ORIGINAL ARTICLE

Formulation and Evaluation of Gastroretentive Floating Pellets of Nizatidine

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Abstract

Aim: The aim of the study was to develop gastroretentive floating pellets containing H_2 –receptor antagonist, nizatidine which is primarily absorbed from stomach and has low oral bioavailability. **Materials and Methods:** The gastroretentive floating pellets of nizatidine were formulated using hydroxypropyl methylcellulose (HPMC) K100M and ethyl cellulose (EC) as sustained-release polymer, and $NaHCO_3$ as a gas-forming agent. Pellets were prepared by extrusion–spheronization technique using microcrystalline cellulose as spheronizing agent. A 3^2 full factorial design was applied to investigate the effect of the two independent variables, that is, concentration of HPMC K100M (X_1) and concentration of EC (X_2) on the dependent variables, *in vitro* drug release at 1 h (Y_1), *in vitro* drug release at 4 h (Y_2), *in vitro* drug release at 8 h (Y_3), and floating lag time (Y_4). **Results:** The optimized formulation (F0) exhibits a floating lag time of around 70 ± 2 s and *in vitro* drug release of 99.89% at 12 h. The *in vitro* release of F1-F9 batches were found in between 99.87% and 84.43% at 12 h. Floating lag time of F1-F9 batches was found to be 36 ± 1 s–84 ± 3 s. **Conclusion:** HPMC K100 M and EC had a significant effect on floating lag time and *in vitro* drug release. Scanning electron microscope photomicrograph of pellets revealed that the surface was rough and the pellets were spherical shaped in nature. The *in-vitro* release kinetics revealed Korsmeyer-Peppas model is followed and drug release is by anomalous diffusion.

Key words: Ethyl cellulose, gastroretentive floating pellets, hydroxypropyl methylcellulose K100M, nizatidine

INTRODUCTION

Oral dosage forms have been developed from the past four decades due to their significant therapeutic advantages such as ease of administration, patient compliance, and flexibility in formulation. Nowadays, the trend is going toward the preparation of novel controlled drug delivery systems, in which the active drug can be controlled for a longer period. However, in the controlled drug delivery, the drug absorption is inadequate and highly variable in the individuals due to its physiological variability such as gastrointestinal transit as well as the gastric residence time of the dosage forms.[1,2]

Gastroretentive drug delivery system (GRDDS) is an advanced approach for the novel drug delivery systems in which the drug is retained in the stomach for a prolonged period.[3,4] GRDDS is particularly suitable for drugs having a narrow absorption window, drugs that act locally in a part of the gastrointestinal tract, drugs that are unstable in intestinal fluids, and drugs that exhibit poor solubility in the intestinal tract.[5,6]

Floating drug delivery system (FDDS) is one of the most prominent approaches of GRDDS, characterized by the capacity of the formulation to float in and over the gastric contents. In the development of FDDS based on the mechanism of buoyancy, the widely employed technology is effervescent systems. In effervescent systems, carbon dioxide gas production occurs due to the reaction of carbonates and bicarbonates present in the formulation with gastric fluid. The gas that forms is entrapped in the polymers, which allows the system to remain buoyant. The FDDS is effectively used

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to design sustained drug delivery systems and improve the overall oral bioavailability of drugs.[7-9]

A wide range of single unit and multiparticulate FDDS was designed and developed, the multiparticulate FDDS was preferred over a single-unit system due to minimum inter and intrasubject variability in drug absorption and lower possibility of dose dumping.[10] Nizatidine is a histamine H_2-receptor antagonist that inhibits stomach acid production and commonly used in the treatment of peptic ulcer and gastroesophageal reflux disease. Nizatidine has a short biological half-life (1–2 h) and susceptible to metabolism by colonic bacteria.[11] It has been reported that the local delivery of H_2 receptor antagonist increases the stomach wall receptor site bioavailability and increases efficacy of these drugs to reduce acid secretion.[11,12] Based on the mentioned criteria, nizatidine is a suitable candidate for GRDDS.

Multiparticulate system like pellets has several therapeutic and technological advantages over single unit dosage form like tablets. Hence, pelletization of nizatidine reduces the risk of dose dumping unlike in tablet dosage form. Pelletization provides uniform distribution of drug.

Hence, the objective of present research work is to formulate and develop gastroretentive floating pellets of nizatidine using extrusion and spheronization technique. The floating pellets were prepared using hydroxypropyl methylcellulose (HPMC) K100M and ethyl cellulose (EC) as release retardant polymers and sodium bicarbonate ($NaHCO_3$) as a gas-forming agent. The effect of the HPMC K100M and EC on floating and drug release behavior was studied using 3^2 factorial design.

MATERIALS AND METHODS

Materials

Nizatidine was obtained a gift sample from Shasun Pharmaceutical Ltd., Cuddalore. HPMC K100M, EC, and microcrystalline cellulose were purchased form Yarrow chem. Products, Mumbai. Magnesium stearate, talc, and polyvinylpyrrolidone (PVP) K-30 were purchased from Estron Chemicals Limited, Ahmedabad. Isopropyl alcohol and sodium bicarbonate were procured from RFCL Ltd. Delhi.

Drug excipient compatibility study by differential scanning calorimetry (DSC)

DSC has been used to study the physical and chemical interactions between drug and excipients used. DSC spectra of (i) nizatidine (ii) nizatidine and polymer mixture (HPMC K100M and EC) were recorded using DSC instrument (DSC-60, Shimadzu, Japan). The samples were heated in sealed aluminum pans under the airflow (30 ml/min) at a scanning rate 10°C/ min from 35 to 250°C.[13]

Method

Pellets were prepared by extrusion-spheronization method. Drug, HPMC K100M, EC, sodium bicarbonate, microcrystalline cellulose, PVP K-30, talc, and magnesium stearate were sifted through sieve no. 40 and accurately weighed. The ingredients were blended in geometric fashion using mortar and pestle for 10 min. A mixture of IPA:water in proportion of 1:1 was gradually added to the powder blend. The dough mass was extruded through mini screw extruder (1 mm pore size) at speed of 20 rpm. The extrudates were collected and cut it in small size. Small size extrudates were spheronized in spheronizer (Cronimach Machinery, Ahmedabad) at 800 rpm for 20 min. The obtained pellets were dried at 50°C for 60 min in a hot air oven. Hard gelatin capsules were filled with floating pellets containing 150 mg drug. [14]

Experimental design

In this design, two factors were evaluated, each at three levels and experimental trials was performed using all possible nine combinations. In this present study, concentration of HPMC K100 M (X_1) and concentration of EC (X_2) were selected as independent variables. The % *in vitro* drug release at 1 h, 4 h, 8 h, and floating lag time was selected as dependent variables. A statistical model, incorporating interactive and polynomial terms, was used to evaluate the response.

$$Y = b_0 + b_1X_1 + b_2X_2 + b_{12}X_1X_2 + b_{11}X_1^2 + b_{22}X_2^2 \quad (1)$$

Where Y is the dependent variable, b_0 is the arithmetic mean response and b_1 and b_2 are the estimated coefficient for the factor X_1 and X_2, respectively. The main effect (X_1 and X_2) represents the average result of changing one factor at a time from its low to high value. The interaction term (X_1X_2) shows how the responses change when two factors are changed simultaneously. The polynomial terms (X_1^2, X_2^2) are included to investigate nonlinearity [Tables 1 and 2]. Nine formulations were prepared by varying quantity of ingredients, as shown in Table 3.

Dependent variables: Y_1: *In vitro* drug release at 1 h, Y_2: *In vitro* release drug 4 h, Y_3: *In vitro* drug release at 8 h, and Y_4: floating lag time (s).

Evaluation of pellets

Particle size distribution

The particle size distribution of pellets was carried out by sieve analysis using mesh fractions (American Society for Testing and Materials) 16/18, 18/20, 20/30, 30/44, and 44/60 for 5 min on

a mechanical sieve shaker. Pellets retained on each mesh were weighed, and the resulting data were used to obtain the mean geometric diameter by plotting cumulative percentage undersize versus the average particle size on log probability paper. The study was performed in triplicate for each batch of pellets.[15,16]

Drug content

Pellets were crushed in mortar and pestle. Accurately weighed powder equivalent to 150 mg drug was dissolved in 100 ml 0.1 NHCl. The resulting solution was sonicated. The solution was filtered, after suitable dilution. The filtrate was analyzed at 313 nm using an ultraviolet (UV) spectrophotometer.[17]

Table 1: Variables in 3^2 factorial designs

Independent variables	Levels		
	−1	0	+1
X_1: HPMC K100M	15% (90 mg)	17.5% (105 mg)	20% (120 mg)
X_2: Ethyl cellulose	15% (90 mg)	17.5% (105 mg)	20% (120 mg)

Table 2: Factorial design of batches

Batch no.	X1	X2	Actual value(mg)	
F1	−1	−1	90	90
F2	0	−1	105	90
F3	+1	−1	120	90
F4	−1	0	90	105
F5	0	0	105	105
F6	+1	0	120	105
F7	−1	+1	90	120
F8	0	+1	105	120
F9	+1	+1	120	120

Floating studies (in vitro buoyancy studies)

The *in vitro* floating study was carried out using USP dissolution apparatus II having 900 ml of 0.1 NHCl. The temperature of medium is kept at 37 ± 0.5°C. The pellets (600 mg) were spread over the surface of the dissolution medium and medium was agitated by paddle at 50 rpm. After agitation, the pellets floating over the surface of the medium were counted. The time to float and duration of floating (floating time) was measured by visual observation.[18]

In vitro drug release study

In vitro drug release studies were performed using the USP type II dissolution apparatus (Electrolab Dissolution Tester (USP) TDT- 08L) at 50 rpm using 0.1 NHCl as dissolution medium at temperature 37 ± 0.5°C.[18] Aliquots (5 ml) were withdrawn at different time intervals. Samples were replaced by its equivalent volume of dissolution medium. The samples were filtered through Whatman filter paper and solutions were analyzed at 313 nm using UV spectrophotometer.

Friability

The friability test of pellets was performed to ensure its mechanical strength. Lower friability values indicate good mechanical strength. Pellets of known mass were placed in Roche friabilator and subjected to impact testing at 25 rpm for 4 min.[19]

Surface morphology

The shape and surface characteristics of pellets were determined by scanning electron microscopy (SEM). The samples for SEM were prepared by lightly sprinkling the pellets on the double-sided adhesive tape stuck to an aluminum stub. The stub was then coated with gold. The samples were

Table 3: Composition of factorial batches

Ingredients	Batches (Qty. in mg)								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Nizatidine	150	150	150	150	150	150	150	150	150
HPMC K100M	90	105	120	90	105	120	90	105	120
Ethyl cellulose	90	90	90	105	105	105	120	120	120
Microcrystalline cellulose	162	147	132	147	132	117	132	117	102
Sodium bicarbonate	72	72	72	72	72	72	72	72	72
PVP K-30	12	12	12	12	12	12	12	12	12
Magnesium Stearate	12	12	12	12	12	12	12	12	12
Talc	12	12	12	12	12	12	12	12	12
Water:IPA (1:1)	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S	Q.S
Total	600	600	600	600	600	600	600	600	600

then randomly scanned and microphotographs were taken on different magnification and higher magnification was used for surface morphology.

In vitro release kinetic study

The drug release data of floating pellets were fitted to kinetics models, that is, zero order, first order, Higuchi, and Korsmeyer-Peppas to find out drug release pattern and mechanism.[13]

RESULTS AND DISCUSSION

Drug–excipient compatibility study by DSC

The thermal behavior of the pure drug and the combination of drug and excipients was compared. The DSC thermogram of nizatidine showed a sharp endothermic peak at 136.82°C. In the DSC data of mixture of nizatidine and excipients, the sharp endothermic peak was observed near to 133.24°C. Melting endothermic peak of the drug was well observed with a slight change in term of broadening of peak or shifting toward the lower temperature. Thus, these minor changes in the melting endothermic peak of drug could be due to the mixing of drug and excipients, which lowers the purity of each component in the mixture and may not necessarily indicating potential incompatibility. There was no change in the melting endotherm of the drug and drug-polymers mixture. Hence, it was concluded that drug and polymers were compatible with each other [Figures 1 and 2].

Result of factorial batches of nizatidine pellets

Results of nizatidine floating pellets as shown in Tables 4 and 5.

In vitro drug release study

The aqueous medium on contact with polymer matrix gradually begins to hydrate from the periphery toward the center, forming a gelatinous swollen mass, which controls the diffusion of drug molecules through the polymeric material into aqueous medium.[14] Drug release was generally linear for most of the formulation such linear release from polymeric matrices has been attributed to synchronization between swelling and erosion of the polymer in maintaining a constant gel layer. The polymer concentration had an effect on drug release. As the concentration of HPMC K100M and EC was increased, the drug release was retard. However, EC has a major role as a drug release controlling factor than HPMC K100M. In batch F1 to F3, the concentration of EC was less, so does not gives drug release up to 12 h. F6 batch gives drug release up to 12 h (99.56 ± 1.18). In batch F6 to F9, the concentration of both polymers was more, so retards the drug for more than 12 h [Figure 3].

Regression analysis for the effect of X_1 and X_2 on *in vitro* drug release at 1 h [Table 6]

Full model equation

$$Y_1 = +20.25 - 2.53 * X_1 - 5.64 * X_2 + 0.56 * X_1 * X_2 + 1.04 * X_1^2 + 2.54 * X_2^2 \quad (2)$$

Reduced model equation on the basis of *P* value

$$Y_1 = +20.25 - 2.53 * X_1 - 5.64 * X_2 + 2.54 * X_2^2 \quad (3)$$

% *in vitro* drug release showed a correlation 0.9705. Here *P* value for X_1 and X_2 was <0.05. Hence, HPMC K100M and EC both had a significant effect on % CR at 1 h. The coefficients b_1, b_2, and b_2^2 were found to be significant at $P < 0.05$ and thus, were retained in the reduced model equation. Here in equation (3), b_2 value is more negative than b_1 which indicated that EC had more release retardant effect compare to the HPMC K100M at 1 h [Figures 4 and 5].[20]

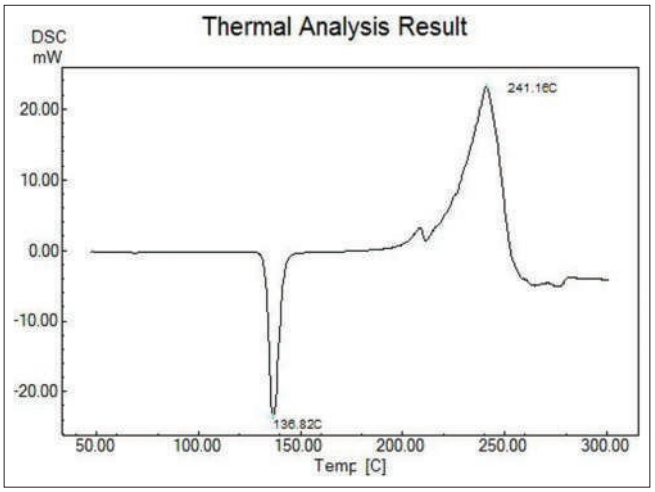

Figure 1: Differential scanning calorimetry data of pure nizatidine

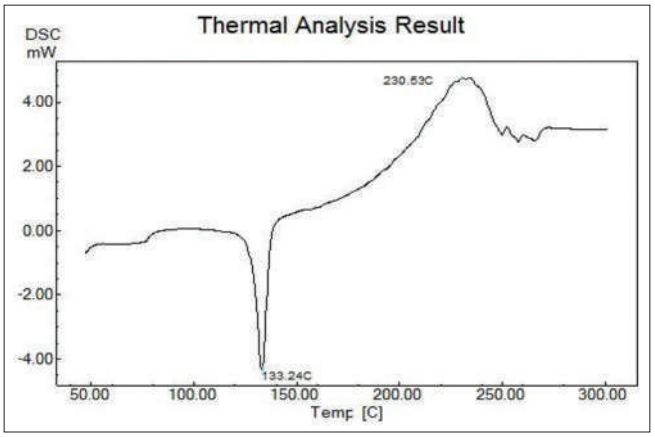

Figure 2: Differential scanning calorimetry data of nizatidine and polymer mixture (hydroxypropyl methylcellulose K100M and ethyl cellulose)

Table 4: Evaluation of pellets

Batch no	Particle size distribution (mm) (M i)	% Drug content	Buoyancy time (h)	% Friability
F1	1.15	96.43±0.05	8	0.56±0.07
F2	1.12	98.72±0.04	8	0.74±0.09
F3	1.09	97.81±0.06	8	0.35±0.05
F4	1.11	98.15±0.04	10	0.82±0.09
F5	1.18	96.82±0.06	11	0.65±0.12
F6	1.05	99.01±0.03	>12	0.79±0.11
F7	1.19	97.42±0.05	>12	0.89±0.08
F8	1.13	96.17±0.04	>12	0.81±0.13
F9	1.18	98.43±0.07	>12	0.41±0.06

Data are represented as mean±SD, *n*=3

Table 5: Observed response in 3^2 full factorial design for nizatidine floating pellets

Batch no	Independent variables		Dependent variables			
	X_1	X_2	Y_1: *In vitro* drug release at 1 h	Y_2: *In vitro* drug release at 4 h	Y_3: *In vitro* drug release at 8 h	Y_4: Floating lag time (s)
F1	90	90	31.75±1.03	68.35±0.99	99.89±1.14	36 ±1
F2	105	90	28.47±1.12	65.56±1.34	98.54±1.23	43±2
F3	120	90	27.15±1.93	63.71±1.43	99.5±1.56	50± 2
F4	90	105	25.64±1.08	55.46±1.32	86.72±1.50	56±3
F5	105	105	20.15±1.45	50.38±1.21	83.64±1.69	63±3
F6	120	105	17.43±1.03	48.39±1.98	81.13± 1.43	68±2
F7	90	120	19.14±1.07	38.64±1.03	64.43± 1.6	73±3
F8	105	120	17.61±1.64	37.89±1.56	60.10± 1.65	78±4
F9	120	120	16.78±1.34	35.44±1.03	57.72± 1.43	84±3

Table 6: Regression statistics Y_1

R square	0.9705
Adjusted R square	0.9494

Source	Sum of squares	*P*-value
Model (quadratic)	261.32	<0.0001
X_1	38.35	0.0007
X_2	190.86	<0.0001
X_1*X_2	1.25	0.3281
X_1^2	2.97	0.1497
X_2^2	17.85	0.0054

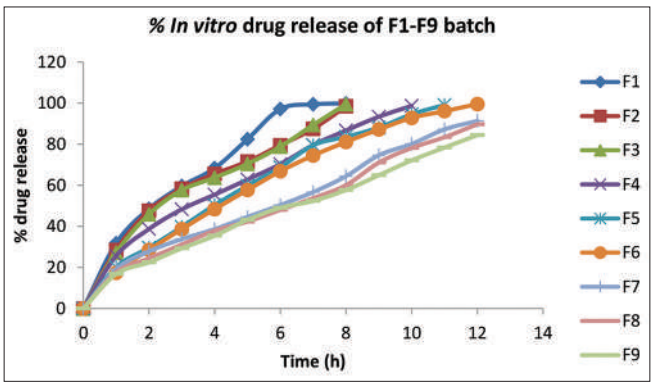

Figure 3: *In vitro* drug release profile

Regression analysis for the effect of X_1 and X_2 on *in vitro* drug release at 4 h [Table 7]

Full model equation

$$Y_2 = +51.18 - 2.48 * X_1 - 14.27 * X_2 \quad (4)$$

Reduced model equation on the basis of P value

$$Y_2 = +51.18 - 2.48 * X_1 - 14.27 * X_2 \quad (5)$$

% *in vitro* drug release showed a correlation 0.9923. Here *P* value for X_1 and X_2 was <0.05. Hence, HPMC K100M and EC both had a significant effect on % CR at 4 h [Figures 6 and 7].

Regression analysis for the effect of X_1 and X_2 on *in vitro* drug release at 8 h [Table 8]

Full model equation

$$Y_3 = +83.53 - 2.11 * X_1 - 19.28 * X_2 - 1.58 * X_1 * X_2 + 0.66 * X_1^2 - 3.94 * X_2^2 \quad (6)$$

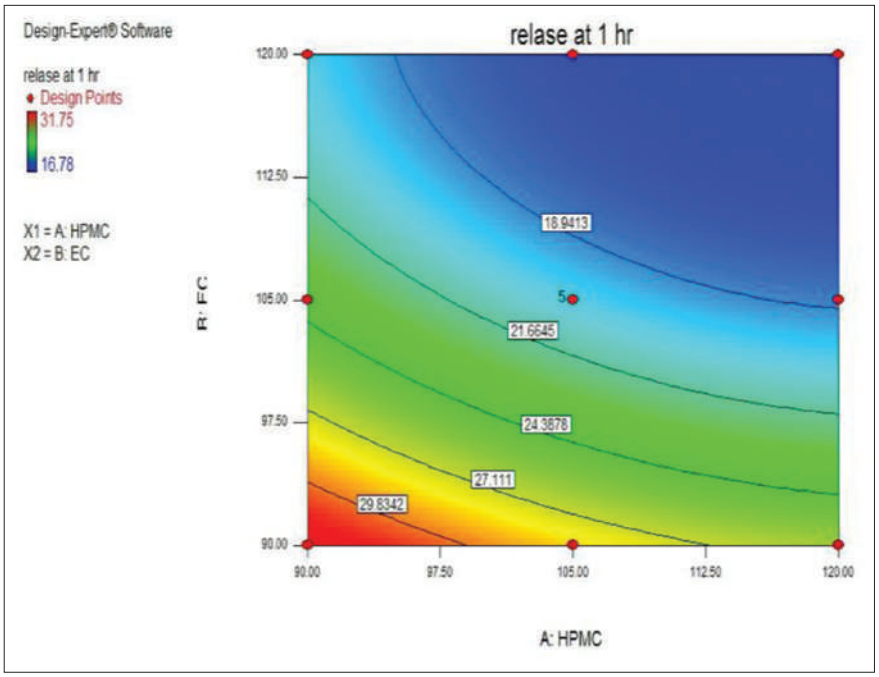

Figure 4: Contour plot of response Y_1

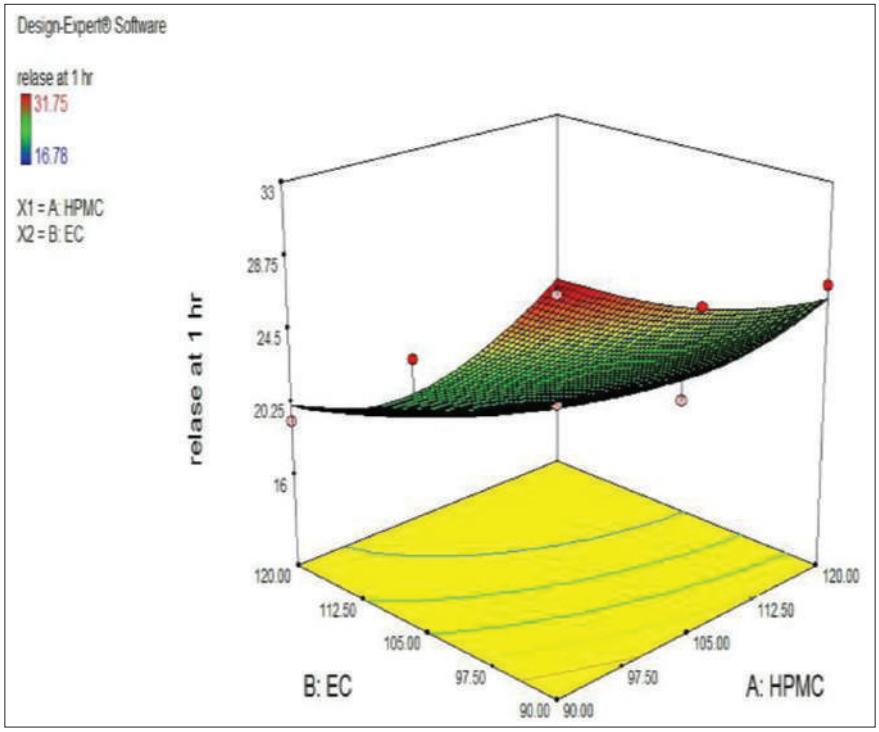

Figure 5: Surface response plot of response Y_1

Table 7: Regression statistics Y_2

R square	0.9923	
Adjusted R square	0.9907	
Source	**Sum of squares**	***P*-value**
Model (Linear)	1259.71	<0.0001
X_1	37.05	0.0001
X_2	1222.65	<0.0001

Reduced model equation on the basis of *P* value

$$Y_3 = +83.53 - 2.11 * X_1 - 19.28 * X_2 - 1.58 * X_1 * X_2 - 3.94 * X_2^2 \quad (7)$$

% *in vitro* drug release showed correlation 0.9992. Here *P* value for X_1 and X_2 was <0.05. Hence, HPMC K100M and EC both had significant effect on % CR at 8 h [Figures 8 and 9].

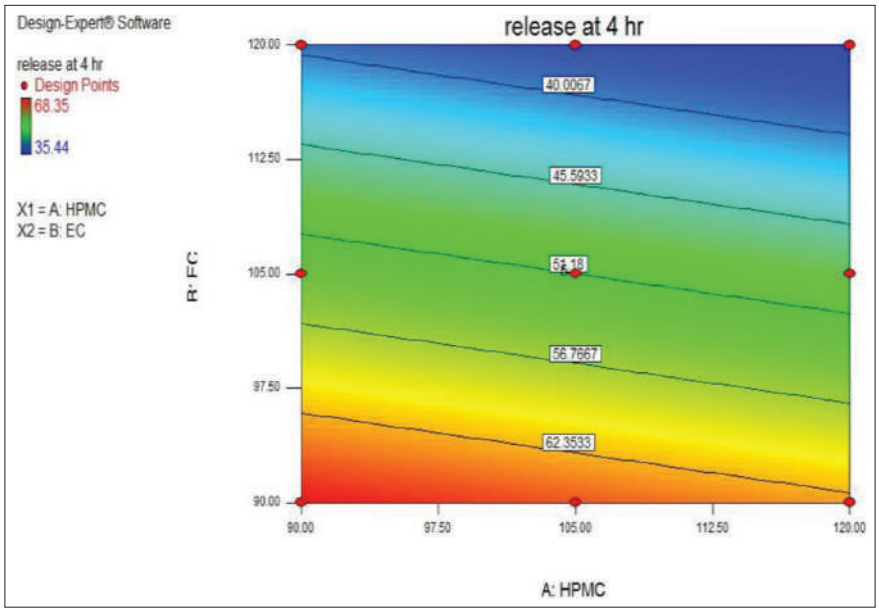

Figure 6: Contour plot of response Y_2

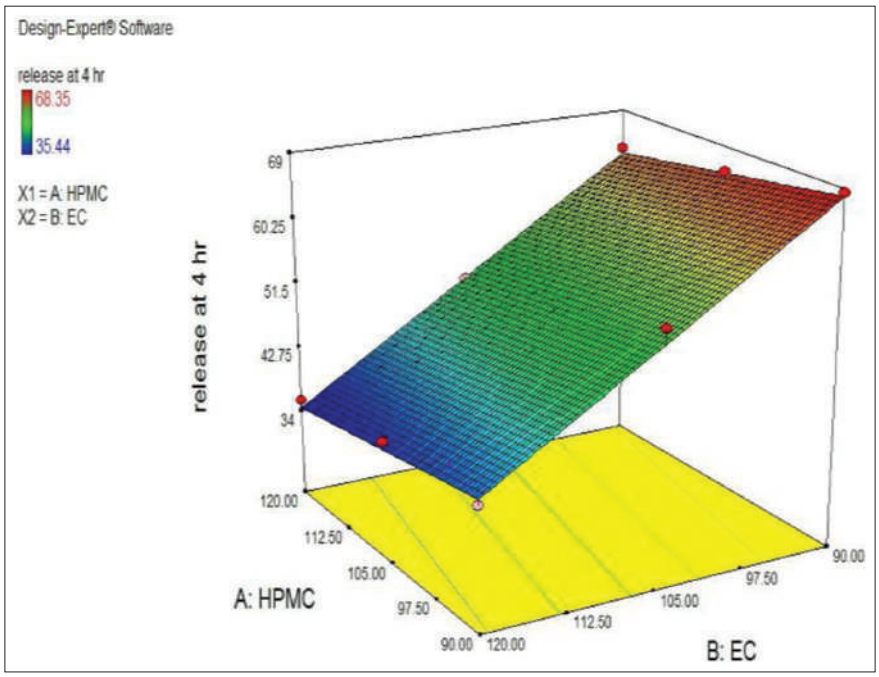

Figure 7: Surface response plot of response Y_2

Table 8: Regression statistics Y_3

R square	0.9992	
Adjusted r square	0.9987	
Source	**Sum of squares**	***P*-value**
Model (Quadratic)	2312.37	<0.0001
X_1	26.84	<0.0001
X_2	2230.31	<0.0001
X_1*X_2	9.99	0.0004
X_1^2	1.21	0.0678
X_2^2	45.95	<0.0001

Regression analysis for the effect of X_1 and X_2 on floating lag time (Y_4) [Table 9]

Full model equation:

$$Y_4 = +62.83 + 6.17 * X_1 + 17.67 * X_2 - 0.75 * X_1 * X_2 - 0.40 * X_1^2 - 1.90 * X_2^2 \quad (8)$$

Reduced model equation on the basis of *P* value

$$Y_4 = +62.83 + 6.17 * X_1 + 17.67 * X_2 - 0.75 * X_1 * X_2 - 1.90 * X_2^2 \quad (9)$$

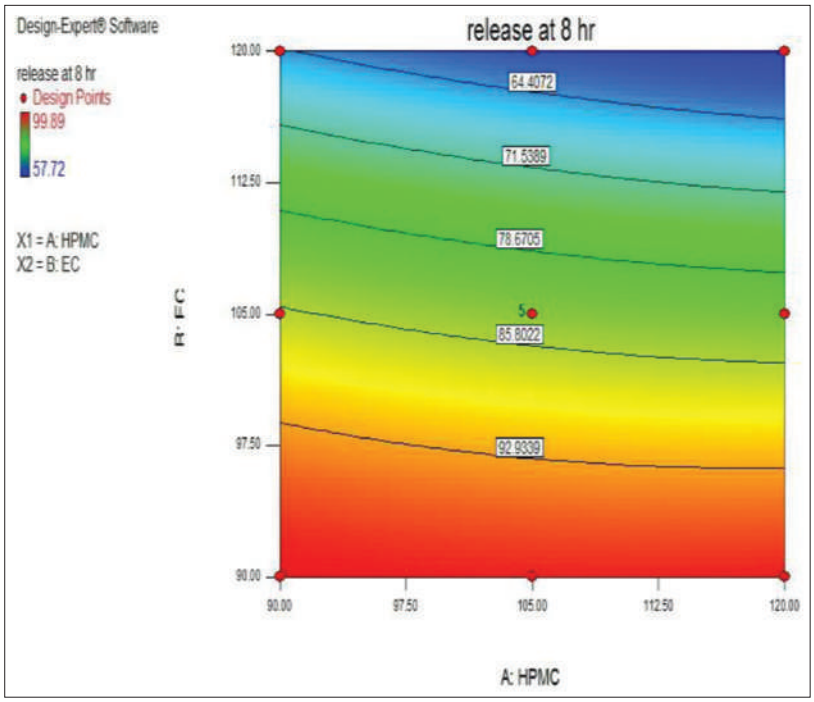

Figure 8: Contour plot of response Y_3

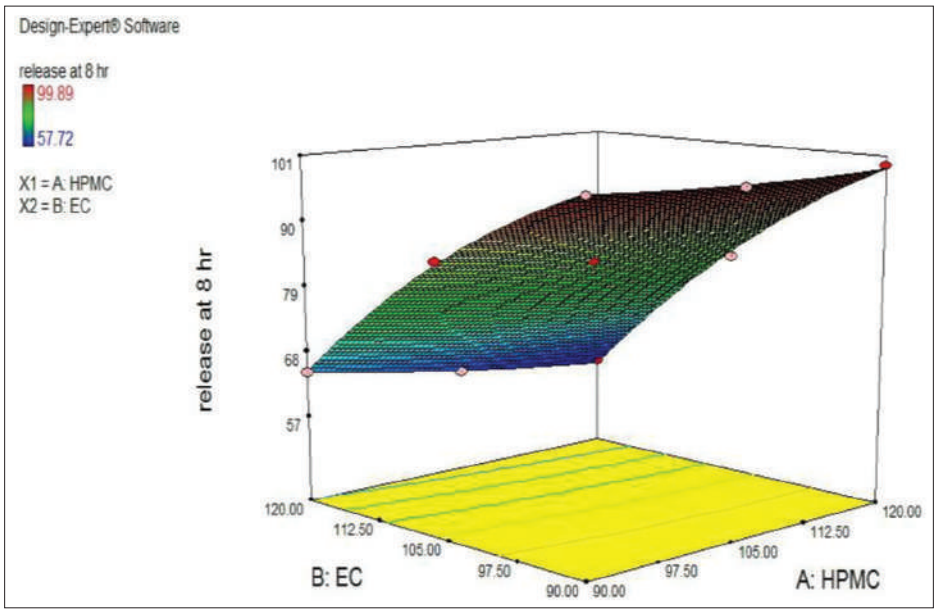

Figure 9: Surface response plot of response Y_3

Table 9: Regression statistics Y_4

R square	0.9994	
Adjusted R square	0.9990	
Source	**Sum of squares**	***P*-value**
Model (Quadratic)	2117.06	<0.0001
X_1	228.17	<0.0001
X_2	1872.67	<0.0001
X_1*X_2	2.25	0.0092
X_1^2	0.43	0.1620
X_2^2	9.93	0.0001

Floating lag time showed correlation 0.9994. Here P value for X_1 and X_2 was <0.05. Hence, HPMC K100M and EC both had significant effect on floating lag time. Here floating lag time was increased with increasing concentration of polymer [Figures 10 and 11].

Validation of design model

Preparation of checkpoint batch from overlay plot

Two checkpoint batches C1 and C2 were prepared and evaluated for *in vitro* drug release at 1 h, *in vitro* drug release at 4 h, *in vitro*

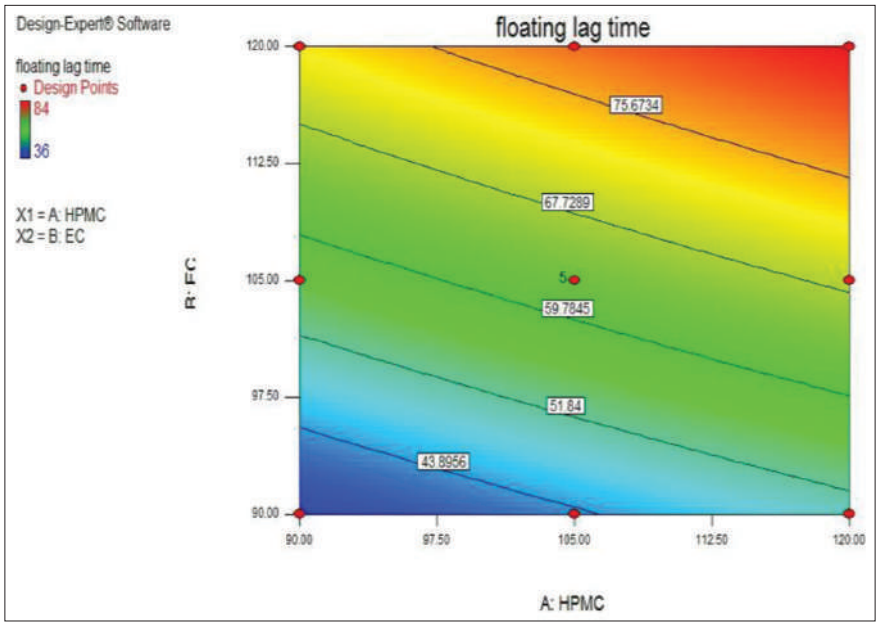

Figure 10: Contour plot of response Y_4

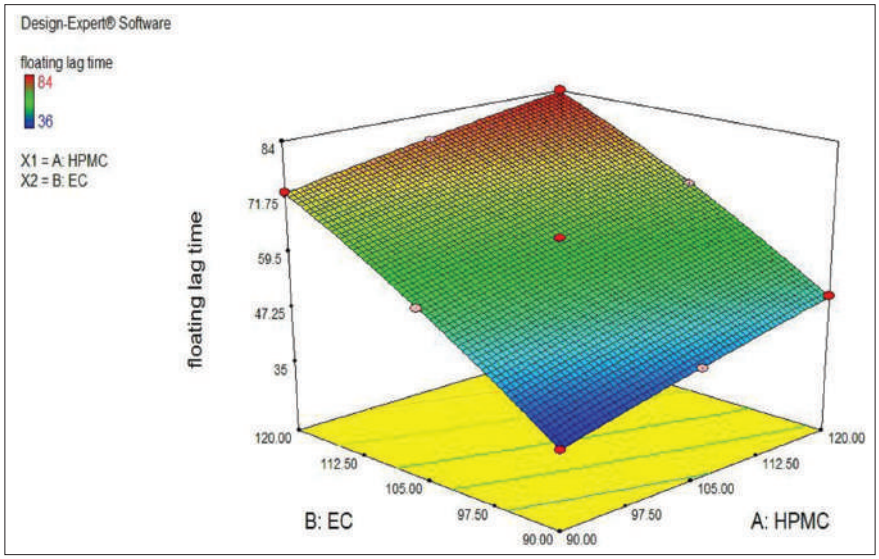

Figure 11: Surface response plot of response Y_4

Table 10: Predicted response and actual response of checkpoint batch

Evaluation parameters	Batch C1			Batch C2		
	Predicted value	Actual value	% error	Predicted value	Actual value	% error
In vitro drug release at 1 h	19.13	19.51	1.99	21.01	21.48	2.23
In vitro drug release at 4 h	47.06	47.59	1.13	54.18	55.12	1.73
In vitro drug release at 8 h	77.47	78.56	1.40	88.65	90.42	1.79
Floating lag time (s)	67.24	69	2.61	61	63	3.28

drug release at 8 h, and floating lag time, as shown in Table 10. When measured *in vitro* drug release and floating lag time value was compared with predicted *in vitro* drug release and floating lag time value, the differences were found to be <5% of all the responses. Hence, this model was valid and optimized batch can be selected from the overlay plot of this model [Figure 12].

Optimization of batch

The contour plots are evolved for each response which divides the plot surface into a desirable and not desirable zone. Here in Figure 13 shows the yellow area was the optimized area and batch F0 was fall in the yellow region. Hence, optimized

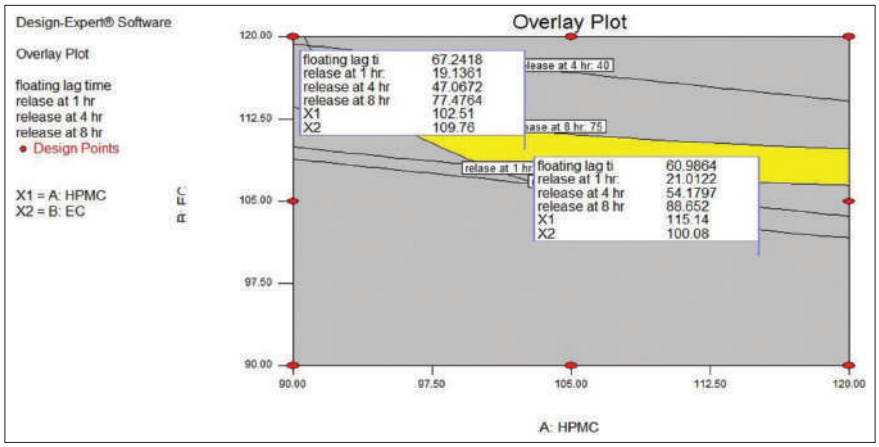

Figure 12: Overlay plot of response variables

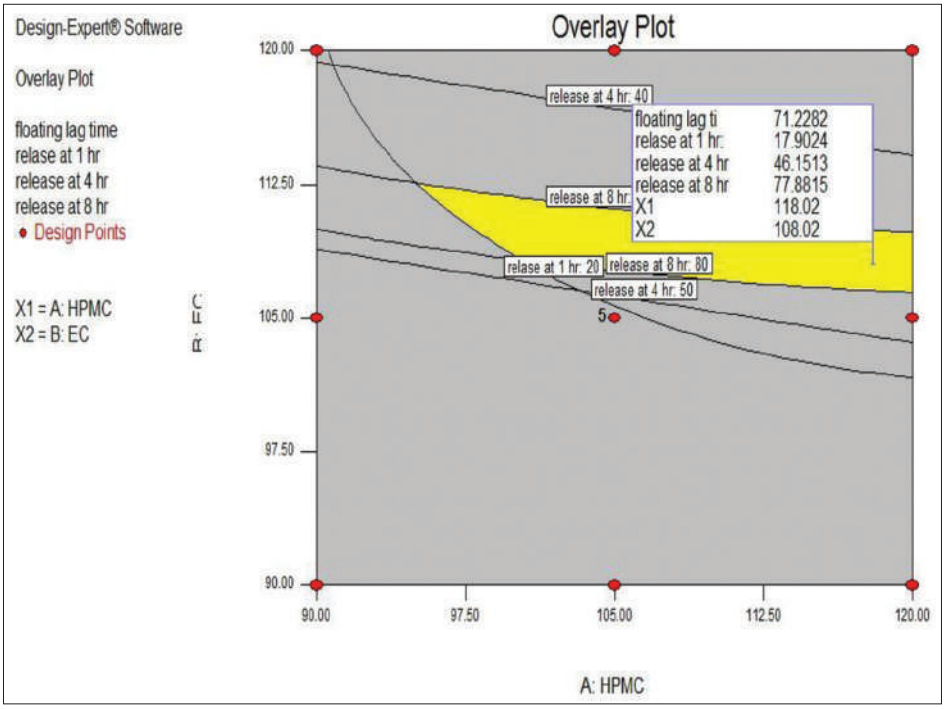

Figure 13: Overlay plot of optimized batch

Table 11: Result of evaluation parameters of optimized batch (F0)

Parameters	Result
% Friability	0.85±0.07
Floating lag time (s)	70 ±2 s
Buoyancy time (h)	>12 h
Particle size distribution	1.17 mm
% Drug content	99.43±0.07
In vitro drug release at 1 h	17.84±1.34
In vitro drug release at 4 h	47.10±1.78
In vitro drug release at 8 h	80.45±1.89

batch F0 was prepared and results of optimized batch are shown in Table 11.

Evaluation of optimized batch (F0) [Table 11]

In vitro release kinetic study

The *in vitro* release profile of drug from all the formulations could be best expressed by Korsmeyer-Peppas model, as the plot shows high linearity (R^2 = 0.996). To confirm the diffusion mechanism, the data were fit into Korsmeyer-Peppas equation; here "*n*" value was found to be 0.727, so it follows anomalous diffusion mechanism [Table 12]. This

Table 12: *In vitro* ***release*** **kinetic study**

Model	*In vitro* release kinetic study of optimized batch			
	Zero order	First order	Higuchi	Korsmeyer -Peppas
R^2	0.981	0.885	0.994	0.996
Slope (*n*)	7.690	0.062	35.74	0.727
Intercept	14.97	1.356	22.15	1.235

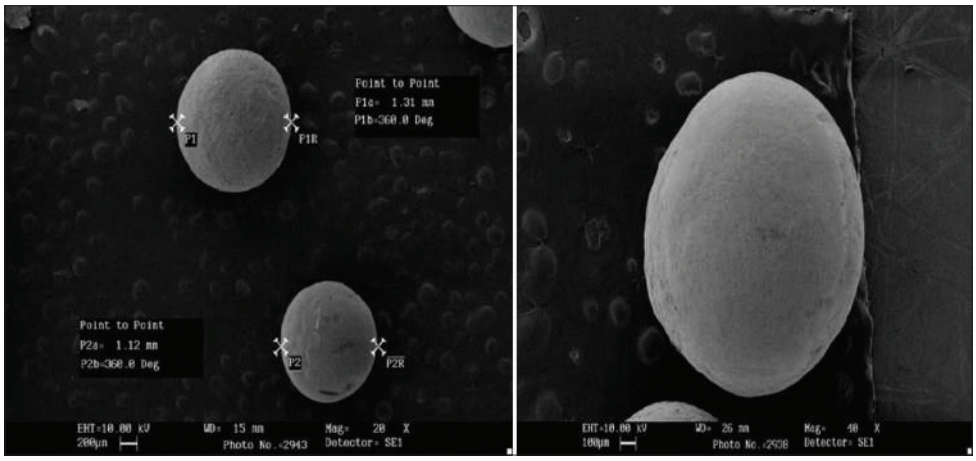

Figure 14: Scanning electron microscopy images (surface morphology) of batchF0

behavior was responsible for maintaining zero-order release in which the increase diffusion path length due to swelling is balanced with a decrease in diffusion path length due to matrix erosion.

Surface morphology (SEM analysis)

Shape analysis and surface morphology of pellets of optimized batch were carried out by SEM. SEM photomicrograph of pellets revealed that the surface was rough and the pellets were spherical shaped in nature [Figure 14].

CONCLUSION

The floating pellets of nizatidine are prepared by extrusion and spheronization method using polymers such as HPMC K100M and EC. Concentration of HPMC K100M and EC had significant effect on % *in vitro* drug release and floating lag time. It was found that increase the concentration of polymers resulted that increased floating lag time and decreased the release rate. EC had a major role as drug release controlling factor than HPMC K100M. The optimized batch F0 containing 118 mg HPMC K100M and 108 mg of EC was considered as the best product with respect to size, shape of pellets, and *in-vitro* drug release up to 12 h. SEM study near to 1 mm confirmed that the prepared formulation was spherical in nature. The *in vitro* release kinetics revealed Korsmeyer-Peppas model is followed and drug release is by anomalous diffusion.

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