986), less inter-and intra subject variability, less variation in gastric transit time (Osawa et al., 1991; Follonier and Doelker, 1992), and gastric emptying that is relatively independent of the nutrition state (Davis, 1986). According to drug release mechanisms from the formulations, they are classified as either membrane-controlled drug loaded beads (Singh et al., 1995, 1996) or matrix-type pellets (Kleinebudde et al., 1999; Heng et al., 2000).

Coating of drug-loaded beads can be achieved by organic or aqueous based coating systems. 'Criteria Pollutants', a term used in Clean Air Act, refers to carbon monoxide (CO), nitrogen oxides (NO_x), nonmethane volatile organic compounds (NMVOCs), and sulfur dioxide (SO_2). Though these criteria pollutants do not have a direct global warming effect, they indirectly affect terrestrial radiation absorption by influencing the formation and destruction of tropospheric and stratospheric ozone, or, in the case of SO_2, by affecting the absorptive characteristics of the atmosphere. Therefore, the use of organic solvents has been discouraged for the coating of pharmaceutical dosage forms by regulatory agencies such as food and drug administration (FDA) and environmental protection agency (EPA). Potential hazards, limits of solvent residue in the product (USP 23, 1995; ICH Guidelines, 1997) and environmental concerns with volatile organic constituents (VOCs) (http://www.epa.gov/oppeoeel/globalwarming/emissions/national/crit-pol.html, 2001) have led to the development of aqueous-based systems for pharmaceutical coating. The Clean Air Act of 1970 and its amendment in 1990 regulate the amount of VOCs that can be allowed into the atmosphere. Additionally, the OSHA, 1976 regulations restrict the exposure of an employee to several VOCs. Therefore, a customized aqueous based pseudolatex dispersion of cellulose acetate butyrate (CAB) was used in this study to provide the controlled release coating.

The release kinetics of beads is a function of process and product factors. Preparation and optimization of controlled release multi-particulate system can be simplified by employing response surface methodology (RSM), which consists of techniques used in the empirical study of relationship between one or more measured responses such as cumulative percent released and hardness of a tablet as well as a number of input variables such as coating weight gain and temperature. These techniques offer solutions to critical questions such as how particular response is affected by a given set of input variables over some specified region of interest, what settings of factors will give a product simultaneously satisfying desired specifications, and what values (in range) of the factors will yield a maximum for a specific response (Box et al., 1976).

Artificial neural network (ANN) imitates the learning capabilities of neurological systems to learn the hidden relationship between independent and dependent variables in a system. Once the ANN is trained to a desired accuracy, it can be utilized to determine influential inputs and generate predictions for product properties resulting from a given set of ingredients. ANN has been successfully applied to many pharmaceutical development areas in recent years. Some examples include solubility of structurally related drugs (Huuskonen et al., 1997), scale-up of fluidized bed granulation, simulation of medical aerosols (Richardson and Barlow, 1996), pharmacokinetic-pharmacodynamic analysis (Gobburu and Chen, 1996), and prediction of human pharmacokinetic parameters from animal data (Hussain et al., 1993). Usually, the data is obtained randomly from different sources or from a set of experiments. With the help of this data ANN is trained to recognize the relationship between independent and dependent variables. After obtaining the relationship, ANN generates a non-parametric, linear or nonlinear model that is subjected to validation with a test dataset. A successful model predicts the responses with reasonable accuracy for a given set of independent variables and optimizes the product or process.

The objectives of the present investigation were: (1) to model the effect of process and formulation

variables viz. coating weight gain, duration of curing, and plasticizer concentration on in-vitro release profile of verapamil HCl from multi-particulate beads formulated with a novel aqueous-based pseudolatex dispersion; (2) to optimize the formulation by RSM and ANN; and (3) to characterize the optimized product by thermal and X-ray analyses.

2. Materials and methods

2.1. Materials

The following materials were received as gifts: verapamil HCl from Geneva Pharmaceuticals, Dayton, NJ; Nupareil® beads (mesh 18/20) from Ingredient Technology Corporation™, Mahwah, NJ; Polydextrose/HPMC (Opadry II®) from Colorcon, West Point, PA; CAB from FMC Inc., Philadelphia, PA. Sodium acetate, glacial acetic acid, and acetonitrile were purchased from VWR Scientific, Minneapolis, MN. All other chemicals were of reagent grade and used as received. Water used in all experiments was deionised and distilled.

2.2. Design of experiments

Coating weight gain, duration of curing and plasticizer level were identified as three important factors responsible for cumulative percent of verapamil HCl released in 12 h in a prior study (Vaithiyalingam, 2001). Therefore a three factor, three level, central composite face-centered design (CCF) was employed to generate factor combinations by using a statistical software, Statgraphics® Plus. Table 1 summarizes the factors and their levels and responses. A total of 16 runs with duplicate center points were generated. Coated beads were formulated accordingly and subjected for dissolution to obtain release profiles.

2.3. Response surface methodology

A second order model was employed to fit the data individually for the responses $Y_1 - Y_5$ by the general model:

$$Y = b_0 + b_1X_1 + b_2X_2 + b_3X_3 + b_{12}X_1X_2 + b_{13}X_1X_3 + b_{23}X_2X_3 + b_{11}X_1^2 + b_{22}X_2^2 + b_{33}X_3^2$$

With three factors and each factor coded to be in the range of -1, 0, $+1$, CCF has eight vertex points, six axial points and two identical central points. The coded points for this experimental design are given in Table 2. Models were evaluated in the terms of statistically significant coefficient, standardized main effects (SME), R-squared values and lack-of-fit.

2.4. Artificial neural network

CAD/Chem® Modeling and Optimization System version 5.1 was used in this study. The input data obtained from CCF and the responses obtained from dissolution studies were used for training and testing the ANN. The model training parameters chosen were: number of hidden layers, two; number of nodes in hidden layer, two; maximum system error, 0.0001; maximum iterations 2000; network scheme, independent outputs; node outputs, sigmoidal slope of 0.1, and learning al-

Table 1
Face centered central composite design: factors and response

Factors	Levels used			Responses
	−1	0	1	
X_1 = Coating weight gain	8%	11%	14%	Y_1 = Cumulative% drug released in 2 h
X_2 = Duration of curing	24 h	36 h	48 h	Y_2 = Cumulative% drug released in 4 h
X_3 = Amount of plasticizer	60%	90%	120%	Y_3 = Cumulative% drug released in 6 h
				Y_4 = Cumulative% drug released in 9 h
				Y_5 = Cumulative% drug released in 12 h

Table 2
Face centered central composite design: factors and response: randomized runs and the response (refer to Table 1 for factors and response)

Runs	Factors			Response				
	X_1	X_2	X_3	$^*Y_1$	$^*Y_2$	$^*Y_3$	$^*Y_4$	$^*Y_5$
1	−1	1	1	15.4 ± 0.45	32.6 ± 0.69	47.6 ± 2.4	73.5 ± 1.4	93.4 ± 1.2
2	0	1	0	11.5 ± 1.1	25.7 ± 2.1	39.4 ± 1.9	76.4 ± 2.0	76.4 ± 2.0
3	1	−1	1	12.4 ± 0.42	26.1 ± 1.4	40.4 ± 2.3	62.3 ± 1.5	79.4 ± 0.6
4	−1	1	−1	13.4 ± 1.44	28.7 ± 1.8	44.7 ± 2.9	67.5 ± 1.8	86.4 ± 1.5
5	1	1	1	10.4 ± 1.74	22.7 ± 1.0	34.7 ± 2.4	52.4 ± 1.9	67.1 ± 2.0
6	1	−1	−1	10.9 ± 1.23	23.3 ± 1.8	32.9 ± 2.0	53.2 ± 2.0	70.4 ± 2.0
7	1	1	−1	9.2 ± 0.58	18.6 ± 1.3	31.4 ± 1.7	44.5 ± 2.1	59.4 ± 1.3
8	−1	0	0	14.5 ± 1.39	33.1 ± 1.0	49.4 ± 2.5	78.4 ± 1.4	95.5 ± 2.5
9	0	0	0	13.2 ± 0.89	26.9 ± 1.3	43.5 ± 1.6	64.7 ± 2.1	82.7 ± 2.1
10	0	0	−1	12.3 ± 1.31	27.4 ± 1.1	40.5 ± 1.6	62.2 ± 1.4	78.0 ± 1.7
11	0	0	0	13.0 ± 1.45	26.7 ± 1.2	41.5 ± 1.7	64.2 ± 1.5	81.8 ± 1.9
12	−1	−1	−1	16.2 ± 0.62	34.1 ± 1.3	51.3 ± 1.8	78.1 ± 1.9	96.5 ± 2.0
13	0	−1	0	13.8 ± 1.13	28.2 ± 1.7	46.4 ± 1.3	68.4 ± 2.0	87.7 ± 0.8
14	−1	−1	1	16.6 ± 0.45	36.6 ± 1.0	55.5 ± 1.6	82.5 ± 2.0	101.2 ± 2.0
15	1	0	0	11.6 ± 0.56	22.4 ± 0.8	36.4 ± 3.0	53.9 ± 1.9	68.3 ± 1.9
16	0	0	1	14.0 ± 0.25	28.4 ± 1.0	45.7 ± 1.5	67.5 ± 2.5	87.6 ± 1.9

gorithm, accelerated back propagation. Models were evaluated by system error, test error, training set R-squared value, test set R-squared value and F-ratio. Guided evolutionary simulated annealing was selected for optimization. Further the release profile was optimized for zero-order model and optimized batch was prepared and dissolution studies were conducted. To evaluate the optimization technique, the observed and predicted values were compared.

2.5. Drug loading and seal coating

Approximately, 600 g of inert beads (Nupareil®) were used as initial core to achieve drug loading. Drug loading suspension containing verapamil HCl 20% w/w, Polydextrose/HPMC (Opadry II®) 6 or 12% w/w and talc 2% w/w in water was prepared by dispersing the ingredients in a low speed homogeniser for 30 min. Polydextrose/HPMC (Opadry II®) and talc were used as binder and anti-adherent, respectively. Strea 1® (Niro Inc., Colombia, MD) fluidized bed coater was employed for drug loading, seal coating and controlled release coating. Following operating parameters were selected: method, bottom spray; spray nozzle diameter, 0.8mm; atomizing pressure, 0.75 atm; air volume, 70 m^3 per h; inlet temperature, 40 °C and flow rate, 1.0 ml per min. Seal coating was provided by applying suspension similar to drug loading suspension without verapamil HCl. Following the seal coating, beads were dried for 15 min at 45 °C in the coating chamber, collected in a tray and dried again at 37 °C in an oven for 4 h. Seal coating was applied to drug loaded beads primarily to avoid the leaching of drug into controlled release coating.

2.6. Controlled release coating

A custom designed pseudolatex dispersion of CAB was employed for providing controlled release coating. The coating method, nozzle diameter and air volume, were similar to that of drug loading. Following coating, the beads were cured for 60 min in fluid bed at 40 °C and subsequently collected in a tray and cured further in an oven at 40 °C for 24/36/48 h. Coating weight gain achieved was 8/11/14/% w/w.

2.7. Content uniformity

An accurately weighed sample of coated beads (100 mg) from 16 batches were triturated in a mortar, transferred into standard flask and sonicated for 15 min to extract the verapamil HCl. Samples were filtered, diluted, and analyzed spectrophotometrically for verapamil HCl at 278 nm (8451A Diode Array UV Spectrophotometer, Hewlett Packard, Wilmington, DE).

2.8. Dissolution studies

Coated beads, equivalent to 120 mg of verapamil HCl, were subjected to dissolution studies to determine the in-vitro release profile (VanKel automated dissolution apparatus, Cary, NC). The following parameters were selected: dissolution medium, 900 ml of water; temperature 37 ± 1 °C; frequency of sampling, 0.5, 1, 2, 4, 6, 8 10 and 12 h. The samples were suitably diluted and assayed spectrophotometrically at 278 nm. The total amount of drug released was calculated from the drug concentration of the sample. The dissolution profiles were obtained by plotting the cumulative percent of verapamil HCl released as a function of sampling time. Mean and S.D. of three samples were plotted. Release models viz. zero order, first order, Hixson Crowell, Higuchi's square root of time, two-third model, and Baker-Lonsdale were fitted to the dissolution results and the best fit was estimated by comparing the R-square value.

2.9. Thermal analysis

Thermal behavior of optimized formulation was analyzed by Differential Scanning Calorimetry. Samples were accurately weighed (8–10 mg) and hermetically sealed in flat bottom aluminum pans. Samples were scanned over a temperature range of 50–250 °C at a rate of 20 °C per min under nitrogen atmosphere in DSC 7 (Perkin–Elmer, Norwalk, CT).

2.10. X-ray diffraction study

Change in crystallinity of verapamil HCl and excipient in the optimized formulation was analyzed by X-ray powder diffraction. For this purpose, a Philips Norelco Diffractometer was operated at 40 kV and 20 MA and nickel filtered Cu–Kα radiation was used with a scanning speed of $d°/2\theta$ per min.

2.11. Scanning electron microscopy (SEM)

The nature of coated surface of an optimized formulation and uncoated formulation surface was scanned using a JEM-100 CX Electron Microscope interfaced with KEVEX Image Analyzer. Beads were loaded on the copper sample holder and sputter coated with carbon followed by gold. The topography of the whole beads and cross section were examined for the integrity of coated film.

3. Results and discussion

3.1. Response surface methodology

3.1.1. Design of experiments and model

Central Composite Design(s) were introduced by Box and Wilson (1951). It contains an imbedded factorial or fractional factorial matrix with center points augmented with a group of 'star points' or 'axial points' that allow estimation of curvature. If the distance from the center of the design space to a factorial point is ± 1 unit for each factor, the distance from the center of the design space to an axial point is $\pm \alpha'$, where $|\alpha'| > 1$. The precise value of α' depends on certain properties desired for the design and on the number of factors involved. In CCF, the star points are at the center of each face of the factorial space, so that $\alpha' = \pm 1$. This variety requires three levels of each factor. The CCF allows estimation of first order linear terms and two-factor interactions and results in resolution, $R = V$ (Box et al., 1976). Thus the estimates of the main effects are not confounded with two-factor interactions, and the two-factor interactions are not confounded with each other, but do confound two factor interactions with three factor interaction (Box et al., 1976). The factors and responses are given in Table 1. The experimental runs with coded values

of factors and the actual values of responses are given in Table 2.

3.1.2. Regression equation

The regression equations that have been fitted to the data are given in Table 3. Statistically significant coefficients are included in the regression equation. In all five models for Y_1-Y_5, coating weight gain and duration of curing had a negative impact on the responses and plasticizer concentration had a positive impact on the responses. Though the plasticizers are added in polymeric dispersion to reduce the glass transition temperature (T_g), they also increase the free volume in polymeric film, which, in turn, has been shown to facilitate the release of drug across the membrane (Sastry et al., 1998; Sinko and Amidon, 1989). However, an increase in coating weight gain decreased the rate and extent of release of verapamil HCl from the beads simply, because of the increased permeability distance across the membrane. As the duration of curing increased, it negatively affected the cumulative percent release (Y_{12}). Curing of polymeric film accelerates the rate of coalescence of polymer particles to form a homogenous film. The effect of curing on drug release depends upon physicochemical properties of the drug and polymeric coatings (Bodmeier et al., 1997). During curing, a further gradual coalescence occurs which leads to the formation of a smooth and uniform film. However, a prolonged coalescence may lead to shrinkage of the film that would eventually reduce the rate and extent of drug release across the membrane.

Table 3
Regression equations of the fitted models

$Y_1 = 13.0-4.1A-1.7B+1.7C$
$Y_2 = 26.9-9.1A-3.3B+3.7C$
$Y_3 = 42.7-14.2A-5.7B+4.6C$
$Y_4 = 64.0-21.9A-10.1B+8.6C-2.3AA+4.9BB-3.9BC$
$Y_5 = 82.2-29.9A-11.7B+7.6C-2.5AB+3.0AC$

Statistically significant terms are included.

3.1.3. Interaction

Significant interaction was found between coating weight gain and plasticizer concentration (X_1X_3) and a quadratic term-$(X_3)^2$ in model-Y_4. Likewise, significant interaction was found between coating weight gain and duration of curing (X_1X_2) as well as coating weight gain and plasticizer concentration (X_1X_3) in model-Y_5. From the data it appears that interaction between factors occurs with time. Though time was not considered as a factor, it plays a crucial role in interaction. Generally, an increase in coating thickness would result in longer curing times. As a result, longer curing perhaps facilitates the complete film formation and as a result decreases the rate of dissolution. The X_1X_3 interaction arises from a difference in sensitivity to plasticizer concentration change for the two coating durations. Since the amount of polymer is more with an increase in coating thickness, the increase in plasticizer concentration brings about a uniform film with increased microscopic free volume (Sastry et al., 1998; Sinko and Amidon, 1989). Therefore, the net interaction effect is positive.

3.1.4. Standardized main effects, R-squared values of models and lack of fit

SME given in Table 4 are the ratio of main effects to the standard error of main effects. Only those statistically significant SME at 5% significance level are given in Table 4. Coating weight gain has a larger SME compared with the other factors suggesting the paramount importance of that factor. The percentages of variability in responses that are accounted for by the factors (R-squared values) are given in Table 4 for all the models. The R-squared value of 90 and above for all the models suggest an adequate modeling. Also, the P-value for lack of fit for all models stays above 0.05, suggesting absence of any lack-of-fit. Additionally, absence of several interaction terms suggests a predominantly linear model for Y_1-Y_3.

3.1.5. Response surface

Figs. 1–6 show the three-dimensional response surface and two-dimensional contour plot. It is quite noteworthy that the effects are nearly linear

Table 4
SME of RSM and statistical parameters of ANN

RSM	Standard error of main effects (SME)				
	Y_1	Y_2	Y_3	Y_4	Y_5
Coating wt. gain (A)	11.2	24.2	20.6	6805	81.0
Duration of curing (B)	4.7	8.6	8.3	31.6	31.8
Plasticizer conc. (C)	4.6	9.7	6.7	26.9	20.5
$A \times A$	–	–	–	3.6	–
$A \times B$	–	–	–	–	6.0
$A \times C$	–	–	–	–	7.3
$B \times B$	–	–	–	7.8	–
$B \times C$	–	–	–	10.8	–
$C \times C$	–	–	–	–	–
R-squared	89.7	91.3	91.5	97.9	97.4
Lack of fit	0.8361	0.2923	0.4289	0.1270	0.0730
ANN	Statistical parameters				
System error	0.0037	0.0013	0.0013	0.00046	0.00057
Test error	0.0070	0.0043	0.0020	0.00170	0.00140
Training set R^2	81.1	92.2	91.5	97.8	97.7
Test set R^2	70.4	64.5	84.7	85.1	95.7
F-ratio	6.1	18.4	16.4	69.00	65.3

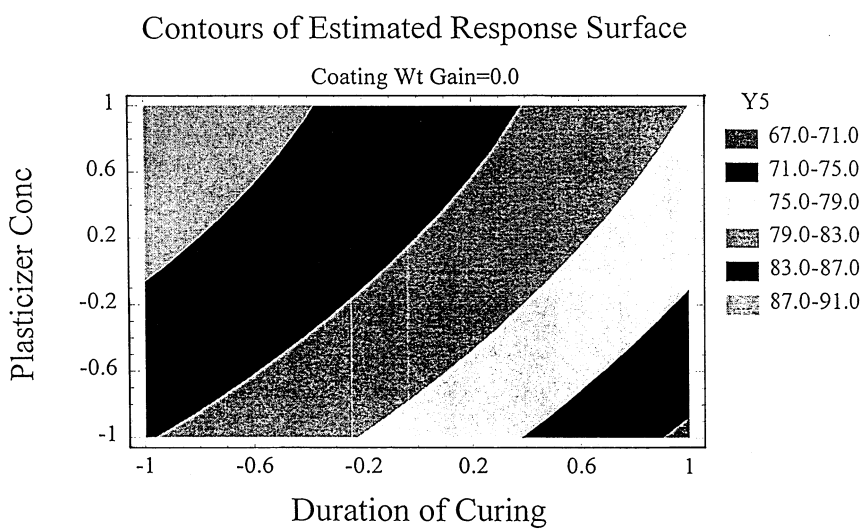

Fig. 1. Contour plot of duration of curing (X_2) and plasticizer concentration (X_3) on the response Y_5.

and the curvatures appeared were due to the non-linear nature of factors. As shown in Fig. 3, regardless of plasticizer concentration, 94–99% of verapamil HCl was released when the coating weight gain and duration of curing were kept at 7% and 36 h, respectively. Contour plots are extremely useful when there is only one response. Three-dimensional plots are useful to depict the interactions. In Fig. 4, when duration of curing was kept at 48 h, an increase in plasticizer concentration increased the response Y_6 by 9% (70–79%). However, when the duration of curing was kept at 24 h, an increase in plasticizer concentration from 60–120% increased the response only

by 6%, which signifies an interaction between these two factors.

3.1.6. Modeling of dissolution profile

The release profile of non-osmotic, membrane controlled, spherical shaped multi-particulate dosage forms was successfully fitted to a zero-order model by several investigators Dyer et al., 1995; Sun et al., 1997; Frohoff-Hulsmann et al., 1999; Wang et al., 1997; Rekhi and Jambhekar, 1996). Time independent mathematical modeling of such spherical shaped diffusion controlled reservoir systems (Peppas, 1995) is given below:

$$\frac{Dm}{dt} = \frac{\Delta C 4\pi D K r_e r_i}{\Delta r} \quad (1)$$

where Dm/dt, release rate; ΔC, difference in concentration between two sides of the membrane; D,

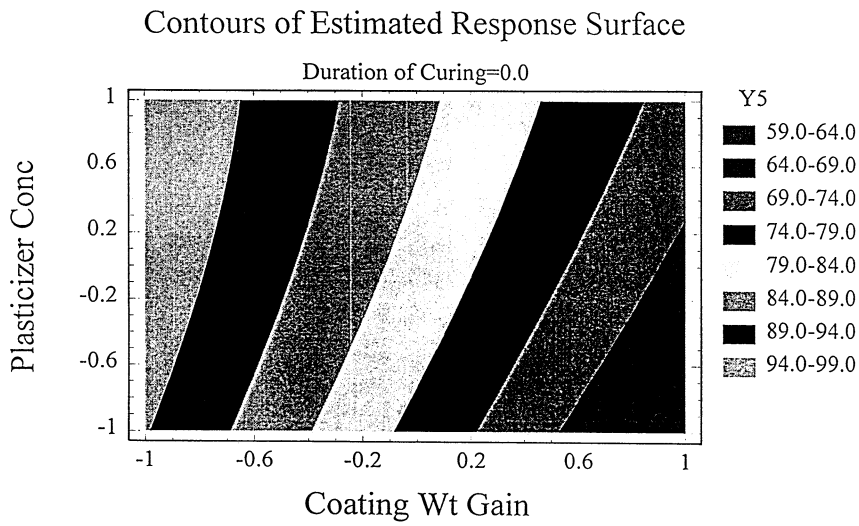

Fig. 2. Contour plot of coating weight gain (X_1) and plasticizer concentration (X_3) on the response Y_5.

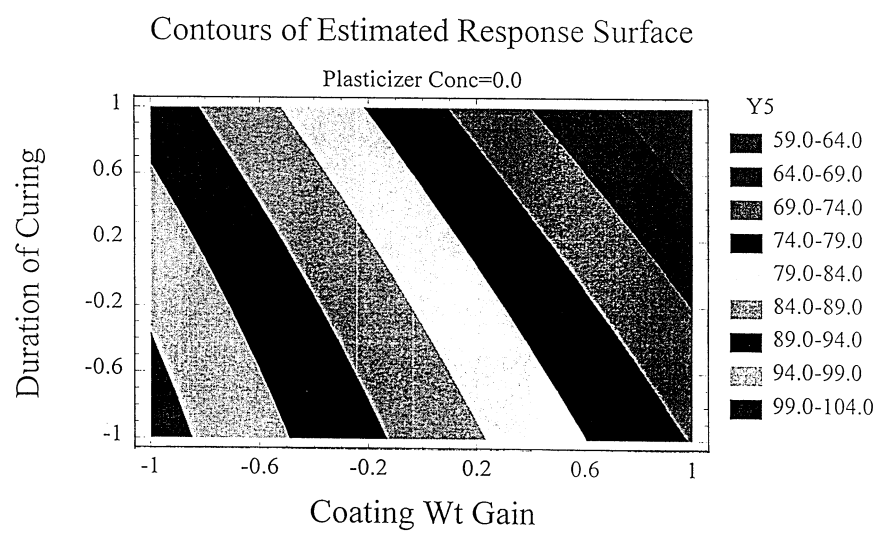

Fig. 3. Contour plot of coating weight gain (X_1) and duration of curing (X_2) on the response Y_5.

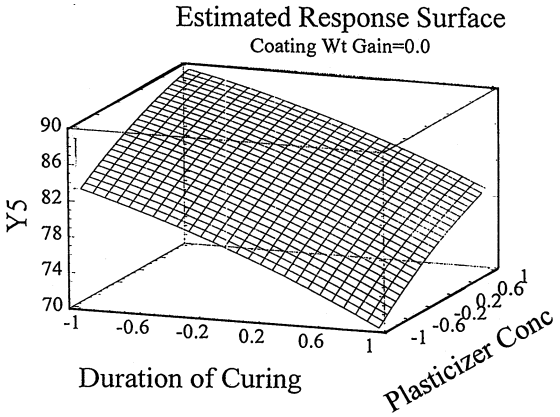

Fig. 4. Response surface plot of duration of curing (X_2) and plasticizer concentration (X_3) on the response Y_5.

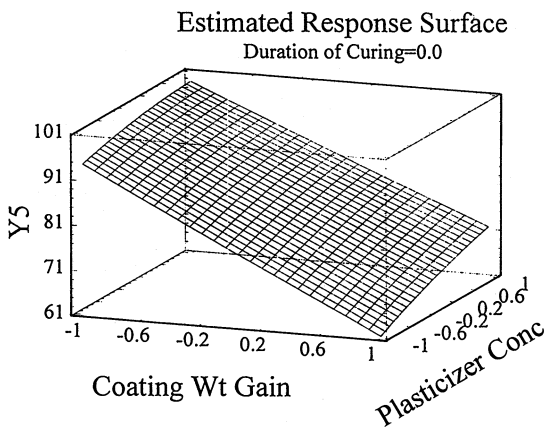

Fig. 5. Response surface plot of coating weight gain (X_1) and plasticizer concentration (X_3) on the response Y_5.

diffusion coefficient of drug through the membrane; K, partition coefficient of the drug between the reservoir and membrane; r_i, internal radius of the bead; r_e, external radius of the bead; and Δr, difference in radii.

Table 5 shows that R-squared values of all the models fitted the dissolution data. Zero order models fitted the results better than that of any other model. However, the coefficient of determination tends to decrease when only more than 80 or 90% of the drug release is taken into account. It explains the fact that, the greater the cumulative percent of drug released, the more it tend to deviate from the zero order profile. Therefore, the formulation was optimized for zero order release with 100% of drug release at 12th hour.

3.1.7. Optimization

The formulation factors were optimized to yield a dissolution profile fitting into zero order models. Factors Y_1-Y_4 were targeted for the theoretical values as constraints and Y_5 was maximized. The optimized values for the factors X_1-X_3 were 8%, 34.9 h, and 107.6%, respectively. Optimized batch was prepared accordingly and the dissolution study was carried out. The difference between the observed and targeted values of the responses Y_1-Y_5 were within the range of experimental error (Table 6).

3.2. Artificial neural network

3.2.1. Training

Modeling parameters were selected by trial and error. When hidden layers were increased more than two, the system error and the test error remained constant. Multiple hidden layers may help dramatically in capturing the non-linear behavior. Since the present data is relatively linear, two hidden layers were sufficient in developing a good model. When the number of nodes was increased to 2, parameters such as desirable system error, test error, test R-squared, and training R-squared were found. The presence of more

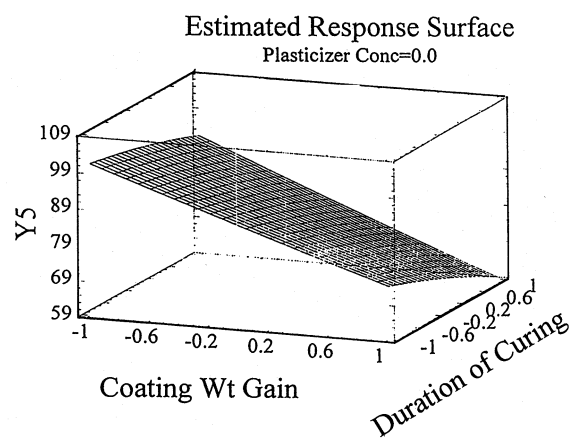

Fig. 6. Response surface plot of coating weight gain (X_1) and duration of curing (X_2) on the response Y_5.

Table 5
R-squared values of dissolution models fitted the release profile

Model	*R*-squared values, mean ± S.D.		
	16 Runs	9 runs with at least 80% drug release at 12 h	4 runs with at least 90% drug release at 12 h
Zero order	0.9978 ± 0.0013	0.9973 ± 0.0016	0.9962 ± 0.0018
First order	0.8432 ± 0.0183	0.8315 ± 0.0130	0.8201 ± 0.0111
Hixson Crowell	0.9537 ± 0.0525	0.9325 ± 0.0632	0.8941 ± 0.0839
Higuchi's $\sqrt{t}$	0.8728 ± 0.0075	0.8750 ± 0.0074	0.8809 ± 0.0076
Two-third	0.9897 ± 0.0052	0.9881 ± 0.0031	0.9866 ± 0.0021
Baker Lonsdale	0.8033 ± 0.05700	0.7722 ± 0.0567	0.7282 ± 0.0569

nodes in the hidden layer may be helpful in modeling complex behavior. However, too many nodes will add significantly to the time involved in training the model and may result in over training or memorization of the data. In the present study, the number of hidden layers was 2 and the number of nodes per hidden layer was 2. An increase in number of iterations would normally improve the reduction of the system error since the learning is incremental. However, no appreciable decrease in system error was observed when number of iterations was increased from 2000 to 10 000, and therefore, number of iterations was kept 2000 for all the models.

3.2.2. Model statistics

System error measurement determines the model's 'tightness of fit' to a particular set of training data. It is a sum of all output errors, measured over the entire set of training data. During training, a sharp decrease in system error was observed followed by a level out as it approached the maximum number of iterations. As long as no increase in the system error or oscillations are observed during training, the modeling can be considered good. Maximum system error of 0.0037 was found in the case of Y_1 and a minimum of 0.00057 in the case of Y_5. The smaller the system error value, the more tightly model will attempt to fit data presented to it during training. Test error is similar to system error except the values are determined from test data. The model developed was validated by a test data set that was not available to the model during training phase. However, at standard intervals during training process, the inputs of test data set were presented to the model for prediction, and the model's predictive results were compared against the actual output values. *R*-squared values depict the percentage of response variability accounted by the model. It appears that both test and training *R*-squared values (Table 4) suggest an adequate model for four out of five responses since all these values remain over 70% (CAD/Chem® manual CAD/Chem Manual, 2000). The ANN modeling is particularly good for Y_5 where the test *R*-squared value is 95.7. This value is comparable with the RSM *R*-squared value of 97.4. F-ratio indicates the extent to which the model fit exceeds the random or experimental error in the system. *F*-ratio of at least above four is usually

Table 6
Optimization: factor levels, expected and observed dissolution values

Factors	Factor levels	
	RSM	ANN
Coating wt. gain	8.0%	9.1%
Duration of curing	34.9 h	32.9 h
Amount of plasticizer	107.6%	118.6%
Responses (expected, %)	Observed (%)	
Y_1(16.7)	15.5 ± 0.5	15.6 ± 0.6
Y_2(33.3)	33.1 ± 1.2	34.3 ± 0.9
Y_3(50.0)	49.2 ± 1.8	51.2 ± 1.5
Y_4(75.0)	74.8 ± 1.9	76.5 ± 1.6
Y_5(100.0)	98.6 ± 1.8	99.6 ± 1.7

required to support the R-square value as a good indicator of fit (CAD/Chem® manual CAD/Chem Manual, 2000). In the present study, the F-ratio remained well above the requirement (Table 4).

3.2.3. Optimization

Similar to RSM optimization, the formulation factors were optimized to yield a dissolution profile fitting into zero-order model. Factors Y_1-Y_4 were targeted for the theoretical values calculated according to zero-order model and Y_5 was maximized. The optimized values for the factors X_1-X_3 were 9.1%, 32.9 h, and 118.6%, respectively. Optimized batch was prepared accordingly and the dissolution study was carried out. The difference between the observed and targeted values of the responses Y_1-Y_5 were within the range of experimental error (Table 6).

3.3. Comparative evaluation of RSM and ANN

Modeling in RSM involves multiple regressions leading to generation of polynomial equations. It could be a first order model, with or without interaction or a second order model. If the interactions are stronger and effects are not linear, first order model may not be adequate. The advantage of second order model such as the one employed in the present study is the flexibility and appropriateness. It can take a wide variety of functional form and appropriately approximate the true response surface (Myers and Montgomery, 1995). Thus the core of the RSM is the graphical perspective of the problem environment, in which the response is viewed as a function of different levels of two factors. Outcome of the RSM is identification of the region of optimum response that is insensitive to factor (environment and component) variation. Simultaneous optimization of all responses is usually carried out by method of steepest ascent (Myers and Montgomery, 1995), desirability function approach and mathematical programming approach (http://www.nist.gov/itl/div898/handbook/pri/section5/pri532.htm, 2001).

Though the modeling and optimization techniques are different in RSM and ANN, the modeling adequateness in describing the data and optimization in the present study are comparable (Table 4). In this study, an attempt was made to test the usefulness of ANN in modeling the data obtained from statistically designed experiments and the results were found to be comparable with that of RSM for the response Y_5. For all other responses RSM was found to have higher R-squared values as compared with ANN.

3.4. X-ray diffraction studies

X-ray powder diffractometry can be used to study the solid-state reactions provided the powder pattern of the reactant is different from that of the reaction product (Suryanarayanan, 1995). Earlier studies on compatibility of excipient with verapamil reported an absence of interaction. However, the aim of this study was to analyze if there was any crystallinity change during the entire process of formulation. Prominent diffraction lines of verapamil HCl, Polydextrose/HPMC (Opadry®) and inert beads (Nupareil®) were identified from the diffraction pattern obtained from finely powdered beads. Presence of all prominent diffraction peaks and absence of new peaks suggested an absence of interaction between verapamil HCl and excipient (Fig. 7).

3.5. Thermal analysis

Thermal analysis of entire formulation is very complicated, because of the possibility of eutectic interactions, solid solution formation, polymorphic and polymeric transitions, instability between ingredients at high temperature, and any physical interaction caused during the formulation process. In Fig. 8, thermograms of verapamil HCl, Polydextrose/HPMC (Opadry®), inert beads (Nupareil®), and optimized formulation are depicted. The physical interaction between verapamil HCl and the excipient were to such an extent that the individual peaks of transitions were broadened. On the contrary, X-ray diffraction and content analysis proved no interaction and degradation of verapamil HCl during

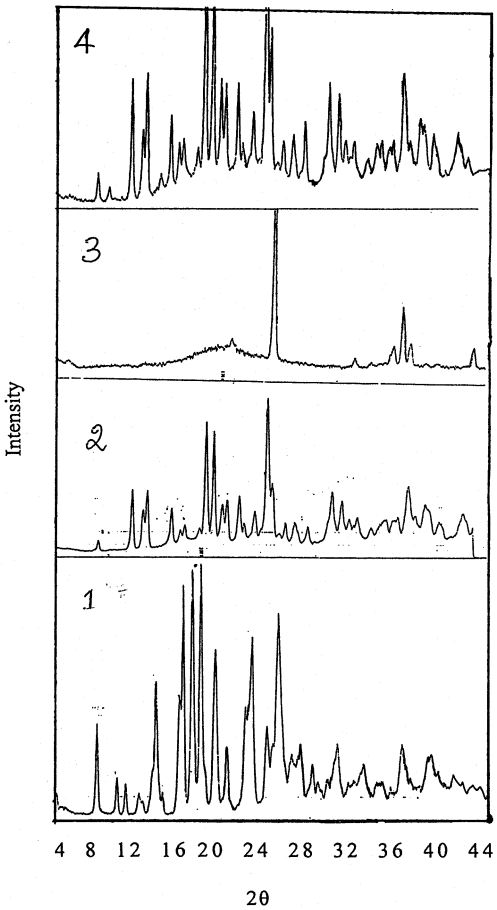

Fig. 7. X-ray diffraction patterns of verapamil HCl, (1) Inert beads (Nupareil®); (2), Polydextrose/HPMC (OpadryII®); (3) and Optimized formulation (4).

the formulation. Therefore, it is concluded that the broadening of individual peaks is due to intermixing of different components of the formulation.

3.6. Scanning electron microscopy

SEM pictures of the optimized beads are given in the Fig. 9. The outer surface looks much smoother due to the CAB pseudolatex coating. The cross section shows the core of inert beads (Nupariel®) and the porous drug loaded layer. The outermost section shows the uniform and intact coating layer of controlled release membrane. The thickness of the membrane remains constant over the entire surface area.

4. Conclusions

A custom designed aqueous-based pseudolatex dispersion successfully provided a controlled release coating on a multi-particulate system containing verapamil HCl. Both RSM and ANN adequately modeled the three selected variables and response dissolution profile. Among the three factors coating weight gain and duration of curing had negative impact on the response, whereas the plasticizer concentration had positive effect. Both RSM and ANN optimized dissolution profile. The difference between observed and predicted dissolution profile of optimized batch was within the experimental error. The modeling abilities of both RSM and ANN were comparable. X-ray powder diffraction study and content analysis suggested absence of any physical interaction and degradation of verapamil HCl.

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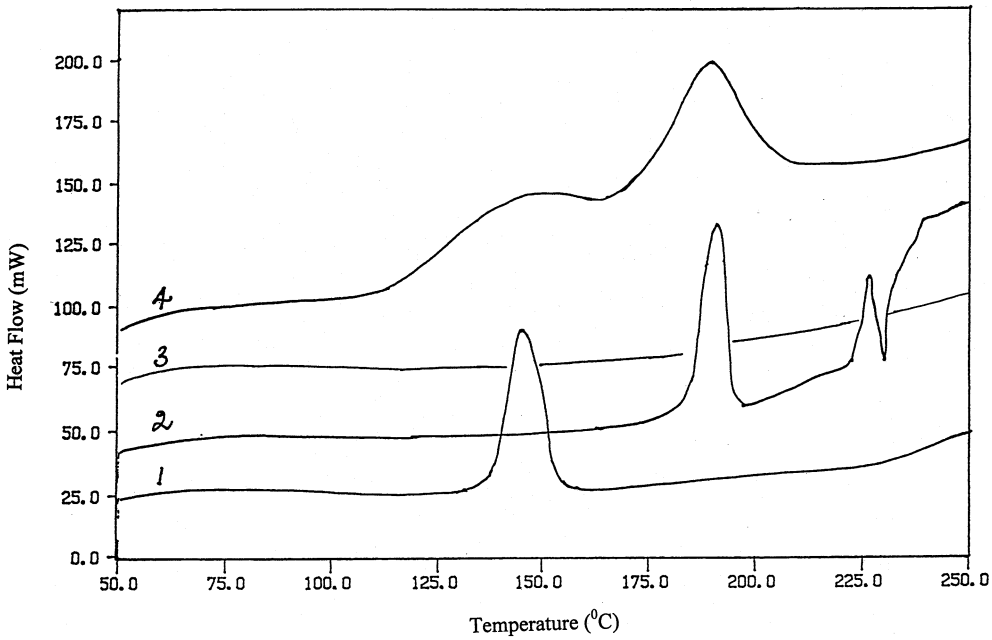

Fig. 8. DSC thermograms of verapamil HCl, (1) inert beads (Nupareil®); (2) Polydextrose/HPMC (OpadryII®); (3) and Optimized Formulation (4).

Fig. 9. SEM pictures of coated beads and its cross-section.

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