ORIGINAL ARTICLE

Response Surface Optimization of Diltiazem HCl Gastric Floating Matrix Tablets

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Abstract

Objective: The objective of the present research work was to formulate and optimize the hydroxyethyl cellulose (HEC) based gastric floating matrix tablets (GFMT) of diltiazem HCl by employing a three factor, three levels statistical design, namely, Box-Behnken design. **Materials and Methods:** Optimization studies were carried out using Box-Behnken statistical design with three factors, three levels, and 15 runs. Selected independent variables include HEC quantity (X1), %w/w of sodium bicarbonate (X2), and %w/w of Pharmatose (lactose monohydrate) (X3). Cumulative percent drug released at 12 h was selected as dependent variable (Y). Tablets were evaluated for *in vitro* buoyancy characteristics, *in vitro* drug release and other tablet characteristics. **Results and Discussion:** The GFMT's of diltiazem HCl prepared with HEC fulfilled all the requirements of tablets. Floating lag times for all the prepared formulations were found to be in the range of 156–2040 s. The obtained optimum values of the independent test variables are; 93.50 mg quantity of HEC (X1), 11.47% w/w of sodium bicarbonate (X2), and 10.40% w/w of Pharmatose (lactose monohydrate) (X3). The model predicts that the formulation with 100% drug release in 12±1 h can be obtained using the above optimum concentrations. Optimized formulation DNAso showed a floating lag time of 405 s. Drug release from DNAs (optimized formulation) and Dilzem SR (commercial sustained release formulation) followed zero-order release kinetics with diffusion mechanism. **Conclusion:** Results demonstrated that significance of Box-Behnken statistical design in the optimization of critical variables of gastric floating matrix tablets of diltiazem HCl for achieving desired *in vitro* buoyancy characteristics and *in vitro* drug release characteristics.

Key words: Box-Behnken design, diltiazem HCl, gastric floating matrix tablets, hydroxyethyl cellulose

INTRODUCTION

Optimization process involving one-variable-at-a-time method is an expensive method and it requires much time. In conventional optimization method, only one factor is varied and all other factors are kept fixed at a specific set of conditions. This method of optimization requires the higher number of experiments and also may lead to unreliable results. In addition, it is inferior to the statistical methods of optimization since it neglects the interaction between the variables and it does not guarantee attaining the optimal point. Statistical experimental designs are useful in minimizing the error in determining the effect of parameters and allow simultaneous, systematic, and efficient variation of all the selected critical variables. These statistical experimental designs can be adopted at various stages such as for the

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selection of critical variables by screening experiments, or for the optimization of selected variables, i.e., finding their optimal conditions.[1-8] Response surface methodology (RSM) is one of the most commonly used method to find the optimal conditions, which is an efficient statistical technique for optimization of the selected multiple critical variables with minimum number of experiments and for prediction of the interactions between different components of a formulation.

The following problems are associated in the design of sustained/controlled release products for the drug substances having a narrow absorption window with site specific absorption and other characteristics such as low solubility in alkaline pH, local action required at stomach, or upper parts of small intestine, since there is a possibility for wide variations in the desired plasma drug concentration when administered orally in the form of conventional/sustained and controlled release dosage forms. Hence, to avoid the above indicated problems, design of drug delivery systems with retention characteristic in the stomach is required, which are called as gastric retentive drug delivery systems (GRDDS).[9-27]

Diltiazem HCl is a calcium ion influx inhibitor and used in the treatment of cardiovascular disorders such as angina, arrhythmias, and hypertension. The maximum dosage is listed as up to 540 mg/day when given orally. Its mean elimination half-life is 3–4.5 h. It is available as immediate release tablet which shall be administered from 3 to 4 times daily and also as sustained release tablet which is suitable for twice daily dosage regimens. Diltiazem HCl is absorbed more predominantly in the upper parts of the gastro intestinal tract.[28,29] Hence, design of GRDDS is a suitable option for improving its oral bioavailability.

The GRDDS of the present investigation are designed to make it retained in the stomach for longer periods of time and deliver the diltiazem HCl effectively. The system provides increased absorption of the diltiazem HCl at a rate such that effective plasma drug levels can be achieved and maintained for a prolonged duration. Based on the results achieved in the preliminary experiments during the development of prototype formulation, HEC polymer quantity, concentrations of sodium bicarbonate and Pharmatose (lactose monohydrate) were identified as critical variables. Selected variables were studied to find the optimized conditions for achieving a formulation which can release the total drug content in 12±1 h with good floating properties using Box-Behnken design, a RSM approach.

MATERIALS AND METHODS

Materials

Diltiazem HCl was gift sample from Sun Pharma Ltd., Baroda, India. Hydroxyethyl cellulose (HEC) was gift sample from Wockhardt Ltd., Aurangabad, India. All other remaining chemicals used in the experiment were of analytical grade.

Box-Behnken experimental design

Box-Behnken statistical design[30] with three factors, three levels, and 15 runs was selected for the optimization of selected variables in the present research study. The experimental design consists of a set of points lying at the midpoint of each edge and the replicated center point of the multidimensional cube which defines the region of interest. The higher order terms show the quadratic nature of the relationships.

The independent and dependent variables of the present research study are listed in Table 1. The polynomial equation generated using Statistica Release 6, Statsoft Inc. is as follows:

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

Where, Y_i is dependent variable; b_0 is intercept; b_1 to b_{33} are the regression coefficients; and X_1, X_2, and X_3 are independent variables that were selected from the initial experiments. Redundancy of the model can be known from the ratio of number of experimental runs to the maximum number of experimental runs. Box-Behnken design requires less number of runs than the full factorial design along with less redundancy. These runs along with the response variable are mentioned in Table 2. Selection of levels of the independent variables was done based on the observations made in the preliminary experimental trials.

Preparation of tablets

All the ingredients were passed through the sieve No. 40 (Diltiazem HCl, HEC, Pharmatose and sodium bicarbonate) and sieve No. 60 (Talc and magnesium stearate). Drug was geometrically mixed with polymer. Polyvinylpyrrolidone (PVP K30) in 70% v/v isopropyl alcohol was used as binder solution for preparing the granules. Prepared wet granulate

Table 1: Variables and their levels in Box-Behnken design

Experimental range and levels of the independent variables	Range and levels		
	–1	0	+1
Quantity of polymer (in mg); X_1	70	90	110
% w/w sodium bicarbonate; X_2 (% w/w to drug and polymer weight)	10	15	20
% w/w lactose monohydrate; X_3 (% w/w to drug and polymer weight)	5	10	15

Dependent variable: Cumulative % drug released at 12 h; Y

was passed through sieve No. 10 and dried at 50±5°C. The dried granules were passed through sieve No. 24 and mixed with the sodium bicarbonate (effervescent agent), Pharmatose (channeling agent) wherever necessary, talc, and magnesium stearate. The granules and the extra-granular excipients were mixed thoroughly using low-density polyethylene bag. Final blend was then compressed into tablets containing diltiazem HCl equivalent to a dose of 90 mg using rotary tablet-punching machine (M/s. Cadmach Machinery Co. Pvt. Ltd., India) fitted with 9 mm round plain punches at a hardness range of about 4–6 kg/cm².

Table 2: Box-Behnken experimental design with measured responses

Formulae	X1	X2	X3	Y
DNAB1	70	10	10	100.00
DNAB2	110	10	10	99.99
DNAB3	70	20	10	100.00
DNAB4	110	20	10	94.99
DNAB5	70	15	5	100.00
DNAB6	110	15	5	97.88
DNAB7	70	15	15	100.00
DNAB8	110	15	15	99.99
DNAB9	90	10	5	100.00
DNAB10	90	20	5	94.05
DNAB11	90	10	15	100.00
DNAB12	90	20	15	100.00
DNAB13	90	15	10	99.99
DNAB14	90	15	10	99.62
DNAB15	90	15	10	100.00

Evaluation of tablets

The floating properties of the prepared gastric floating matrix tablets (GFMT) were assessed by *in vitro* buoyancy test. The prepared GFMT were also evaluated for their physical properties such as hardness (Monsanto Hardness Tester), friability (Labindia Analytical Instruments Private Limited), uniformity of weight and chemical properties such as drug content uniformity and *in vitro* drug release. The results of the physical and chemical evaluation of prepared GFMT formulations are mentioned in Table 3.

Estimation of drug content

Ten tablets from each batch were weighed and transferred to mortar. Tablets were crushed and powder equivalent to 50 mg of diltiazem HCl was transferred to 50 ml volumetric flask. Diltiazem HCl was extracted with 25 ml of 0.1 N hydrochloric acid (HCl) with vigorous shaking using a mechanical shaker for 1 h. The samples were filtered into a 50 ml volumetric flask through nylon filter disk (0.45 µm, Millipore) and volume made up to 50 ml with 0.1 N HCl. Absorbance's were measured at 237 nm with appropriate dilutions against blank (0.1N HCl) using Systronics-117 UV visible spectrophotometer.

In vitro buoyancy determination

Floating characteristics are essential for the gastric floating drug delivery systems, since they influence the *in vivo* behavior of the drug delivery system. All the prepared GFMT formulations of diltiazem HCl were evaluated by the *in vitro* buoyancy test. 900 mL of 0.1 N HCl in 1 L glass beaker was

Table 3: Physical and chemical characteristics of hydroxyethyl cellulose based gastric floating matrix tablets of diltiazem HCl prepared by using Box-Behnken design

Formulation	Weight (mg)	Drug content (%)	Hardness (kg/cm²)	Friability (%)	Floating lag time (sec)
DNAB1	200.13±0.21	100.11±0.79	4–6	0.55	1659
DNAB2	248.10±0.30	100.33±0.70	4–6	0.36	256
DNAB3	216.13±0.25	99.89±0.56	4–6	0.35	1003
DNAB4	268.07±0.15	100.00±0.17	4–6	0.58	156
DNAB5	200.20±0.17	99.67±0.17	4–6	0.61	2040
DNAB6	248.07±0.15	100.33±0.20	4–6	0.23	315
DNAB7	216.03±0.21	100.00±0.26	4–6	0.81	1532
DNAB8	268.07±0.15	100.00±0.36	4–6	0.26	215
DNAB9	214.93±0.15	99.89±0.17	4–6	0.38	1359
DNAB10	232.90±0.26	99.78±0.87	4–6	0.71	303
DNAB11	233.20±0.17	100.11±1.01	4–6	0.11	820
DNAB12	250.80±0.87	100.00±0.70	4–6	0.25	494
DNAB13	232.87±0.21	100.00±0.26	4–6	0.32	451
DNAB14	233.27±0.15	100.22±0.80	4–6	0.27	431
DNAB15	232.93±0.15	100.11±1.11	4–6	0.31	481

used to determine the buoyancy lag time. The time interval between the introduction of the tablet into the medium and its buoyancy to the top of medium was taken as buoyancy lag time. Floating characteristics are shown in Figure 1.

Drug-polymer interaction studies

Fourier transform infrared spectrophotometry (FTIR) using Perkin Elmer (Model Spectrum One), differential scanning calorimetry (DSC) using Mettler Toledo Star^e SW 8.10 (Model no: DSC 822^e) and X-ray diffractometry (XRD) studies was carried out using RIGAKU Diffractometer (D/MAX-B) and CU - Kα radiation, for checking the interactions if any between drug and polymer, as shown in Figures 2-4.

In vitro drug release studies

In vitro dissolution of diltiazem HCl from the prepared GFMT formulations was studied using USP XXIV dissolution rate test Apparatus II (Model: DISSO 2000, M/s. Lab India). 900 ml of 0.1N hydrochloric acid maintained at a temperature of 37±0.5°C was used as dissolution medium and the paddle speed was set at 100 rpm. At each and every time interval, 5 ml of samples were withdrawn by means of a syringe fitted with a pre-filter and immediately replaced with 5 ml of fresh dissolution medium maintained at 37±0.5°C. After suitable dilution with the medium, the samples absorbance was measured at 237 nm using Systronics-117 UV-Visible Spectrophotometer. For comparison, commercially available diltiazem HCl sustained release formulation (Dilzem SR) was also subjected to dissolution studies and the results are shown in Figures 5-8. Dissolution data were fitted to zero-order, first-order, Higuchi, and erosion equations to establish the release kinetics of the drug and its mechanism.

RESULTS AND DISCUSSION

Evaluation of tablets

All the formulations complied with compendia standard for uniformity of weight. A hardness range of 4–6 kg/cm^2 was found for the all the tablet formulations. The percentage weight loss in the friability test was found to be <1% for all the batches. Thus, the GFMT's of diltiazem prepared with HEC fulfilled all the requirements of tablets. These results clearly indicate that the HEC can be used in the design of GFMTs.

Estimation of drug content

The estimated drug content was found to be within the specified limits, i.e., <±10% variation of the stated quantity of diltiazem HCl.

In vitro buoyancy determination

GFMT each comprising 90 mg of diltiazem HCl were prepared using the HEC. $NaHCO_3$ was used as effervescent agent. Carbon dioxide which was liberated on contact with gastric fluid got entrapped in the jellified hydrocolloid. This resulted in an upward motion of the dosage form and maintained its buoyancy to float on the gastric fluids. Floating lag times for the all the prepared formulations were found to be in the range of 156–2040 s.

Drug – polymer interaction studies

FTIR spectrophotometry

The FTIR spectrum of diltiazem HCl exhibited characteristic stretches as followed. Characteristic stretches of Enolic-OH group at 3440 cm^{-1}, tertiary amine –N-CH_3group at 2390 cm^{-1}, -C=O group at 1742 cm^{-1}, -C=CH_2 at 1679 cm^{-1}, asymmetric stretch of-C-O-C at 1247 cm^{-1}, and symmetric stretch of-C-O-C at 1054 cm^{-1}. The FTIR spectrum of HEC exhibited the characteristic stretches of alcoholic -OH group at 3438 cm^{-1}, symmetric stretch of-C-O-C at 1024 cm^{-1}, and -C=CH_2 at 1646 cm^{-1}. Optimized formulation DNAso exhibited all the characteristic peaks of diltiazem HCl with negligible shifts. This spectrum showed stretches related to tertiary amine -N-CH_3 group at 2379 cm^{-1}, -C=O group at 1743 cm^{-1}, enolic-OH group at 3388 cm^{-1}, -C=CH_2 stretch at 1679 cm^{-1}, asymmetric stretch of -C-O-C at 1249 cm^{-1}, and

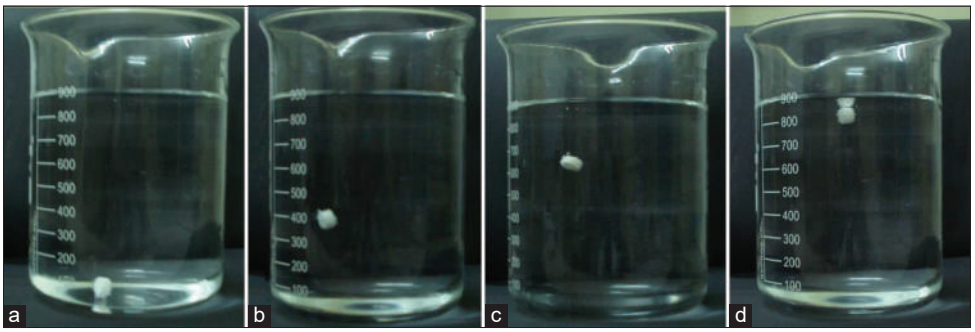

Figure 1: Photographs showing the *in vitro* floating characteristics of gastric floating matrix tablets of the diltiazem HCl (DNAso). (a) Photograph taken immediately after placing the tablet in to beaker; (b) and (c) are the photographs taken during the intermediate stages of tablet floating; (d) Photograph taken immediately after the tablet floated onto the surface

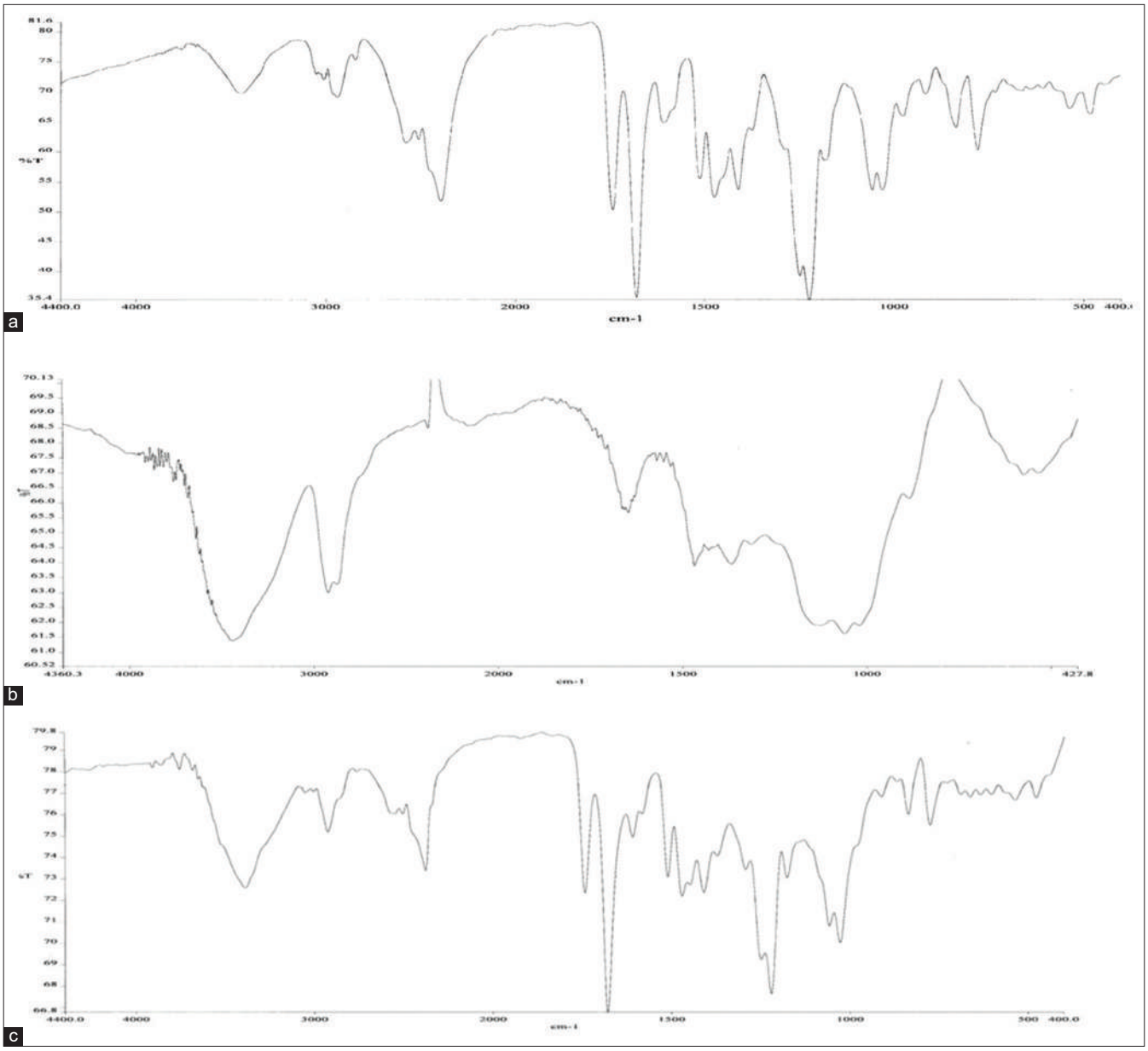

Figure 2: Fourier-transform infrared spectra of (a) diltiazem HCl, (b) hydroxyethyl cellulose (HEC) and (c) formulation DNAso

symmetric stretch of-C-O-C at 1058 cm^{-1}. FTIR spectrum of optimized formulation showed characteristic peaks of pure drug, diltiazem HCl, and HEC indicating compatibility between the drug and polymer, as shown in Figure 2.

DSC

DSC thermogram of diltiazem HCl pure drug substance showed sharp melting peak at 212.94°C, similarly pure polymer HEC at 137.36°C. There is a minor shift in the melting peak of diltiazem HCl in the optimized formulation, i.e., 185.73°C, as shown in Figure 3. This observed minor shift in the melting peak of diltiazem HCl in the test formulation may be due to physical interaction between the drug and polymer leading to partial conversion of its crystalline form to amorphous form during the manufacturing of tablets, which is indicated by the conversion of sharp melting peak of pure drug diltiazem HCl to broadened peak in the formulation. In addition, HEC is hydrophilic in nature with melting point less than that of pure drug diltiazem HCl. The pure polymer which melts before the drug may influence in the shift of melting point of diltiazem HCl in the test formulation. Further, it can be confirmed that the observed minor shift in melting peak of the diltiazem HCl in the test formulation can be only due to partial conversion of its crystalline form to amorphous form and not due to chemical interaction or complexation between the drug and the polymer, by the unaltered characteristic peaks of diltiazem HCl in FTIR spectra of test formulation.

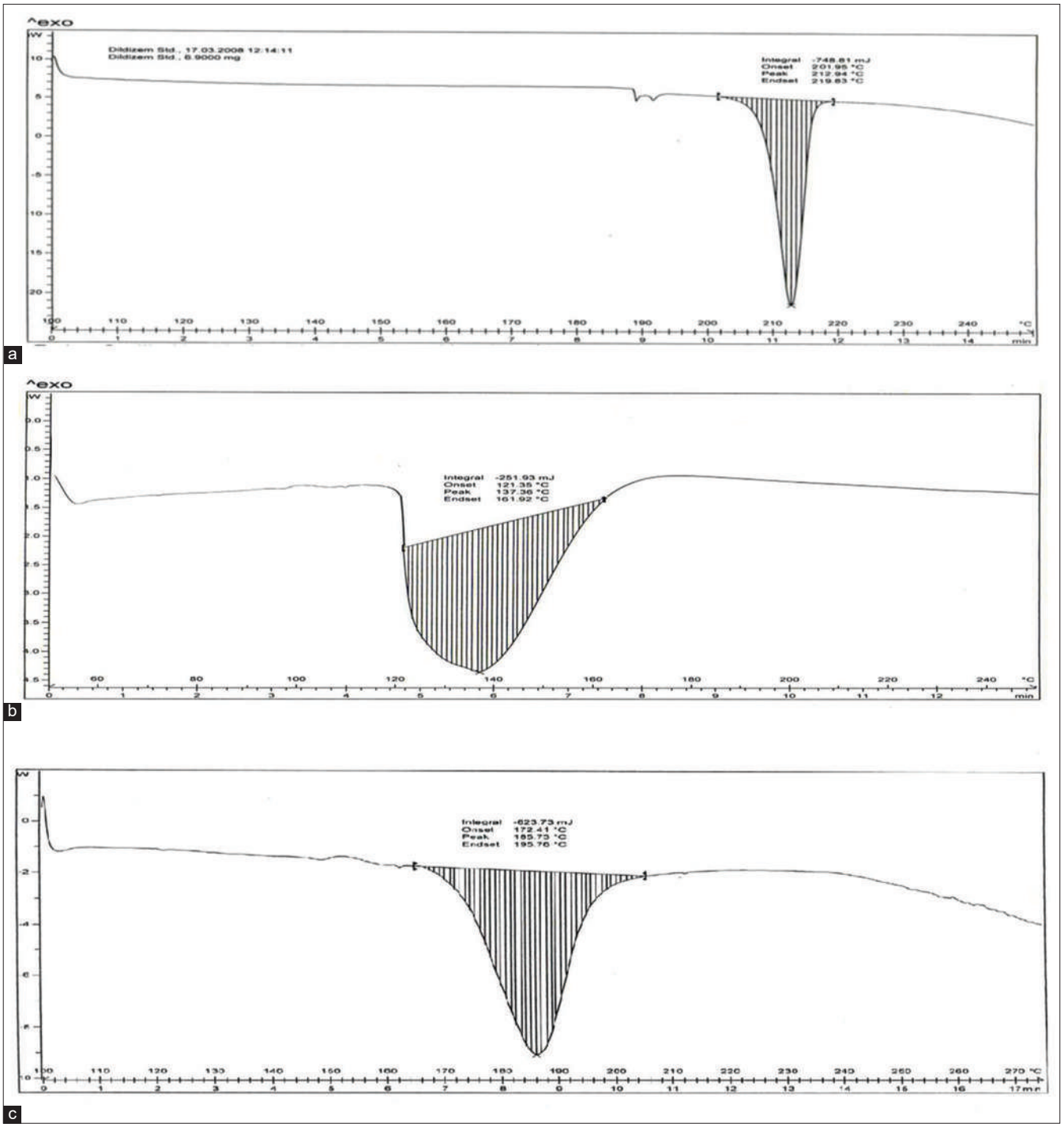

Figure 3: Differential scanning calorimetry thermo grams of (a) Diltiazem HCl (b) hydroxyethyl cellulose and (c) formulation DNAso

XRD

The *XRD* of diltiazem HCl showed sharp peaks due to crystalline nature of the drug substance. However, pure polymer HEC did not show any peaks indicating its amorphous nature. Formulation DNAso showed characteristic peaks of pure drug substance with less intensity, minor shifts in the peaks, disappearance of some peaks, and appearance of new peaks, as shown in Figure 4. The reason for these changes in the XRD pattern, i.e., reduced crystallinity of drug substance in the prepared GFMT's might be due to the fine dispersion of the drug in the polymer during mixing and due to the compression force applied during the preparation of the tablets. Reduce crystallinity of the drug substance in the formulation can also be confirmed by the broadened melting peak observed in the DSC thermogram of formulation to that of sharp melting peak observed in the DSC thermogram of pure drug substance diltiazem HCl.

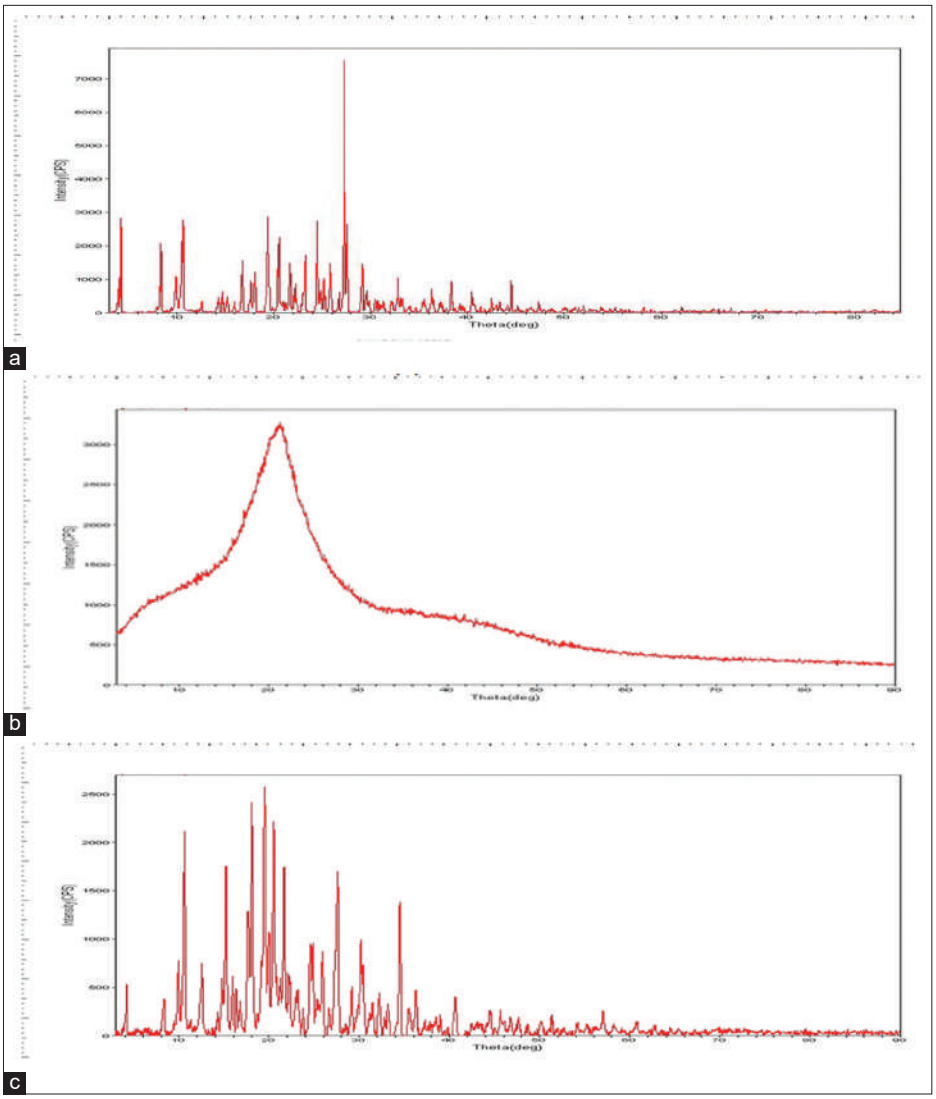

Figure 4: X-ray diffract to grams of (a) diltiazem HCl, (b) hydroxyethyl cellulose and (c) formulation DNAso

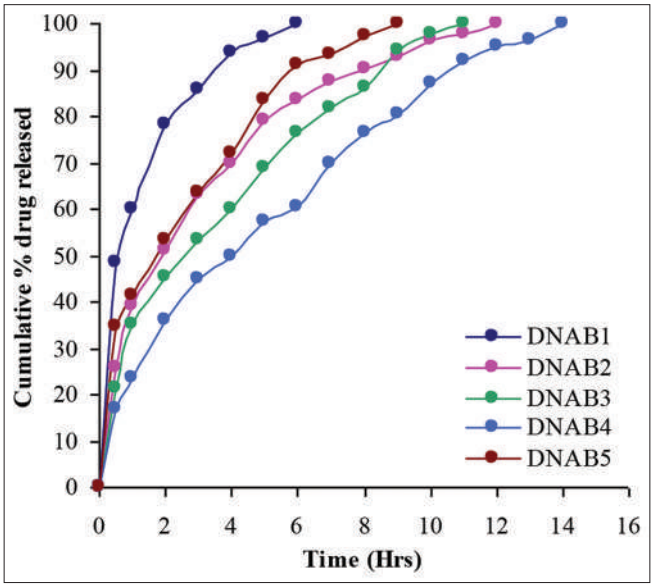

Figure 5: Dissolution profiles of hydroxyethyl cellulose based gastric floating matrix tablet formulations DNAB1 to DNAB5

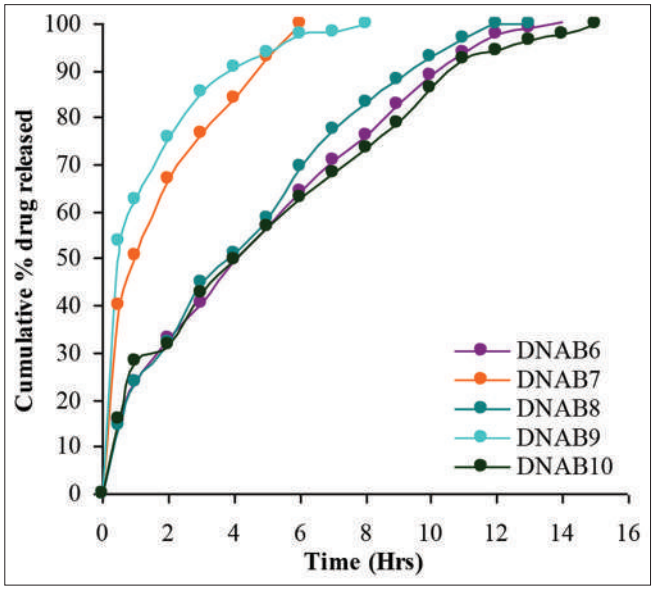

Figure 6: Dissolution profiles of hydroxyethyl cellulose based gastric floating matrix tablet formulations DNAB6 to DNAB10

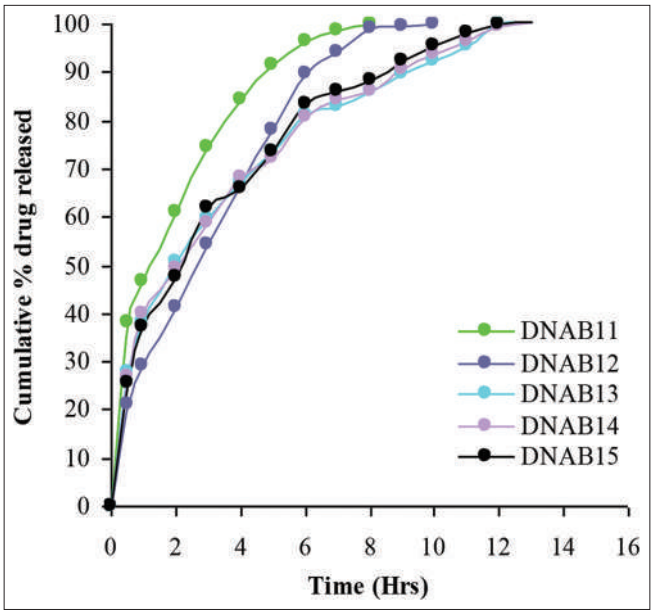

Figure 7: Dissolution profiles of hydroxyethyl cellulose based gastric floating matrix tablet formulations DNAB11 to DNAB15

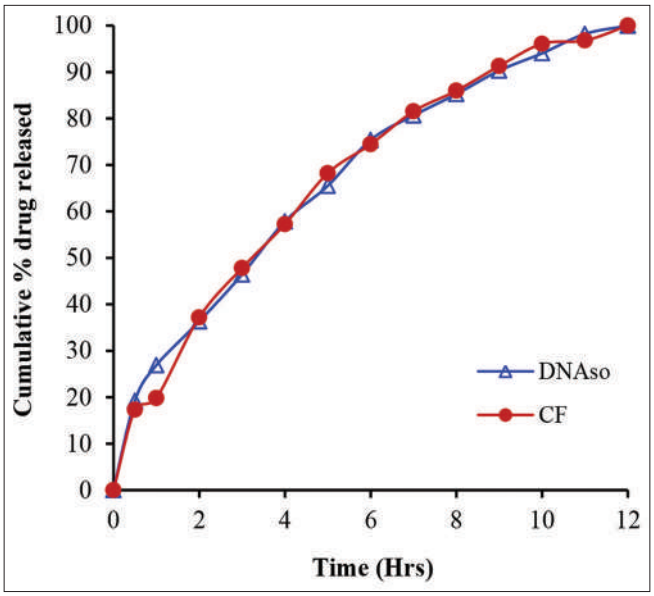

Figure 8: Comparative dissolution profiles of optimized gastric floating matrix tablets formulation (DNAso) with commercial sustained release formulation (Dilzem SR)

In vitro drug release studies

The results of *in vitro* drug release studies of all the prepared diltiazem HCl GFMT formulations indicated slow and extended release of diltiazem HCl for a prolonged period of time, i.e., up to 14 h Release kinetics of the drug from HEC based formulations resulted from Box-Behnken design such as DNAB2, DNAB3, DNAB4, DNAB6, DNAB8, DNAB10, DNAB12, DNAB13, and DNAB14 followed zero-order release kinetics whereas DNAB1, DNAB5, DNAB7, DNAB9, DNAB11, and DNAB15 followed first-order release kinetics. Mechanism of the drug release from formulations, DNAB2, DNAB3, DNAB4, DNAB5, DNAB6, DNAB7, DNAB8, DNAB10, DNAB12, DNAB13, DNAB14, and DNAB15 followed diffusion mechanism while from formulations DNAB1, DNAB9, and DNAB11 followed erosion mechanism.

Statistical application

By subjecting the cumulative percent drug released at 12 h of the formulations generated by Box-Behnken design for the analysis using STASTSTICA®6.0 software gave the optimal values of selected independent variables for obtaining a formulation which can release the total drug content at 12 h. It provides the information about optimal values for attaining the anticipated response and also the potential interaction effects of selected independent variables on the response, i.e., dependent variable.

Analysis of variance (ANOVA) results for second-order response surface model fitting are given in Table 4 with very low probability values (P = 0.01) demonstrate a very high significance for the regression model.[31-35]

The goodness of fit of the model was evaluated by the determination coefficient (R^2). The values of the determination coefficient were found to be (R^2 = 0.9414) indicating only 5.86% of the total variations were not explained by the studied statistical design. The values of the adjusted determination coefficient (Adj. R^2: 0.8359) are also very high and support the high significance of the selected statistical design.[32-35] An excellent correlation between the independent variables[36] was confirmed by higher correlation coefficient (R 0.9703) values.

The application of RSM[36,37] yielded the following regression equation which is an empirical relationship between the logarithmic values of cumulative % drug released at 12 h and test variables in coded unit:

$$Y_{DNAB}=98.9-0.8933*X_1-1.3684*X_2+1.0071*X_3-1.2494*X_1*X_2+1.4875*X_2*X_3$$

Where Y is the response, that is, the cumulative % drug released at 12 h in logarithmic and X_1, X_2, and X_3 are the coded values of the test variables polymer quantity, %w/w of sodium bicarbonate and %w/w of Pharmatose (lactose monohydrate) to the weight of drug and polymer, respectively.

Student's *t*-test and "*P*" values were used to determine the significance of each coefficient and are listed in Table 5. The larger the magnitude of the "*t*" value and smaller the "*P*" value, the more significant is the corresponding coefficient.[34,35]

The first-order main effects of all the selected independent variables such as polymer quantity, %w/w of sodium bicarbonate, and %w/w of Pharmatose (lactose monohydrate)

Table 4: Analysis of variance (ANOVA) for the quadratic model

Source of variations	Sum of squares	Degrees of freedom	Mean square	F-value	Prob. (P)
Regression	49.900	9	5.544	8.928	0.013
Residual	3.105	5	0.621		
Total	53.005				
Regression summary for dependent variable: Y					

R=0.9703; R^2=0.9414; Adjusted R^2=0.83597

Table 5: Model coefficients estimated by multiples linear regression (significance of regression coefficients)

Factor	Coefficient	Computed *t*-value	*P*-value
Intercept	98.9086	434.7803	0.0000
Hydroxyethyl cellulose	−0.8934	−3.2064	0.0238*
Sodium bicarbonate	−1.3685	−4.9117	0.0044*
Pharmatose	1.0071	3.6147	0.0153*
Hydroxyethyl cellulose × Hydroxyethyl cellulose	0.0424	0.2068	0.8444
Sodium bicarbonate × Sodium bicarbonate	0.5207	2.5395	0.0519
Pharmatose × Pharmatose	0.1582	0.7714	0.4753
Hydroxyethyl cellulose × Sodium bicarbonate	−1.2495	−3.1711	0.0248*
Hydroxyethyl cellulose × Pharmatose	0.5268	1.3369	0.2389
Sodium bicarbonate × Pharmatose	1.4875	3.7751	0.0130*

are highly significant which is evident from their respective *P*-values, i.e., 0.0238 (for HEC); 0.0044 (for % w/w of sodium bicarbonate); and 0.0153 (for % w/w of Pharmatose).

The combinatorial effect of polymer concentration and sodium bicarbonate as well as sodium bicarbonate and Pharmatose (lactose monohydrate) was also found to be significant based on their "*P*" values, i.e., 0.0248 (for HEC and %w/w of sodium bicarbonate); and 0.0130 (for %w/w of sodium bicarbonate and %w/w of Pharmatose (lactose monohydrate). However, combined effect of polymer concentration and Pharmatose (lactose monohydrate) is less significant indicated by its "*P*" = 0.2389.

The first-order main effects of all the selected independent variables such as polymer quantity, %w/w of sodium bicarbonate, and %w/w of Pharmatose (lactose monohydrate) are highly significant which is evident from their respective "*P*" values. The combinatorial effect of polymer concentration and sodium bicarbonate as well as sodium bicarbonate and Pharmatose (lactose monohydrate) was also significant based on their "*P*" values. These suggest that the amount of the polymer and concentrations of sodium bicarbonate, Pharmatose (lactose monohydrate), combined effect of polymer concentration and sodium bicarbonate and also sodium bicarbonate and Pharmatose (lactose monohydrate) have got a direct relationship for achieving a formulation which releases the total drug content in 12±1 h. However, combined effect of polymer concentration and Pharmatose (lactose monohydrate) is less significant indicated by its "*P*" values.

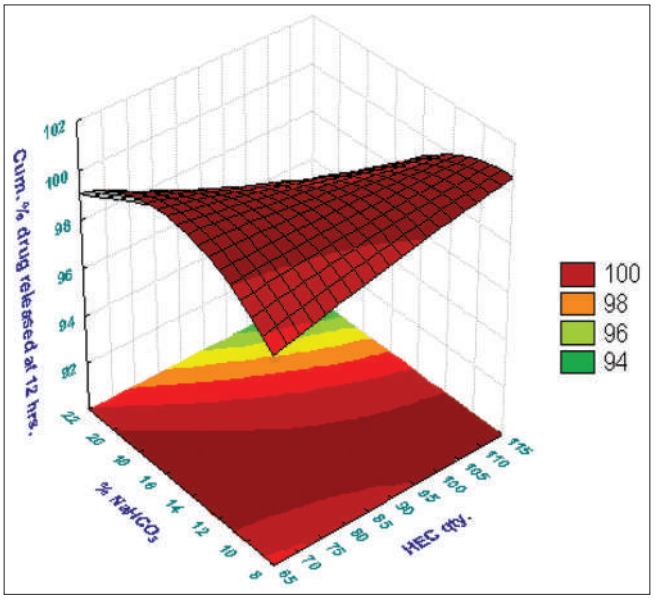

Figure 9: Response surface plot showing the effect of polymer (hydroxyethyl cellulose) and sodium bicarbonate on cumulative % drug released at 12 h

Response surface plots are more useful for understanding both the main and the interaction effects of any two selected factors and keeping all other factors at fixed levels (zero, for instance). These plots can be easily obtained by calculating from the model, the values taken by one factor where the second varies (from −1 to +1, step 5 for instance in case of sodium bicarbonate and Pharmatose [lactose monohydrate] concentrations and 20 in case of polymer quantity). Response

plots drawn in between polymer quantity and %w/w of sodium bicarbonate, polymer quantity, and %w/w of Pharmatose (lactose monohydrate) and %w/w of Pharmatose (lactose monohydrate) and %w/w of sodium bicarbonate are shown in Figures 9-11.

Figure 9 shows that the release of the drug was prolonged with increase in concentration of polymer along with concentration of sodium bicarbonate which may be due to increased intensity of carbon dioxide gas pockets surrounding the sticky surface of the tablet. Increase in the concentration of sodium bicarbonate at a low polymer concentration initially enhanced the release of the drug due to initial channeling effect associated with low intensity of carbon dioxide gas pockets, followed by retardation in release of the drug by the controlling effect associated with increased intensity of carbon dioxide gas pockets.

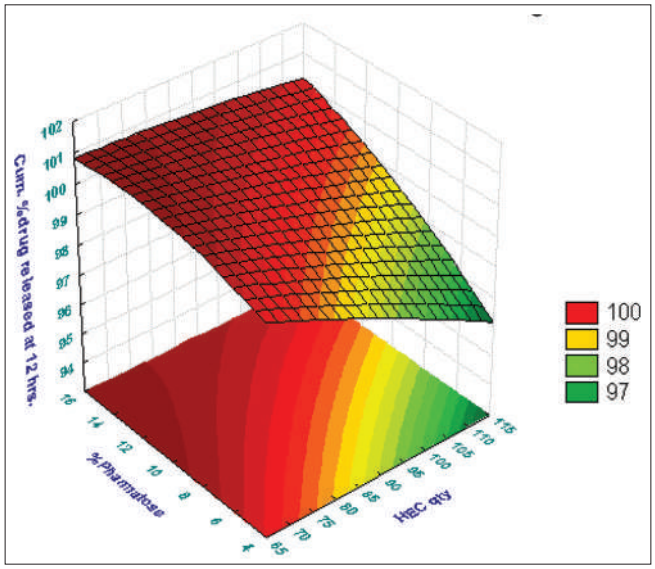

Figure 10: Response surface plot showing the effect of polymer (hydroxyethyl cellulose) and Pharmatose (lactose monohydrate) on cumulative % drug released at 12 h

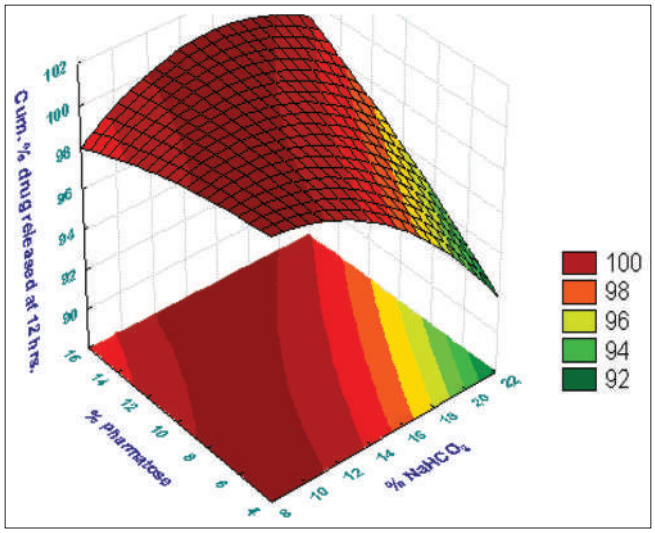

Figure 11: Response surface plot showing the effect of sodium bicarbonate and Pharmatose (lactose monohydrate) on cumulative % drug released at 12 h

The response surface plot [Figure 10] shows that increase in the concentration of Pharmatose greatly enhanced the release of the drug due to its channeling effect despite increased the concentration of the polymer. Similarly, the response surface plot [Figure 11] shows that increase in the concentration of Pharmatose greatly enhanced the release of the drug due to its channeling effect despite the increased intensity of carbon dioxide gas pockets associated with increased concentration of sodium bicarbonate.

Verification of optimized formulations

The obtained optimum values of the independent test variables are as follows; 93.50 mg quantity of HEC (X1), 11.47 % w/w of sodium bicarbonate (X2), i.e., 21 mg and 10.40% w/w of Pharmatose (lactose monohydrate) (X3), i.e., 19.1 mg, as shown in Table 6. The model predicts that the formulation

Table 6: Formula composition of optimized formulation DNAso

Ingredient	mg/tablet
Diltiazem HCl	90.0
Hydroxyethyl cellulose	93.5
Polyvinylpyrrolidone	3.0
Sodium bicarbonate	21.0
Pharmatose	19.1
Magnesium stearate	3.0
Talc	2.0
Tablet weight (in mg)	231.6

Table 7: Observed responses and predicated values

Formulae	Actual value	Predicated value	Residual
DNAB1	100.00	99.76	0.24
DNAB2	99.99	100.47	−0.48
DNAB3	100.00	99.52	0.48
DNAB4	94.99	95.23	−0.24
DNAB5	100.00	99.88	0.12
DNAB6	97.88	97.04	0.84
DNAB7	100.00	100.84	−0.84
DNAB8	99.99	100.11	−0.12
DNAB9	100.00	100.36	−0.36
DNAB10	94.05	94.65	−0.60
DNAB11	100.00	99.40	0.60
DNAB12	100.00	99.64	0.36
DNAB13	99.99	99.87	0.12
DNAB14	99.62	99.87	−0.25
DNAB15	100.00	99.87	0.13

Table 8: Physical and chemical characteristics of optimized formulation DNAso

Formulation	Weight (mg)	Drug content (%)	Hardness (kg/cm²)	Friability (%)	Floating lag time (sec)
DNAso	231.4±0.32	100.4±0.57	4–6	0.22	405

with 100% drug release in 12±1 h can be obtained using the above optimum concentrations. Verification of the optimized conditions was done by carrying out *in vitro* dissolution experiments, which showed a desired dissolution profile. These experimental findings are in close agreement with the model predictions and are shown in Table 7. The results of physical and chemical evaluation of optimized GFMT formulation DNAso were observed to be satisfactory, as shown in Table 8. Floating lag time of optimized formulation DNAs is 405 s. Release of the drug substance from DNAso (optimized formulation) and Dilzem SR (commercial sustained release formulation) followed zero-order release kinetics with diffusion mechanism.

CONCLUSION

Statistical optimization of GFMT of diltiazem HCl resulted in predicting the optimum concentrations of polymer, gas generating agent, and channeling agent for obtaining the desired prolongation of drug release along with the required floating characteristics.

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