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Research paper

Release modulating hydrophilic matrix systems of losartan potassium: Optimization of formulation using statistical experimental design

Shruti Chopra [a,*], Gayathri V. Patil [b], Sanjay K. Motwani [a]

[a] *Department of Pharmaceutics, Faculty of Pharmacy, New Delhi, India*
[b] *Global College of Pharmacy, Ropar, India*

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Abstract

The aim of the present research work was to systemically device a model of factors that would yield an optimized sustained release dosage form of an anti-hypertensive agent, losartan potassium, using response surface methodology by employing a 3-factor, 3-level Box-Behnken statistical design. Independent variables studied were the amount of the release retardant polymers – HPMC K15M (X_1), HPMC K100M (X_2) and sodium carboxymethyl cellulose (X_3). The dependent variables were the burst release in 15 min (Y_1), cumulative percentage release of drug after 60 min (Y_2) and hardness (Y_3) of the tablets with constraints on the $Y_2 = 31$–35%. Statistical validity of the polynomials was established. *In vitro* release and swelling studies were carried out for the optimized formulation and the data were fitted to kinetic equations. The polynomial mathematical relationship obtained $Y_2 = 32.91 - 2.30X_1 - 5.69X_2 - 0.97X_3 - 0.41X_1X_2 + 0.21X_1X_3 - 0.92X_1^2 - 1.89X_2^2$ ($r^2 = 0.9944$) explained the main and quadratic effects, and the interactions of factors influencing the drug release from matrix tablets. The adjusted (0.9842) and predicted values (0.9893) of r^2 for Y_2 were in close agreement. Validation of the optimization study indicated high degree of prognostic ability of response surface methodology. Tablets showed an initial burst release preceding a more gradual sustained release phase following a non-fickian diffusion process. The Box-Behnken experimental design facilitated the formulation and optimization of sustained release hydrophilic matrix systems of losartan potassium.
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Keywords: Hydrophilic matrix tablets; Box-Behnken statistical design; Response surface methodology; Sustained release

1. Introduction

Hydrophilic matrix tablets are among the most popular delivery systems for oral controlled-release dosage forms. These hydrophilic matrices are widely accepted because of their biopharmaceutical and pharmacokinetics advantages over conventional dosage forms [1]. This is largely because they offer precise modulation of drug release as a result of hydration of the constituent polymer(s), flexibility to obtain desired drug release profiles, cost effectiveness, patient compliance, providing a constant, prolonged, and uniform therapeutic effect and broad Food and Drug Administration (FDA) acceptability [2].

From the wide choice of possible matrix materials, e.g., sodium alginate, chitosan, poly (acrylic acids), etc., HPMC has been used most frequently in the formulation of controlled release monolithic matrix tablets because of its hydrophilic gel-forming property, non-toxicity and cost effectiveness [3–5]. The swelling rate and erosion of HPMC-based matrix tablet in aqueous media are very crucial in terms of achieving the desired release profiles, and are affected by parameters such as the physicochemical properties of the polymer and the drug, processing conditions, the testing medium used and the formulation composition [6–8].

* Corresponding author. Department of Pharmaceutics, Faculty of Pharmacy, Jamia Hamdard, Hamdard Nagar, New Delhi 110062, India. Tel.: +91 11 2605 9688; fax: +91 11 2605 9663.
E-mail address: shrutichopra21@yahoo.com (S. Chopra).

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Losartan potassium (LP) is a potent, highly specific angiotensin II type 1 (AT1) receptor antagonist with anti-hypertensive activity. It is readily absorbed from the gastrointestinal tract with oral bioavailability of about 33% and a plasma elimination half-life ranging from 1.5 to 2.5 h [9]. Administration of LP in a controlled release dosage form with dual release characteristics i.e., burst release followed by an extended release over 8 h, would be more desirable as these characteristics would allow a rapid onset followed by protracted anti-hypertensive effects by maintaining the plasma concentrations of the drug well above the therapeutic concentration [10,11].

Response surface methodology (RSM) is one of the popular methods in the development and optimization of drug delivery systems. Based on the principles of design of experiments (DOE), the methodology involves the use of various types of experimental designs, generation of polynomial mathematical relationships and mapping of the response over the experimental domain to select the optimum formulation [12–14]. Central composite design (CCD) [15,16], 3-level factorial design, Box Behnken design [15] and D-optimal design [17] are the different types of RSM designs available for statistical optimization of the formulations. Box-Behnken statistical design is one type of RSM design that is an independent, rotatable or nearly rotatable, quadratic design having the treatment combinations at the midpoints of the edges of the process space and at the center [18–20]. Additionally, it requires fewer experimental runs and less time and thus provides a far more effective and cost-effective technique than the conventional processes of formulating and optimization of dosage forms.

The current study aimed at developing and optimizing an oral sustained release dosage form of LP using computer-aided optimization technique i.e. Box Behnken statistical design with constraints on cumulative percentage release of drug after 60 min (31–35%). The Independent variables for the present study were: amount of release retardant polymers – HPMC K15M (X_1), HPMC K100M (X_2) and sodium carboxymethyl cellulose (X_3). The dependent variables studied were the burst release in 15 min (Y_1), cumulative percentage release of drug after 60 min (Y_2) and hardness of the tablets (Y_3).

2. Materials and methods

2.1. Materials

Losartan potassium was provided ex gratia by Wockhardt Labs. Ltd. (Aurangabad, India). HPMC 2208 of various viscosity grades (Methocel K15M premium CR and Methocel K100M premium CR) were supplied by Colorcon Asia Pvt. Ltd. (Mumbai, India). Pharmatose DCL 21 (lactose) was received as a gift sample from DMV International, Netherlands. Sodium carboxymethyl cellulose (Na-CMC), talc and magnesium stearate were purchased from S.D. Fine Chemicals, India. All other reagents and solvents used were of analytical grade and used as received.

2.2. Preparation of compressed matrices

Drug and the lactose (diluent) were sifted through #40 manually and mixed well to ensure the uniformity of premix blend. Several drug-diluent premixes were then mixed with the selected combination and ratio of hydrophilic polymers (HPMC K15M, HPMC K100M and Na-CMC), previously sifted through #40, for 5 min. Premix blend was wet granulated with isopropyl alcohol and the granules were sized through #18 and were dried at 45 °C for 15 min. Dried LP granules were lubricated with talc and magnesium stearate. The tablets were compressed at an average compression weight of 350 mg by cold compression technique on dialed hydraulic press (Kimaya Engineers, India) at 12.0 mm, circular, flat punches at compressional pressure of 5 tons with 15 s dwell time.

Different formulations of losartan potassium 100 mg sustained release tablets were prepared using the following excipients: HPMC K15M (70–140 mg), HPMC K100M (35–105 mg), Na-CMC (52.5–87.5 mg), talc (10.25 mg), magnesium stearate (1.75 mg) and lactose (q.s. to 350 mg).

2.3. Experimental design

Box-Behnken statistical screening design was used to optimize and evaluate main effects, interaction effects and quadratic effects of the formulation ingredients on the in vitro release of LP sustained release formulations. A 3-factor, 3-level design used is suitable for exploring quadratic response surfaces and constructing second order polynomial models with Design Expert® (Version 7.0.0, Stat-Ease Inc., Minneapolis, MN). This cubic design is characterized by set of points lying at the midpoint of each edge of a multidimensional cube and center point replicates ($n = 3$). The nonlinear computer-generated quadratic model is given as

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

where Y is the measured response associated with each factor level combination; b_0 is an intercept; b_1 to b_{33} are regression coefficients computed from the observed experimental values of Y; and X_1, X_2 and X_3 are the coded levels of independent variables. The terms X_1X_2 and X_i^2 ($i = 1$, 2 or 3) represent the interaction and quadratic terms, respectively [21]. The dependent and independent variables selected are shown in Table 1 along with their low, medium and high levels, which were selected based on the results from preliminary experimentation. The amounts of HPMC K15M (X_1), HPMC K100M (X_2) and Na-CMC (X_3) used to prepare each of the 15 formulations and the observed responses are given in Table 2.

Table 1
Variables in Box Behnken design

Factor	Levels used, actual (coded)		
	Low	Medium	High
X_1 = HPMC K15M (%)[a]	20 (−1)	30 (0)	40 (+1)
X_2 = HPMC K100M (%)[a]	10 (−1)	20 (0)	30 (+1)
X_3 = Na-CMC (%)[a]	15 (−1)	20 (0)	25 (+1)
Dependant variables		Constraints	
Y_1 = % Burst release in 15 min		$10 \leqslant Y_1 \leqslant 15$	
Y_2 = % Dissolution after 60 min		$31 \leqslant Y_2 \leqslant 35$	
Y_3 = Hardness (kg/cm^2)		Maximize (range 3.5–5.5)	

[a] All percentages were calculated with respect to total tablet weight of 350 mg.

2.4. Tablet assay and physical evaluation

The tablets were assayed for drug content using methanol as the extracting solvent, and the samples were analyzed spectrophotometrically (Shimadzu 1601, Shimadzu Corp.) at 205 nm. Tablets were also evaluated for the hardness ($n = 6$) (Monsanto hardness tester), friability ($n = 6$) (Roche Friabilator, 100 rpm), weight variation ($n = 20$) and thickness ($n = 10$) (Mitutoyo digital vernier caliper).

2.5. In vitro drug release studies

Dissolution studies were performed using the USP XXVIII, paddle-rotating method (Electrolab dissolution tester, Electrolab, India) at 37 °C ± 0.5 °C and 75 rpm using 0.1 N HCl (2 h) and phosphate buffered solution, pH 6.8 (PBS) (10 h), as the dissolution media. Dissolution studies were carried out in triplicate, maintaining the sink conditions for all the formulations. A 5 ml aliquot of sample was withdrawn at regular time intervals, filtered and assayed spectrophotometrically at 205 nm. The cumulative % drug release was calculated for the formulations and the drug release data were curve fitted using *PCP Disso v2.08* software to study the possible mechanism of drug release from hydrophilic swollen matrices.

2.6. Swelling and erosion studies

Swelling and erosion studies of the matrix tablets were carried out under conditions identical to those described for the dissolution testing. After 2 h in 0.1 N HCl and 6 h in phosphate buffer, pH 6.8, the tablets were removed, gently wiped with a tissue paper to remove surface water and Scanning Electron Microscopy (SEM) study of the hydrated swollen tablets was carried out. Water uptake and mass loss were determined gravimetrically according to the following equations [22,23]:

$$\text{Degree of swelling(water uptake)} = \frac{\text{Wet weight} - \text{Original dry weight}}{\text{Original dry weight}} \quad (1)$$

$$\text{Erosion (\% mass loss)} = \frac{\text{Original weight} - \text{Remaining dry weight}}{\text{Original weight}} \quad (2)$$

2.7. Thermal properties

Differential scanning calorimetry (DSC) experiments were performed on drug, excipients and the optimized formulation using DSC (Perkin–Elmer, Norwalk, CT). The instrument was calibrated using indium standards. Accurately weighed samples (5–10 mg) were hermetically sealed in flat bottom aluminium pans and heated from 48 to 300 °C at a rate of 10 °C per min under an atmosphere of nitrogen. Thermograms were normalized and rescaled as needed before overlapping.

2.8. Fourier transform infrared spectroscopy (FTIR)

FTIR studies were performed on drug, excipients and the optimized formulation using Shimadzu FTIR (Shimadzu

Table 2
Observed responses in Box Behnken design for losartan potassium SR tablets

Batch	Dependant variables			Independent variables			Burst release rate (mg/h) up to 15 min (Mean ± SEM)
	X_1 (%)	X_2 (%)	X_3 (%)	Y_1 (%)	Y_2 (%)	Y_3 (kg/cm^2)	
1	20	10	20	11.87	37.53	3.5	47.48 ± 0.873
2	40	10	20	9.63	34.27	4.0	38.52 ± 0.732
3	20	30	20	7.16	26.76	5.0	28.64 ± 1.246
4	40	30	20	6.81	21.84	5.5	27.24 ± 0.541
5	20	20	15	10.45	35.63	4.5	41.80 ± 1.276
6	40	20	15	8.56	30.12	4.0	34.24 ± 0.346
7	20	20	25	9.27	33.41	3.5	37.08 ± 0.673
8	40	20	25	8.13	28.73	5.5	32.52 ± 0.347
9	30	10	15	12.41	37.61	3.5	49.64 ± 0.324
10	30	30	15	7.23	26.48	5.5	28.92 ± 1.561
11	30	10	25	10.71	35.54	3.5	42.84 ± 1.212
12	30	30	25	6.69	24.39	5.5	26.76 ± 0.881
13	30	20	20	8.87	33.74	5.0	35.48 ± 0.924
14	30	20	20	8.13	32.21	4.0	32.52 ± 0.731
15	30	20	20	7.33	32.79	4.5	29.32 ± 1.579

Corp., India). Background spectrum was collected before running each sample. The samples were analyzed between wavenumbers 4000 and 400 cm^{-1}.

2.9. Optimization data analysis and validation of optimization model

Statistical validation of the polynomial equation generated by Design Expert® was established on the basis of ANOVA provision in the software. A total of 15 runs with triplicate center points were generated. The models were evaluated in terms of statistically significant coefficients, standardized main effects (SME) and R^2 values.

Various feasibility and grid searches were conducted to find the compositions of optimized formulation. Various 3-D response surface graphs were provided by the Design Expert software. By intensive grid search performed over the whole experimental region, nine optimum checkpoints formulations were selected to validate the chosen experimental domain and polynomial equations. The optimized checkpoint formulations were prepared and evaluated for various response properties. The resultant experimental values of the responses were quantitatively compared with that of the predicted values. Also, linear regression plots between actual and predicted values of the responses were produced using MS-Excel.

2.10. Stability studies

Stability study of the optimized matrix tablets was carried out as per ICH guidelines at 25 °C ± 2 °C/60% ± 5% RH and 40 °C ± 2 °C/75% ± 5% RH. Physical attributes of the tablets, % drug content and *in vitro* drug release profiles were studied over a period of 6 months.

3. Results and discussion

3.1. Drug content and physical evaluation

Drug content of the formulations was assayed spectrophotometrically at 205 nm. The assayed content of drug in various formulations varied between 98.12% and 100.65% (average 99.39%). Tablet weights varied between 347.93 and 352.79 mg (average 350.36 mg), hardness between 3.5 and 5.5 kg/cm^2 (average 4.5 kg/cm^2), thickness between 3.10 and 3.20 mm and friability ranged from 0.32% and 0.47% (average 0.40%). Thus all the physical parameters of the compressed matrices were found to be practically within controls.

3.2. Mechanism of drug release studies

To study the release mechanism, various dissolution models were applied to the in vitro release profiles of the 15 different formulations. The kinetic models included zero order-, first order-, Higuchi's-, Korsmeyer-Peppas and Hixson-Crowell model. Table 3 shows the equations used to determine the appropriate models and presents the mean and standard deviation of R^2-values for all formulations.

Table 3
Dissolution model study by fitting in vitro release study[a]

Model	Equation	R^2 Value (15 runs)	
		Y_1 (%)	Y_2 (%)
Zero order	$m_0 - m = kt$	0.9953 ± 0.0243	0.8991 ± 0.0357
First order	$\ln m = kt$	0.9107 ± 0.0188	0.9249 ± 0.0286
Higuchi's Model	$m_0 - m = kt^{1/2}$	0.9526 ± 0.0322	0.8874 ± 0.0198
Korsmeyer-Peppas	$\log(m_0 - m) = \log K + n \log t$	0.8995 ± 0.0209	0.9931 ± 0.0339
Hixson-Crowell	$m_0^{1/3} - m^{1/3} = kt$	0.9238 ± 0.0361	0.9168 ± 0.0217

[a] m_0 is the initial drug amount (100%, when represented as percentage); m the amount of drug remaining at a specific time (calculated as % of m_0); k the rate constant; t is the time.

Overall curve fitting showed that the drug release from sustained release matrix tablets followed zero-order model for burst release and Korsmeyer-Peppas model for dissolution after 60 min (the critical value of $n = 0.5143$–0.6897 suggesting non-Fickian diffusion). This is further supported by the fact that the combinations of polymer swelling, drug dissolution and matrix erosion determine the drug release from swellable matrices, either on a macroscopic or on a molecular level [11,24]. Water-soluble drugs are released primarily by diffusion of dissolved drug molecules across the HPMC gel layer, while poorly soluble drugs are primarily released by erosion mechanism [25]. The formulations with lower level of polymers exhibited higher burst release which can be ascribed to dissolution of the drug present initially at the surface of the matrix tablets as the tablet imbibes water and starts swelling. As dissolution progresses, the gradual swelling of the outer layer creates proportionately new areas for drug diffusion. Since the matrix is hydrophilic, the permeation of dissolution medium takes place in the matrix and initiates dissolution of drug from the inner layers. The dissolution rate is counter-balanced by gel formation of the matrix, which takes place simultaneously. The balance between the swelling and gelling characteristics of the matrix system is critical in maintaining the desired drug release rate [11,24].

3.3. Fitting of data to the model

A three-factor, three-level Box-Behnken statistical experimental design as the RSM requires 15 experiments. The independent variables and the responses for all 15 experimental runs are given in Table 3. Eleven batches showed the burst release (Y_1) of less than 10% and the range of Y_1 for all batches was 6.69–12.41%. The ranges of other responses, Y_2 (% dissolution after 60 min) and Y_3 (hardness of the tablets, kg/cm^2), were 21.84–37.53%

Table 4
Summary of results of regression analysis for responses Y_1, Y_2 and Y_3

Models	R^2	Adjusted R^2	Predicted R^2	S.D.	% C.V.	Remarks
Response (Y_1)						
Linear model	0.9935	0.9894	0.9827	0.71	3.29	Suggested
Second order	0.9101	0.8427	0.7901	0.72	8.12	–
Quadratic model	0.9653	0.9028	0.7965	0.57	6.39	–
Response (Y_2)						
Linear model	0.9441	0.9288	0.9046	1.29	4.10	–
Second order	0.9467	0.9067	0.8189	1.48	4.70	–
Quadratic model	0.9944	0.9842	0.9893	0.61	1.93	Suggested
Response (Y_3)						
Linear model	0.7514	0.6835	0.6217	0.46	7.23	–
Second order	0.9976	0.9894	0.9827	0.30	4.70	Suggested
Quadratic model	0.9255	0.8915	0.8532	0.37	8.30	–

Regression equations of the fitted model[a]

$$Y_1 = 8.88 - 0.70X_1 - 2.09X_2 - 0.48X_3$$

$$Y_2 = 32.91 - 2.30X_1 - 5.69X_2 - 0.97X_3 - 0.41X_1X_3 + 0.21X_2X_3 - 0.92X_1^2 - 1.89X_2^2$$

$$Y_3 = 4.47 + 0.31X_1 + 0.87X_2 + 0.063X_3 + 0.63X_1X_3$$

[a] Only the terms with statistical significance are included.

and 3.5–5.5 kg/cm^2, respectively. All the responses observed for 15 formulations prepared were simultaneously fitted to first order-, second order- and quadratic models using Design Expert® and the comparative values of R^2, S.D. and % C.V. are given in Table 4 along with the regression equation generated for each response. Responses Y_1, Y_2 and Y_3 were found to follow linear, quadratic and second order model, respectively. Only statistically significant ($p < 0.05$) coefficients are included in the equations.

A positive value represents an effect that favors the optimization, while a negative value indicates an inverse relationship between the factor and the response. It is evident that the HPMC K15M (X_1), HPMC K100 (X_2) and Na-CMC (X_3) have negative effects on the responses Y_1 and Y_2 in the following order;

$$\text{HPMC K100M}(X_2) > \text{HPMC K15M}(X_1) > \text{Na-CMC}(X_3)$$

Coefficients with higher order terms or more than one factor term in the regression equation represent quadratic relationships or interaction terms, respectively. It also shows that the relationship between responses and factors is not always linear. Used at different levels in a formulation or when more than one factors are changed simultaneously, a factor can produce different degree of response. The interaction effect of X_1 was seen with X_2 and X_3 for response Y_2; and between X_1 and X_3 for response Y_3. X_2 also showed a higher quadratic effect as compared to X_1 on response Y_2.

Percentage burst release (Y_1) and hardness of the tablets (Y_3) were found to fit the linear and second order models, respectively. In absence of the quadratic effects, Y_1 was mainly dependent upon the amount of HPMC K100M. For Y3, the critical parameters were found to be the HPMC K15M and the HPMC K100M.

3.4. Standardized main effects and reliability of the models

Standardized Main Effects (SME), presented in Table 5, were calculated by dividing the main effects with the standard error of the main effects [26]. Only statistically significant ($p < 0.05$) values are given. The larger SME value of X_2 suggested the paramount importance of HPMC K100M on drug release. R^2-value signifies the percentage of variability in responses that are fitted to the models. In the present study, the high R^2-value of >99% represents the reliability of the design. Additionally, the p-values of lack of fit was greater than 0.05, which further strengthened the reliability of the models.

Table 5
Standardized main effects of the factors on the responses[a]

	Standardized main effects (SME)		
	Burst release (Y_1) linear model	Dissol. 60 min. (Y_2) quadratic model	Hardness (Y_3) second order model
X_1	2.80	10.95	2.82
X_2	8.36	27.10	7.91
X_3	1.92	4.62	0.42
$X_1 * X_2$	–	–	–
$X_1 * X_3$	–	1.37	4.20
$X_2 * X_3$	–	0.70	–
$X_1 * X_1$	–	2.88	–
$X_2 * X_2$	–	5.91	–
$X_3 * X_3$	–	–	–
R^2	99.35%	99.44%	99.76%
p-value of lack of fit	0.6624	0.7910	0.4678

[a] Only the terms with statistical significance are included.

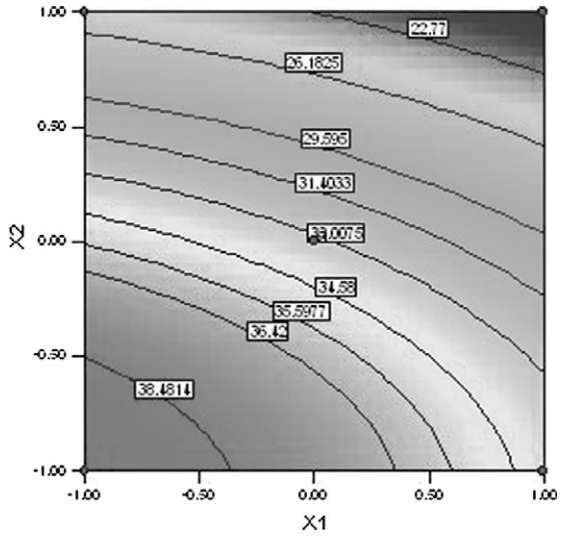

Fig. 1. Contour plot showing the effect of HPMC K15M (X_1) and HPMC K100M (X_2) on response Y_2.

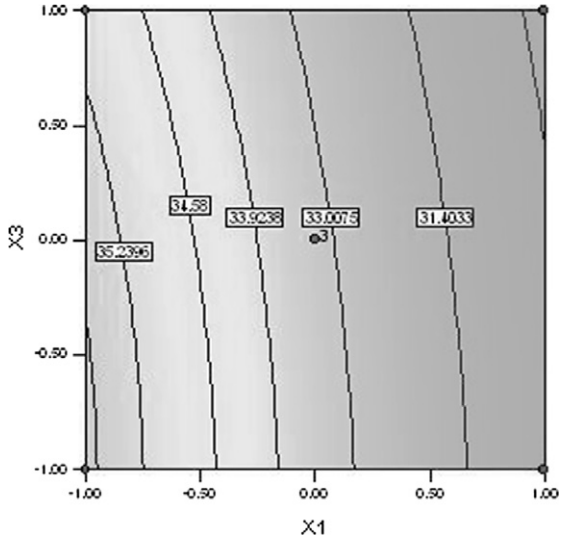

Fig. 2. Contour plot showing the effect of HPMC K15M (X_1) and Na-CMC (X_3) on response Y_2.

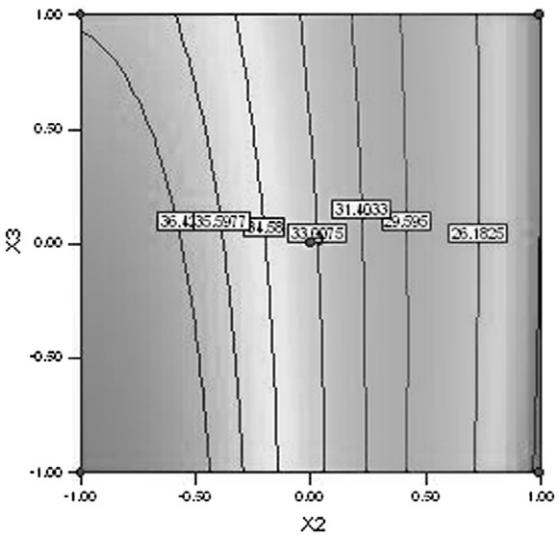

Fig. 3. Contour plot showing the effect of HPMC K100M (X_2) and Na-CMC (X_3) on response Y_2.

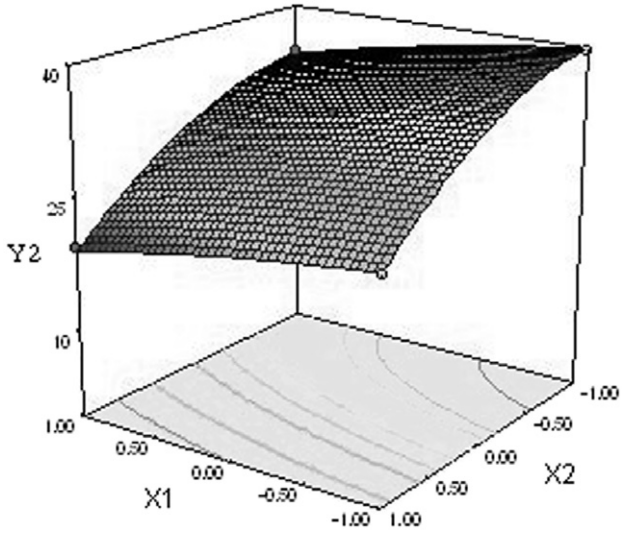

Fig. 4. Response surface plot showing the effect of HPMC K15M (X_1) and HPMC K100M (X_2) on response Y_2.

3.5. Contour plots and response surface analysis

Two-dimensional contour plots and three-dimensional response surface plots are presented in Figs. 1–6, which are very useful to study the interaction effects of the factors on the responses. These types of plots show the effects of two factors on the response at a time. In all the presented figures, the third factor was kept at a zero level. Figs. 2, 3 exhibit a nearly linear relationship of factor X_3 with factors X_1 and X_2, in the form of almost straight lines. However, factors X_1 and X_2 have non-linear relationship (Fig. 1). Response surface plots show the relationship between these factors even more clearly. Fig. 4 shows that about 39.5% drug is released after 60 min (Y_2) when both the HPMC K15M and HPMC K100M are at lowest level and the decrease in % drug release was polymer concentration dependent. Also the HPMC K100M resulted in greater reduction in % release at 30% level as compared to the HPMC K15M at 40% concentration. This indicates a slight non-linear trend between the factors X_1 and X_2. Figs. 5 and 6 show an increasing trend for Y_2 upon the replacement of either of HPMC K15M or K100M with Na-CMC.

3.6. Optimization

The optimum formulation was selected based on the criteria of attaining the maximum hardness for tablets and applying constraints on Y_1 ($10 \leqslant Y_1 \leqslant 15$) and

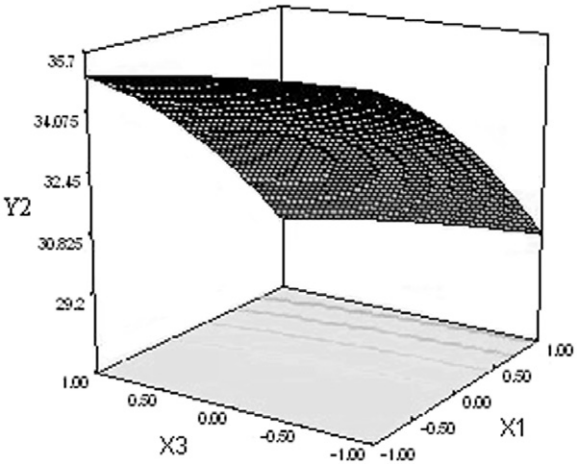

Fig. 5. Response surface plot showing the effect of HPMC K15M (X_1) and Na-CMC (X_3) on response Y_2.

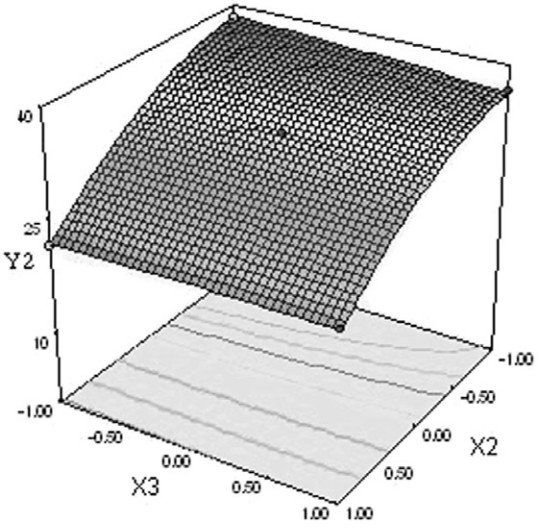

Fig. 6. Response surface plot showing the effect of HPMC K100M (X_2) and Na-CMC (X_3) on response Y_2.

$Y_2(31 \leqslant Y_2 \leqslant 35)$. Upon 'trading off' various response variables and comprehensive evaluation of feasibility search and exhaustive grid search, the formulation composition with polymer levels of HPMC-K15M, 37.40 mg, HPMC-K100 M, 10 mg and Na-CMC, 24.91 mg, was found to fulfill the maximum requisite of an optimum formulation because of better regulation of % burst release and % dissolution after 1 h time interval. The optimized formulation was found to release about 99.12% drug in sustained release manner for 12 h. Study of the in vitro release profiles in 0.1 N HCl (for 2 h) and in phosphate buffer, pH 6.8 (for 10 h), of the formulations showed a burst release of 33.76% during 1 h followed by a gradual release phase for about 10 h. Fig. 7 shows the complete dissolution profile of the optimized formulation. The release pattern of the optimized formulation was best fitted to both the zero-order (burst release) and Korsmeyer-Peppas kinetics

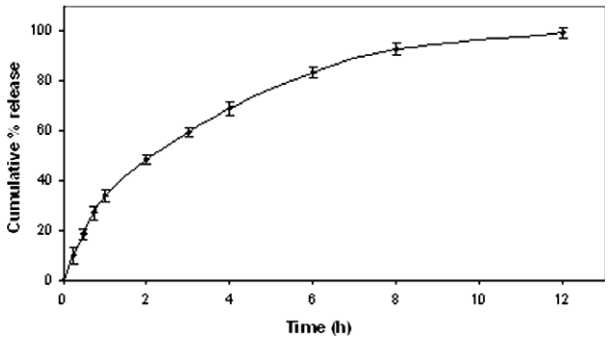

Fig. 7. Dissolution profile of the optimized formulation.

(sustained release phase) with R^2 values of 0.9948. The value of $n = 0.3387$ suggested the release to be primarily by non-Fickian diffusion.

3.7. Validation of RSM results

For all of the 9 checkpoint formulations, the results of the physical evaluation and tablet assay were found to be within limits. Table 6 shows the composition of optimum checkpoint formulations, their predicted and experimental values of all the response variables, and the percentage error in prognosis. Linear correlation plots between the actual and the predicted response variables were plotted and the residual plots, showing the scatter of the residuals versus actual values, are presented in Fig. 8.

For validation of RSM results, the experimental values of the responses were compared with that of the anticipated values and the prediction error was found to vary between –0.746% and 1.283%. The linear correlation plots drawn between the predicted and experimental values demonstrated high values of r^2 (ranging between 0.9712 to 0.9938) indicating excellent goodness of fit ($p < 0.001$). Thus the low magnitudes of error as well as the significant values of r^2 in the present investigation prove the high prognostic ability of the RSM.

3.8. Swelling studies

The swelling and erosion behavior of the optimized matrix tablet in 0.1N HCl and in PBS, pH 6.8, as a function of time, is shown in Fig. 9. It can be observed that the hydrophilic matrix tablets underwent both swelling and erosion at the same time. The tablets achieved maximum swelling after 1 h, which can be linked to the initial burst release of LP. Constant release can be obtained from such hydrophilic systems because of the simultaneous swelling and erosion of the matrix tablets. Constant release in such situations occurs because the increase in diffusional path length due to swelling is compensated by continuous erosion of the matrix [27,28]. The cross-sectional SEM images of matrix tablets after 2 h in acidic and 6 h in basic media are shown in Figs. 10(a) and (b). SEM study of the

Table 6
Composition of optimum checkpoint formulations, the predicted and experimental values of response variables and percentage prediction error

Optimized formulation composition (X_1:X_2:X_3)	Response variable	Experimental value	Predicted value	Percentage prediction error
20.00:21.71:15.00	Y_1 (%)	9.9865	10.0019	−0.154
	Y_2 (%)	34.3814	34.4938	−0.326
	Y_3 (kg/cm^2)	4.7842	4.7801	+0.087
21.11:21.13:15.00	Y_1 (%)	9.9365	10.0007	−0.642
	Y_2 (%)	34.8472	34.7371	+0.317
	Y_3 (kg/cm^2)	4.7108	4.7023	+0.229
37.40:10.00:24.91	Y_1 (%)	9.9863	10.0568	−0.701
	Y_2 (%)	33.7613	33.9955	−0.689
	Y_3 (kg/cm^2)	4.3360	4.3437	−0.093
36.47:10.00:24.50	Y_1 (%)	10.1007	10.0609	+0.396
	Y_2 (%)	34.0837	34.3399	−0.746
	Y_3 (kg/cm^2)	4.2093	4.2361	−0.449
35.12:10.00:23.46	Y_1 (%)	10.1715	10.1444	+0.267
	Y_2 (%)	35.0314	34.8974	+0.384
	Y_3 (kg/cm^2)	4.0867	4.0793	+0.411
34.95:10.00:23.19	Y_1 (%)	10.0456	10.0746	−0.288
	Y_2 (%)	34.8295	34.9933	−0.468
	Y_3 (kg/cm^2)	4.0918	4.0409	+1.283
33.22:15.97:15.00	Y_1 (%)	10.0175	10.0761	−0.582
	Y_2 (%)	35.3410	35.2146	+0.359
	Y_3 (kg/cm^2)	3.9522	3.9332	+0.566
34.77:14.54:15.64	Y_1 (%)	9.9654	10.0042	−0.388
	Y_2 (%)	35.2133	35.0029	+0.601
	Y_3 (kg/cm^2)	3.8075	3.8116	−0.065
37.24:10.00:19.14	Y_1 (%)	10.1115	10.0939	+0.174
	Y_2 (%)	34.9139	35.0267	−0.322
	Y_3 (kg/cm^2)	3.7706	3.7948	−0.513

dissolving matrix tablets showed a uniform swelling of the matrix and further supported the fact of drug release by a diffusion process from the highly porous and swollen matrix tablets.

3.9. Thermal properties

DSC thermograms of the drug, excipients and the optimized formulation were recorded, in order to determine the thermal changes of polymers and drug before and after preparation. The characteristic endothermic peak of the drug at 274 °C was observed in formulation also. However, the broadening of the drug peak in optimized formulation was related more to the impurities from excipients than physical interaction of the drug with the components.

3.10. Fourier transform infrared spectroscopy (FTIR)

FTIR spectra of the drug, excipients and the optimized formulation were recorded in range of 4000 - 400 cm^{-1}. LP showed some prominent and characteristic peaks at 3394, 1026, 1643, and 764 cm^{-1}, which could be assigned to stretching vibrations of O—H and C—O bond of primary alcohols, N=N stretching and C—Cl bond, respectively. In the optimized formulation, the presence of all the characteristic peaks of the LP indicates lack of any strong interaction between the drug and the excipients.

3.11. Stability studies

Stability studies of the optimized formulation under accelerated storage conditions as per ICH guidelines did not reveal any degradation of the drug and changes in the *in vitro* release profiles of the optimized formulation after storage for 6 months were statistically insignificant as compared to the refrigeration control sample (ANOVA, $p > 0.05$).

4. Conclusion

Hydrophilic matrix tablets of LP with HPMC K15M, HPMC K100M and Na-CMC were prepared and optimized using a three-factor, three-level Box Behnken design. The quantitative effect of these factors at different levels on the release rate could be predicted by using polynomial equations. Linearity observed between the actual and predicted values of the response variables suggested the prognostic ability of the RSM design. The quadratic response surface methodology studied for the release rate helped in understanding the interaction effects between the combination and ratio of the three polymers. DSC and FTIR studies combined with the stability study of the optimized formulation proved the integrity of the developed hydrophilic matrix tablets. Thus, high degree of prediction obtained using RSM is quite efficient in optimizing drug delivery systems that exhibit non-linearity in responses.

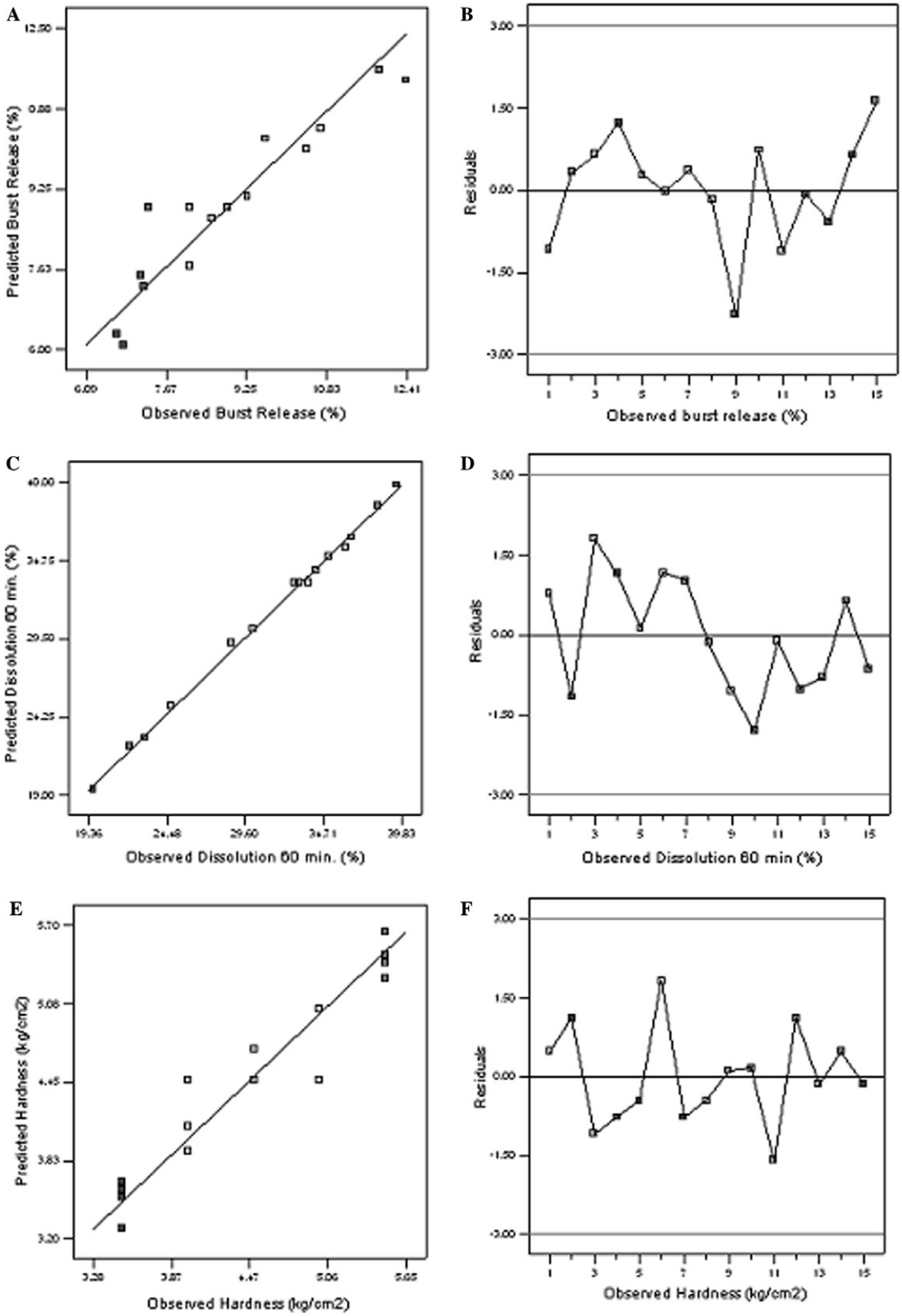

Fig. 8. Linear correlation plots (A, C, E) between actual and predicted values and the corresponding residual plots (B, D, F) for various responses.

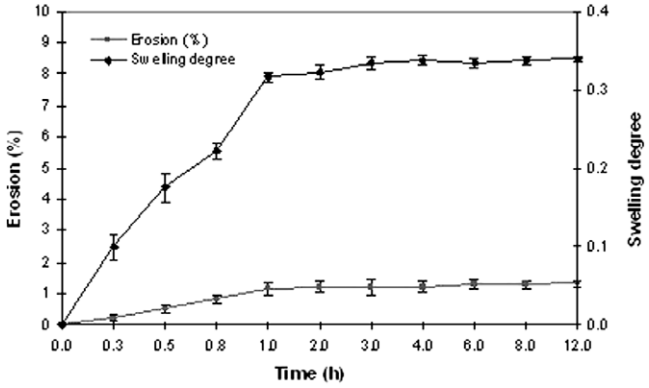

Fig. 9. Erosion and swelling behavior of optimized formulation.

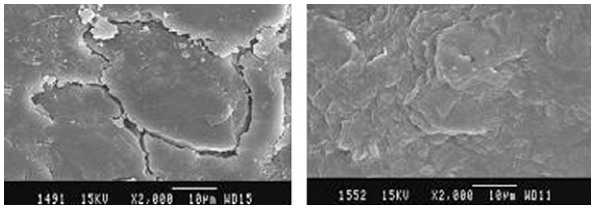

Fig. 10. SEM photomicrographs showing surface topography of hydrated matrices in (A) acidic media, 2 h and (B) basic media, 6 h.

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