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Design, statistical optimization of Nizatidine floating tablets using natural polymer

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Abstract

Background: The present research was aimed in developing gastroretentive tablets of Nizatidine, in order to increase the bioavailability of the drug. Nizatidine belongs to BCS class 3 and thus formulating into gastroretentive tablets helps to achieve a better therapeutic effect. There were no reports available on the use of Mimosa gum in the design of gastroretentive drug delivery systems. Response surface methodology was employed to optimize the formulation with suitable experimental design. The goal of the response surface methodology was to obtain a regression model and to find a suitable approximation for the true functional relationship between the response and the set of independent variables. Hence, the statistical approach like full factorial design was utilized to obtain optimized formulation with a smaller number of experiments.

Results: DSC study justified no interaction of the drug with excipients. The floating lag time was observed to be less than 20 s, total floating time was in the range of 8–24 h, hardness ranges from 4 to 5 kg/cm^2, and friability was less than 1%. Dissolution data indicated that the higher viscosity of Mimosa (2%) delayed the drug release for extended period of time up to 23 h when compared to lower viscosity Mimosa (1%), which controlled the release of the drug up to 12 h only. The '*n*' values of all the prepared formulations were found to be 0.59 to 0.81 indicating that the release mechanism followed anomalous (non-Fickian) diffusion. The optimal values of independent test variables were obtained from the overlay plots. The optimized formulation of Mimosa gum (2%) ($M2\%_{opt}$) contained 170 mg of polymer and 25.5 mg (15%) of sodium bicarbonate. Similarly, the optimized formulation of Mimosa (1%) ($M1\%_{opt}$) contained 255 mg of polymer and 34 mg (10%) of sodium bicarbonate.

Conclusion: The results clearly indicated that the optimized formulations followed zero-order release kinetics with diffusion mechanism as per the predicted theoretical release rate confirming the suitability of the predicted theoretical release profile.

Keywords: Gastroretentive drug delivery system, Mimosa gum, Nizatidine, Statistical optimization

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Background

The primary objective of gastroretentive drug delivery systems (GRDDS) is to ensure safety of drugs as well as patient compliance. Gastric floating tablets have less density than gastric fluid and consequently they are able to float in the stomach for prolonged period of time releasing the drug slowly at the required rate from the system which results an elevated gastric retention time.

In the present study, Nizatidine [1] was selected as drug of choice to design the effervescent gastric floating matrix tablets (EGFMT) [2–4] using Mimosa gum [5–7] as a matrix forming polymer.

EGFMT of Nizatidine were designed to retain the tablets in the stomach for longer periods of time and deliver Nizatidine effectively to the absorption window for maintaining the effective plasma levels for a prolonged time thereby decreasing the frequency of administration of drug. Nizatidine is a histamine H_2 receptor antagonist used to treat and prevent the recurrence of ulcers and occasional heartburn, acid indigestion, or sour stomach. It decreases the amount of acid made in the stomach.

Many naturally available polymers [8] were being studied for their future prospects in the development of prolonged active ingredient release. It was observed that there was difference in properties from one batch to the other when natural excipients were used. The observed changes were due to change in the physicochemical properties. Hence in the present investigation, the properties of Mimosa gum were evaluated and its applicability in the design of floating tablets was studied.

One of the statistical optimization techniques, response surface methodology (RSM), was utilized for the development and optimization of EGFMT. RSM was employed to observe the empirical relationship between one or more measured responses and a number of independent variables in the form of polynomial equations, mapping of the response over the experimental domain, with the ultimate goal of obtaining an optimal formulation [9–11].

Methods and materials

Materials

Nizatidine was received as a gift sample from Aurobindo Pharma (Hyderabad, India). Mimosa gum was kindly provided by Govt. Co-operative stores (Mumbai). Sodium bicarbonate was provided as gift sample from Kartikeya Chemicals. (Hyderabad, India). All other chemicals and solvents were of analytical grade or highest quality and were used as such as obtained.

Methods

Physicochemical characterization of mimosa gum

Mimosa seed gum hydrates well and swells swiftly when comes in contact with water. Mimosa gum has greatest advantage of degrading into biologically acceptable molecules that are easily metabolized and removed from the body. It sustains the release of drug from the dosage form by following diffusion mechanism at higher proportions. For this reason, it was selected for the present study.

The physiochemical properties of Mimosa gum such as particle size distribution, surface characteristics, bulk density, tapped density, compressibility, moisture content, pH, volatile acidity, swelling, and water absorption properties were measured [12, 13].

Preparation of tablets

All the ingredients sufficient for a batch of 100 tablets according to the formulae shown in Tables 1 and 2 were passed through #30 mesh (600 μm). Active ingredient was mixed geometrically with specified excipients in order to get a uniform blend and the produced blend was lubricated with magnesium stearate and aerosil and compressed into tablets on a 16 station rotary tablet punching machine (M/s. Cadmach Minipress Machinery Co. Pvt. Ltd, India) using 12 mm round, flat, plain punches using sufficient compression force to obtain a hardness of 4 to 5 kg/cm^2 containing 85 mg of Nizatidine per tablet.

Evaluation of tablets

In vitro floating characteristics So far, prepared tablets of Nizatidine were studied for floating lag time (FLT) and total floating time (TFT). FLT and TFT were determined for 3 tablets of each batch in the 1 L glass beaker containing 900 ml of 0.1 N HCl [14].

Table 1 Formulae of Nizatidine EGFMT using Mimosa gum (2%)

Ingredients (mg/tablet)	FNM1	FNM2	FNM3	FNM4	FNM5	FNM6	FNM7	FNM8	FNM9
Nizatidine	85	85	85	85	85	85	85	85	85
Mimosa gum (2%) high viscosity	85	85	85	170	170	170	255	255	255
Sodium bicarbonate	17	25.5	34	25.5	38.25	51	34	51	68
Aerosil	2	2	2	3	3	3	4	4	4
Magnesium stearate	1	1	1	1	1	1	1	1	1

Table 2 Formulae of Nizatidine EGFMT using Mimosa gum (1%)

Ingredients (mg/tablet)	FNW1	FNW2	FNW3	FNW4	FNW5	FNW6	FNW7	FNW8	FNW9
Nizatidine	85	85	85	85	85	85	85	85	85
Mimosa gum (1%) Low viscosity	85	85	85	170	170	170	255	255	255
Sodium bicarbonate	17	25.5	34	25.5	38.25	51	34	51	68
Aerosil	2	2	2	3	3	3	4	4	4
Magnesium stearate	1	1	1	1	1	1	1	1	1

Swelling index The drug release from any tablet depends upon the % of intake of medium; here, the medium used was 0.1 N HCl. The medium temperature was maintained at 37 ± 0.5 °C throughout the study.

$$\text{Swelling index (S.I)} = \{(W_t - W_O)/W_O\} \times 100$$
$$\text{Where S.I} = \text{Swelling index}$$
$$W_t = \text{Weight of swollen tablet}$$
$$W_O = \text{Initial weight of tablet}$$

Uniformity of weight test As per official pharmacopeia, 20 tablets were taken in random, studied for difference in weight both individually and in group. The mean and percent deviations were determined [15].

Hardness test The strength of each tablet was measured using tablet hardness tester (Monsanto type, MHT-20). The mean hardness was determined and expressed in kg/cm^2. Five tablets were taken to perform the above phenomenon [16].

Friability test The friability test was carried out in Roche Friabilator (PANOMEX Inc., PX/FTA-201). The tablets equivalent to weight of 6.5 g were selected randomly and initial weight (w_o) was noted down after de-dusting and placed in a rotating drum. They were subjected to 100 falls of 6 in height (25 rpm for 4 min) [17]. The percent loss in weight (or friability) was calculated by the formula given below.

$$f = \left(1 - \frac{w}{w_0}\right) \text{x } 100$$

Uniformity of content test To study this, 10 tablets were taken and crushed; from this, 50 mg was taken in to the volumetric flask. The drug was extracted into 25 ml of 0.1 N HCl with vigorous shaking on a mechanical shaker for 1 h and the volume was made up to the mark with 0.1 N HCl. The solution was filtered through 0.45 μm Millipore nylon filter disc and appropriate dilutions were further made with 0.1 N HCl. The dilutions were measured for the absorbance by UV spectrophotometer (UV-1800, Shimadzu, Japan) at 325 nm against blank (0.1N HCl). Content of each individual preparations were determined and the average of 10 was calculated.

In vitro drug release studies The drug release from the prepared floating tablets was studied using USP XXIV dissolution rate test apparatus (LABINDIA). Then, 900 ml of 0.1 N HCl was used as dissolution medium maintained at a temperature of 37 ± 0.5 °C and the paddle was rotated at 50 rpm. The procedure was studied and the samples were suitably diluted and the absorbance was measured by UV spectrophotometer (UV-1800, Shimadzu, Japan) at 325 nm. Drug release from commercial release formulation of Nizatidine was also studied.

Comparison of dissolution data

The differences in the rate and extent of drug release due to formulation and process variables can be studied by model independent and model dependent approaches [18–21].

Model independent approaches Model independent approaches are based on dissolution efficiency (DE) or on mean dissolution time (MDT) or on time to release certain percentage of drug like T_X (time to release X% of drug), difference factor (f_1), and similarity factor (f_2), etc.

In the present investigation, three responses; floating lag time (Y_1), swelling index at first hour (Y_2), and time to release 100% of drug (T_{100}) (Y_3) were studied.

Another model independent approach is based on comparing the similarities of experimental formulations with reference formulation. Comparing the parameters obtained similar to methods proposed by Moore and Flanner which involves calculation of f_1 and f_2. The f_1 and f_2 were calculated using the equations given below.

$$f2 = 50* \log\left\{\left[1 + (1/n) \sum_{j=1}^{j=n} \left(R_j\text{-}T_j\right)^2\right]^{-0.5*} 100\right\}$$

$$f1 = [\sum_{j=1}^{j=n}(R_j - T_j) / \sum_{j=1}^{j=n} R_j] * 100$$

where n is sampling number, R_j and T_j are respectively % drug dissolved from reference and experimental formulations at time j [22, 23].

Model dependent approaches The order of drug release from matrix systems was described by using zero-order [24] or first -order kinetics [25, 26]. The mechanism of drug release from matrix systems was studied by using Higuchi diffusion model [27] and Hixon–Crowell erosion model [28]. Korsemeyer–Peppas [29, 30] support the drug release mechanism for further judgments.

Data analysis, optimization, and cross-validation of model

Data analysis DESIGN EXPERT (Stat-Ease Inc., Minneapolis, USA) software was used for analyzing the data. It selects and suggests the highest order polynomial model as a suitable model based on coefficient of determination (R^2) and predicted residual sum of squares (PRESS) values where the additional terms are significant. Analysis of variance (ANOVA) was performed on the suggested model for the responses Y_1, Y_2, and Y_3 to identify significant effect.

Multiple regression analysis was performed on the dependent variables to know the significance of the regression coefficients on the model. The models generated were used to construct contour (2D) and response surface (3D) plots for floating lag time, swelling index at first hour, and time to release 100% of drug responses of Mimosa gum (2%) and Mimosa gum (1%) based formulations to understand the main and the interaction effects of these three factors [31–33].

Optimization Desirability and graphical optimization technique (overlay plots) were employed to optimize the formulations with the desired responses (responses from theoretical profile values).

Optimization was performed with constraints of Y_1 Floating lag time = 9 s, Y_2 swelling index at first hour = 16%, and Y_3 time to release 100% of drug = 16.2 h, which were obtained from the theoretical profile. For finalizing the optimum formulation, targets were set for these constraints for getting respective desirability function response and overlay plots.

Cross-validation of model Optimized EGFMT of FNM_{opt} and FNW_{opt} were evaluated for uniformity of weight, hardness, friability, uniformity of content, in vitro floating, and in vitro dissolution. Pictures were taken for optimized formulations during in vitro floating. The f_1 and f_2 values were determined for optimized formulations using theoretical release profile as reference formulation.

The experimental values of the responses (floating lag time, swelling index at first hour, and time to release 100% of drug) were determined from the in vitro dissolution data of the optimized EGFMT.

The percentage relative error between predicted values and experimental values of each response was calculated using the below equation.

Drug-polymer interaction studies

Fourier transform infrared spectroscopy Fourier transform infrared spectroscopy (FTIR) spectra of samples were obtained on a Perkin Elmer 2000 FTIR system (Perkin–Elmer, Norwalk, CT) using the KBr disk method (2 mg sample in 200 mg KBr). The scanning range was 450–4000 cm^{-1} and the resolution were 1 cm^{-1}.

Differential scanning calorimetry Differential scanning calorimetry (DSC) was performed using a differential scanning calorimeter (DSC 220C, Seiko, Japan) at a heating rate of 10 °C/min from 30 to 300 °C in nitrogen atmosphere.

Table 3 Characterization of Mimosa gum

Property	Results obtained
Tapped density (g/cc)	0.702 ± 0.02
Bulk density (g/cc)	0.632 ± 0.04
Bulkiness (cc/g)	1.58 ± 0.04
Angle of repose (°)	28.20 ± 1.28
Compressibility index (%)	10.42 ± 1.34
Hausner's ratio	1.2 ± 1.54
pH	4.8 ± 0.20
Water retention capacity	19 ± 1.67
Swelling index (%)	120 ± 10.00
Volatile acidity (%)	17.2 ± 2.98
Moisture content	14.96 ± 1.12
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Table 4 Angle of repose (θ) values of Drug- Polymer physical mixtures

Drug: Polymer Ratio	Mimosa gum(2%)		Mimosa gum(1%)	
	Angle of repose(θ)	Inference	Angle of repose(θ)	Inference
Nizatidine				
1:0	52.1^0	Poor	52.1^0	Poor
1:1	29.2^0	Good	32.4^0	Passable
1:2	27.7^0	Good	28.2^0	Good
1:3	24.9^0	Excellent	25.5^0	Excellent

X-ray diffraction studies X-ray diffraction patterns of powdered samples were recorded on a Philips powder X-ray diffractometer (with Philips, PW 1140/90 X-ray generator) using Ni-filtered, CuKα radiation, at 45 KV and 25 mA between 5 and 60° 2θ values with 2° /2 cm/ 2θ chart speed.

Results

Physicochemical characterization of mimosa gum

The physicochemical properties of gum are shown in Table 3.

Flow properties

Nizatidine showed an angle of repose value of 52.1° indicating poor flow and flow characteristics changed to excellent flow with increase in polymer content. The results of angle of repose values of all drug-polymer physical mixtures are represented in Table 4.

In vitro floating characteristics

In the present work, EGFMT were designed using hydrophilic polymer (Mimosa gum) and a gas generating agent (sodium bicarbonate). Mimosa is a low-density hydrophilic polymer, rapidly hydrates, and produces hydrogel to control the drug release. Upon contact with gastric contents, sodium bicarbonate in the tablets liberates carbon dioxide which is entrapped in hydrocolloid causes a decrease in the density and results an upward movement of the dosage form and keeps it afloat. The results of in vitro floating behavior of EGFMT are summarized in Table 5.

Table 5 In vitro floating properties and tabletting characteristics of Nizatidine EGFMT

EGMFT	FLT (s)	TFT (h) [of weighta]	Uniformity of weight[a]	Uniformity content[b] (%)	Hardness[c] (kg/cm^2)	Friability (%)
FNM1	9	14	190.0 ± 1.97	102.92 ± 1.05	4–5	0.06
FNM2	5	13	198.5 ± 2.91	99.44 ± 1.34	4–5	0.13
FNM3	2	12	207 ± 1.42	101.4 ± 1.45	4–5	0.17
FNM4	14	18	284.5 ± 1.34	98.24 ± 1.76	4–5	0.09
FNM5	8	18	297.25 ± 0.4	96.52 ± 0.09	4–5	0.14
FNM6	6	16	310.0 ± 0.98	99.64 ± 0.47	4–5	0.03
FNM7	18	24	379.0 ± 1.56	98.64 ± 0.97	4–5	0.15
FNM8	13	24	396.0 ± 1.45	99.82 ± 1.57	4–5	0.19
FNM9	8	24	413.0 ± 1.31	97.12 ± 1.85	4–5	0.17
FNW1	5	8	190.1 ± 1.23	99.95 ± 1.48	4–5	0.08
FNW2	3	8	198.5 ± 1.75	103.40 ± 0.15	4–5	0.16
FNW3	1	8	207.0 ± 0.93	101.52 ± 1.57	4–5	0.19
FNW4	7	11	284.5 ± 0.2	99.92 ± 1.49	4–5	0.17
FNW5	5	10	297.25 ± 1.6	97.30 ± .049	4–5	0.18
FNW6	4	10	310.0 ± 1.24	99.66 ± 0.15	4–5	0.06
FNW7	13	13	379.0 ± 0.97	99.92 ± 1.43	4–5	0.01
FNW8	10	12	396.0 ± 0.98	97.60 ± 1.46	4–5	0.03
FNW9	5	12	413.0 ± 1.46	99.74 ± 1.54	4–5	0.15

FLT floating lag time, *TFT* total floating time
[a]Mean ± % deviation, $n = 20$
[b]Mean ± s.d., $n = 10$
[c]Mean, $n = 5$

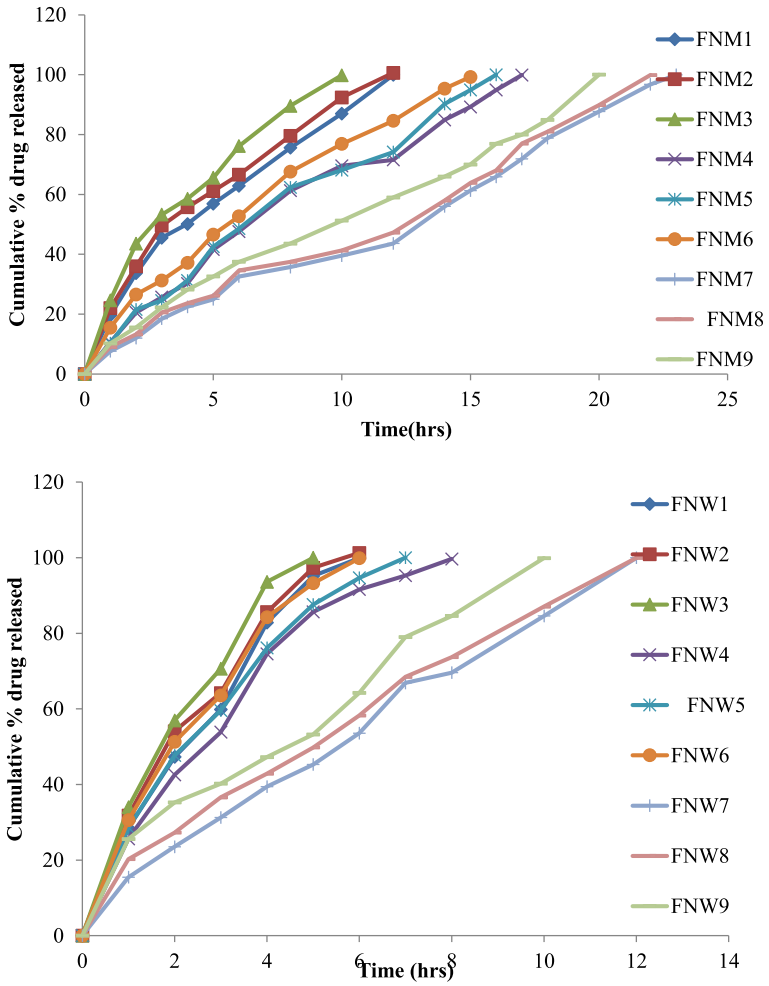


Fig. 1 Dissolution profiles of Mimosa gum (2%), (1%) based EGFMT

Table 6 T_{100} values of the EGFMT

EGFMT	T_{100} (h)	EGFMT	T_{100} (h)
FNM1	12	FNW1	6
FNM2	12	FNW2	6
FNM3	10	FNW3	5
FNM4	17	FNW4	8
FNM5	16	FNW5	7
FNM6	15	FNW6	6
FNM7	23	FNW7	12
FNM8	22	FNW8	12
FNM9	20	FNW9	10

The floating lag time was observed to be less than 20 s for all the prepared formulations. Total floating time was observed to be in the range of 8–24 h.

Uniformity of weight, hardness, friability, and uniformity of content

The results of uniformity of weight, hardness, friability, and uniformity of content are represented in Table 5.

In vitro drug release studies

The percent of Nizatidine released data of Mimosa (2%) and Mimosa (1%) based EGFMT drug release profiles are shown respectively in Fig. 1.

The results indicated slow and controlled release of Nizatidine from Mimosa (2%) and Mimosa (1%) based EGFMT. During the first hour, the % drug released values were found to be in the range of 7–25% from the Mimosa (2%) based EGFMT and 15–34% from Mimosa (1%). The drug release was extended from 10 to 23 h for Mimosa (2%) formulations. About 100%

Table 7 Correlation coefficient (*r*) values of Nizatidine EGFMT

EGFMT	Zero order		First order		Higuchi	Hixon–Crowell	Korsmeyer–Peppas	
	K_0	*r*	K_1	*r*	*r*	*r*	*r*	*n*
FNM1	7.56	0.9757	− 0.19	0.8966	0.9943	0.9441	0.9962	0.63
FNM2	7.69	0.9663	− 0.33	0.9313	0.9965	0.9512	0.9951	0.60
FNM3	9.19	0.9633	− 0.26	0.9245	0.9966	0.9804	0.9931	0.59
FNM4	5.51	0.9899	− 0.20	0.9021	0.9856	0.9510	0.9966	0.77
FNM5	5.93	0.9911	− 0.20	0.8591	0.9817	0.9402	0.9953	0.80
FNM6	6.25	0.9885	− 0.25	0.9187	0.9885	0.9402	0.9978	0.69
FNM7	4.10	0.9933	− 0.14	0.8446	0.9600	0.9057	0.9930	0.81
FNM8	4.16	0.9928	− 0.09	0.5762	0.9629	0.8969	0.9920	0.77
FNM9	4.41	0.9944	− 0.14	0.8150	0.9785	0.8810	0.9978	0.74
FNW1	16.74	0.9840	− 0.73	0.9413	0.9839	0.9739	0.9956	0.73
FNW2	16.70	0.9755	− 0.77	0.9553	0.9915	0.9389	0.9961	0.67
FNW3	19.79	0.9806	− 0.87	0.9379	0.9895	0.9655	0.9960	0.68
FNW4	12.61	0.9630	− 0.54	0.9596	0.9967	0.9926	0.9913	0.69
FNW5	13.89	0.9742	− 0.47	0.9759	0.9932	0.9511	0.9969	0.66
FNW6	16.35	0.9776	− 0.70	0.9411	0.9909	0.9769	0.9962	0.67
FNW7	8.02	0.9959	− 0.30	0.8636	0.9717	0.9165	0.9959	0.76
FNW8	7.87	0.9915	− 0.28	0.7985	0.9823	0.9323	0.9933	0.66
FNW9	9.21	0.9860	− 0.33	0.7667	0.9783	0.9263	0.9809	0.60

Table 8 Summary of model statistics for responses Y_1, Y_2, and Y_3

Model R^2	R^2	Adjusted R^2	Predicted R^2	PRESS	s.d.	*F* value	*p* value	Remarks
Mimosa (2%) based EGFMT								
Response Y_1 (floating lag time)								
Linear	0.9670	0.9576	0.9311	13.70	0.9686	102.51	< 0.0001	Suggested
Interactive	0.9783	0.9674	0.9613	7.70	0.8482	3.13	0.1274	
Quadratic	0.9904	0.9783	0.9318	13.57	0.6922	2.50	0.1971	
Response Y_2 (swelling index at 1 h)								
Linear	0.9812	0.9758	0.9600	21.10	0.7367	182.29	< 0.0001	Suggested
Interactive	0.9820	0.9729	0.9312	13.87	0.7788	0.2638	0.6259	
Quadratic	0.9915	0.9786	0.8954	8.07	0.6986	1.79	0.2781	
Response Y_3 (T_{100}) time to release 100% of drug								
Linear	0.9896	0.9866	0.9790	4.00	0.50	333.49	< 0.0001	Suggested
Interactive	0.9911	0.9866	0.9810	3.24	0.50	0.98	0.358	
Quadratic	0.9971	0.9935	0.9765	3.57	0.35	4.2	0.1036	
Mimosa (1%) based EGFMT								
Response Y_1 (floating lag time)								
Linear	0.9077	0.8813	0.7743	40.76	1.19	34.41	0.0002	Suggested
Interactive	0.9449	0.9173	0.8091	20.55	0.9944	4.04	0.0910	
Quadratic	0.9637	0.9183	0.6212	24.28	0.9880	1.04	0.4331	
Response Y_2 (swelling index at 1 h)								
Linear	0.8999	0.8713	0.8000	23.38	1.29	31.47	0.0003	
Interactive	0.9021	0.8513	0.6526	4.37	1.38	0.1310	0.7298	
Quadratic	0.9966	0.9923	0.9626	40.61	0.3160	55.32	0.0012	Suggested
Response Y_3 (T_{100}): time to release 100% of drug								
Linear	0.8885	0.8567	0.7929	12.20	0.96	23.89	0.0005	
Interactive	0.8928	0.8391	0.7426	4.00	1.03	0.24	0.6433	
Quadratic	0.9917	0.9814	0.9321	15.16	0.34	27.88	0.0005	Suggested

Table 9 ANOVA for the responses of Mimosa 2% and 1% based EGFMT

Source	SS	df	MS	*F* value	*p* value
Mimosa 2%-response Y_1 (linear model)					
Model	192.33	2	96.17	102.51	< 0.0001*
X_1-Mimosa 2%	88.17	1	88.17	93.98	< 0.0001*
X_2-Sodium bicarbonate	104.17	1	104.17	111.04	< 0.0001*
Residual	6.57	7	0.9381		
Total	198.90	9			
Response Y_2 (linear model)					
Model	197.88	2	98.94	182.29	< 0.0001*
X_1-Mimosa 2%	92.04	1	92.04	169.58	< 0.0001*
X_2-Sodium bicarbonate	105.84	1	105.84	195.00	< 0.0001*
Residual	3.80	7	0.5428		
Total	201.68	9			
Response Y_3 (linear model)					
Model	168.33	2	84.17	333.4	< 0.0001*
X_1-Mimosa 2%	160.17	1	160.17	634.6	< 0.0001*
X_2-Sodium bicarbonate	8.17	1	8.17	32.4	0.0007*
Residual	1.77	7	0.28		
Total	170	9			
Mimosa 1%-response Y_1 (linear model)					
Model	97.67	2	48.83	34.41	0.0002
X_1-Mimosa 1%	60.17	1	60.17	42.20	0.0003
X_2-Sodium bicarbonate	37.50	1	37.50	26.43	0.0013
Residual	9.93	7	1.42		
Total	107.60	9			
Response Y_2 (quadratic model)					
Model	116.50	5	23.30	233.29	< 0.0001*
X_1- Mimosa 1%	8.40	1	8.40	84.12	0.0008
X_2-Sodium bicarbonate	96.80	1	96.80	969.17	< 0.0001*
X_1X_2	0.2500	1	0.2500	2.50	0.1888**
X_1X_1	0.0430	1	0.0430	0.4303	0.5477**
X_2X_2	10.93	1	10.93	109.43	0.0005
Residual	0.3995	4	0.0999		
Total	116.90	9			
Response Y_3 (quadratic model)					
Model	58.41	5	11.68	95.74	0.0003*
X_1-Mimosa 1%	48.17	1	48.17	394.73	0.0001*
X_2-Sodium bicarbonate	4.17	1	4.17	34.51	0.004
X_1X_2	0.25	1	0.25	2.05	0.22**
X_1X_1	5.76	1	5.76	47.22	0.0023
X_2X_2	0.428	1	0.428	3.51	0.1342**
Residual	0.4881	4	0.122		
Total	58.90	9			

SS sum of squares, *MS* mean sum of squares, T_{100} time to release 100% of drug
*Significant ($p < 0.05$); ** not significant ($p > 0.05$)

of the drug was released from FNM1 to FNM9 in 12, 12, 10, 17, 16, 15, 23, 22, and 20 h respectively. Almost all the drug (> 99%) was released from the Mimosa (1%) formulations in 5–12 h.

T_{100} values were determined as model independent approaches and summarized in Table 6 and they were found to be in the range of 10–23 h and 5–12 h for Mimosa (2%) and Mimosa (1%) based formulations respectively and results are shown in Table 6.

Model dependent approaches

Drug release kinetics

The zero- and first-order correlation coefficient (*r*) values of EGFMT are presented in Table 6. In all the cases, the appropriate correlation coefficient (*r*) values were in favor of zero-order release rather than first order release.

Drug release mechanisms

The correlation coefficient (*r*) values of Higuchi, Hixon–Crowell and Korsmeyer–Peppas models are represented in Table 7. It was found that EGFMT prepared with both the percentages of Mimosa gum showed predominating diffusion mechanism than erosion mechanism as indicated by higher correlation coefficient values of Higuchi model.

Plots of log fraction of Nizatidine released versus log time of all EGFMT were found to be linear. The '*r*' values of these matrices were found to be 0.9809 to 0.9978 indicating that the release followed Korsmeyer–Peppas model also. The exponential '*n*' values of all the prepared formulations were found to be 0.59 to 0.81 indicating that the release mechanism followed anomalous (non-Fickian) diffusion, i.e., the polymer swelling and polymer and drug dissolution governs the drug release from the matrix. This behavior indicating that the release of the drug depends simultaneously on the matrix swelling and diffusion phenomena.

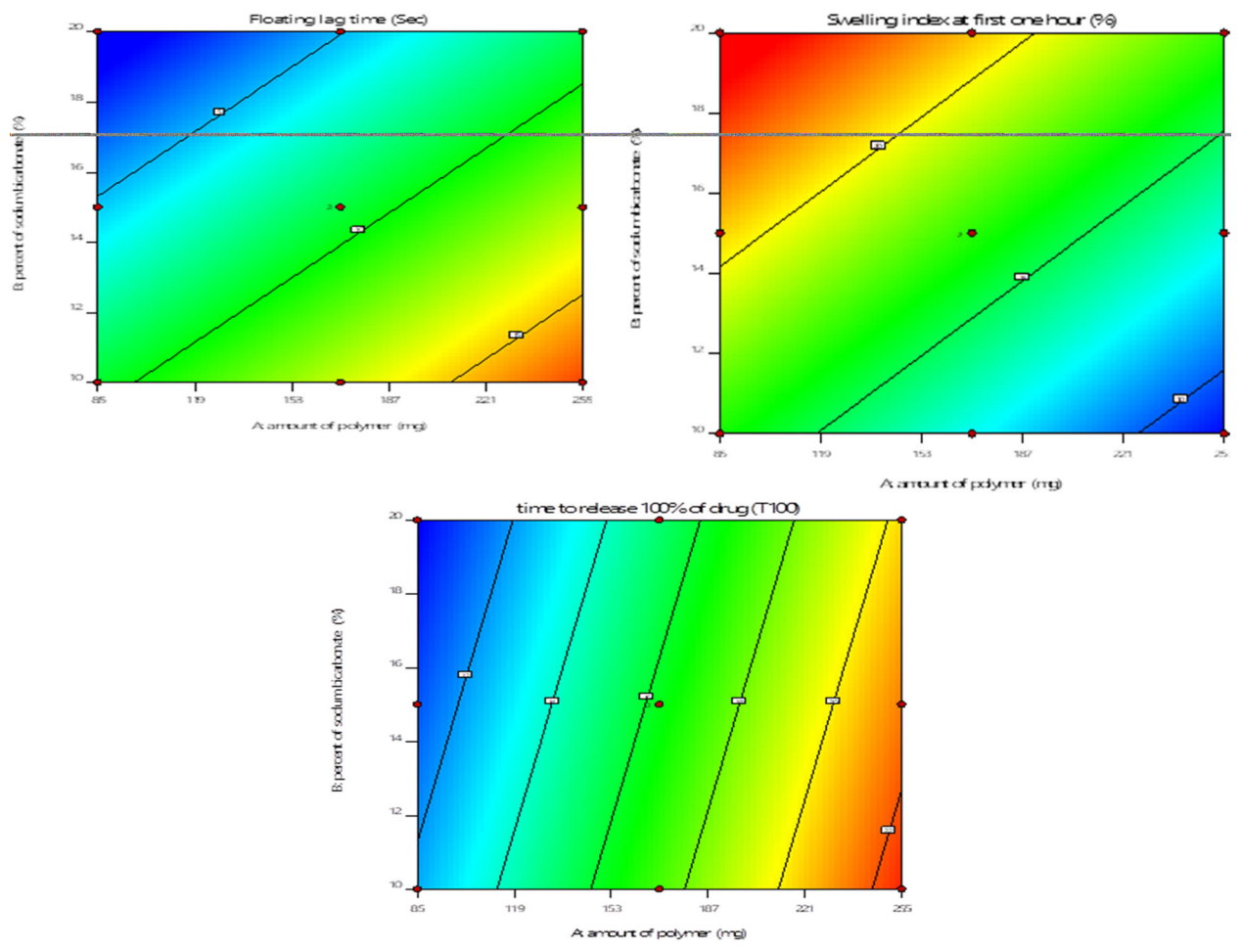


Fig. 2 Contour plot showing the influence of Mimosa gum (2%) (X_1) and sodium bicarbonate (X_2) on Floating lag time (s), swelling index at first 1 h (%), and time to release 100% of drug (T_{100})

Data analysis, optimization, and cross-validation of model

Data analysis

Three responses, i.e., Y_1 (floating lag time), Y_2 (swelling index at 1 h), and Y_3 (T_{100}) were selected for statistical optimization and fitted to linear, interactive, and quadratic models. The summary of statistics was presented in Table 7 and the comparative R^2, adjusted R^2, predicted R^2, PRESS, s.d., F values, and p values were determined using DESIGN EXPERT (Stat-Ease Inc., Minneapolis, USA). A suitable polynomial model for describing the data was selected based on correlation (R^2) and PRESS values. Response Y_1, response Y_2, and response Y_3 followed linear model for Mimosa (2%) based EGFMT. Quadratic models were followed by responses Y_2 and Y_3 respectively for Mimosa (1%) based EGFMT, whereas linear model was followed by Y_1.

The results of the second-order response surface model fitting in the form of ANOVA are given in Table 8 respectively for Mimosa (2%) and (1%) based formulations. These parameters were used to construct the independent variables on the responses.

The F value for the responses, floating lag time (Y_1), swelling index at 1 h (Y_2), and T_{100} (Y_3) were found to be 102.51, 182.29, and 333.4 respectively for Mimosa 2% based EGFMT and 34.41, 233.29, and 95.74respectively for Mimosa 1% based EGFMT, which indicated that the models were significant. The values of Prob>F (less than

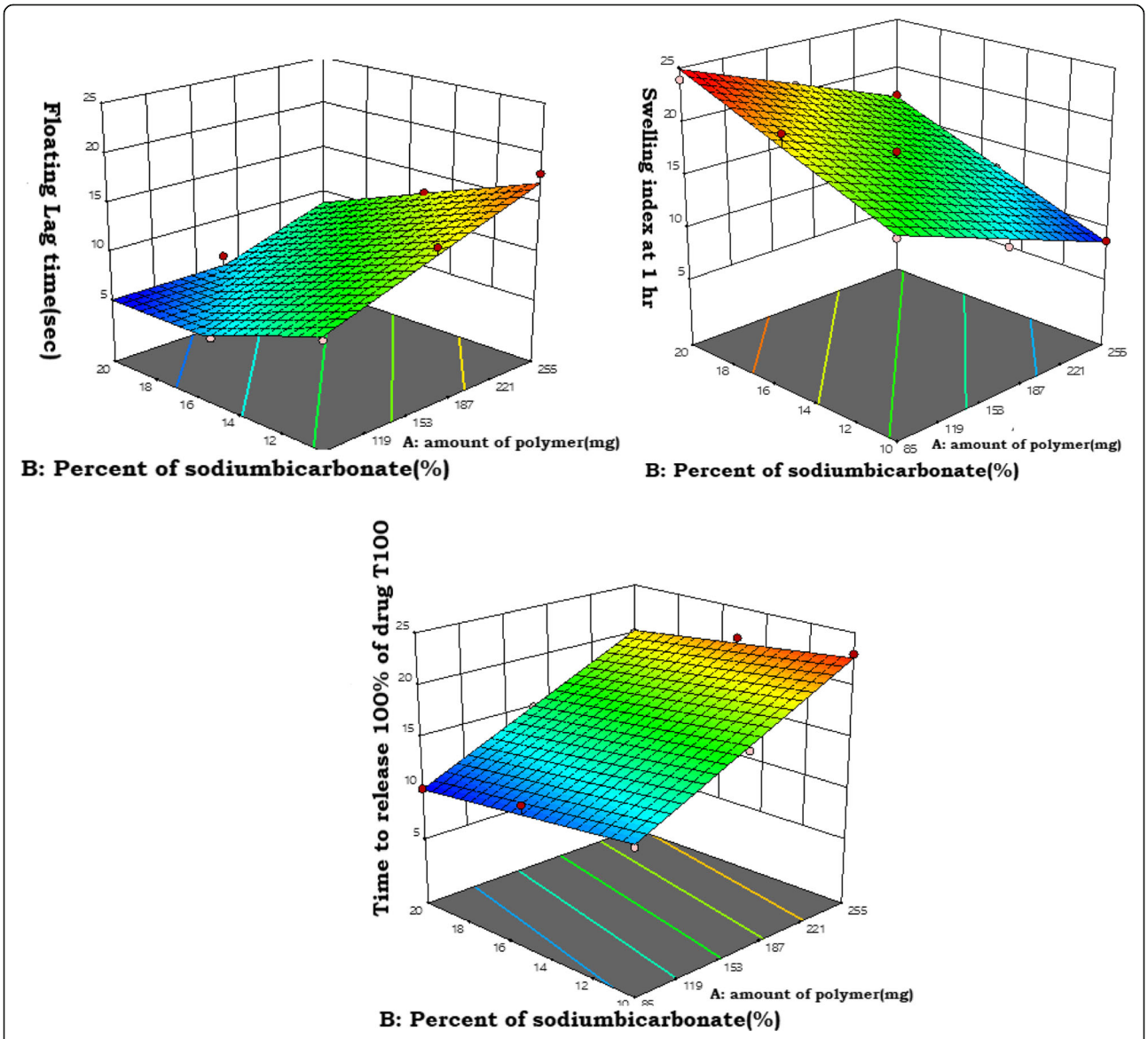


Fig. 3 Response surface plot showing the influence of Mimosa gum (2%) (X_1) and sodium bicarbonate (X_2) on FLT (s), SWI (%), and T_{100}

0.05) for all the responses indicated the significance of the models.

The goodness of fit of the model was checked by the coefficient of determination (R^2). The R^2 values of floating lag time (Y_1), swelling index at 1 h (Y_2), and T_{100} ($Y3$) responses of Mimosa 2% (0.9670, 0.9812, and 0.9896 respectively) and Mimosa 1% (0.9077, 0.9966, and 0.9917 respectively) based formulations indicated a good correlation between the independent and dependent variables. The model was found to be significant with respect to adjusted coefficient of determination (Adj R^2 > 0.9000) values for both polymers. In all the cases, 'Predicted R^2' values were in reasonable agreement with the Adj R^2 values.

The application of response surface methodology yielded the following regression equations which are an empirical relationship between the logarithm values of %DR1 and T_{100}.

For Mimosa 2% based EGFMT:

$$\text{Floating lag time} = 9.10 + 3.83X_1 - 4.17X_2$$

$$\text{Swelling index at 1 h} = 16.77 - 3.92X_1 + 4.20\ X_2$$

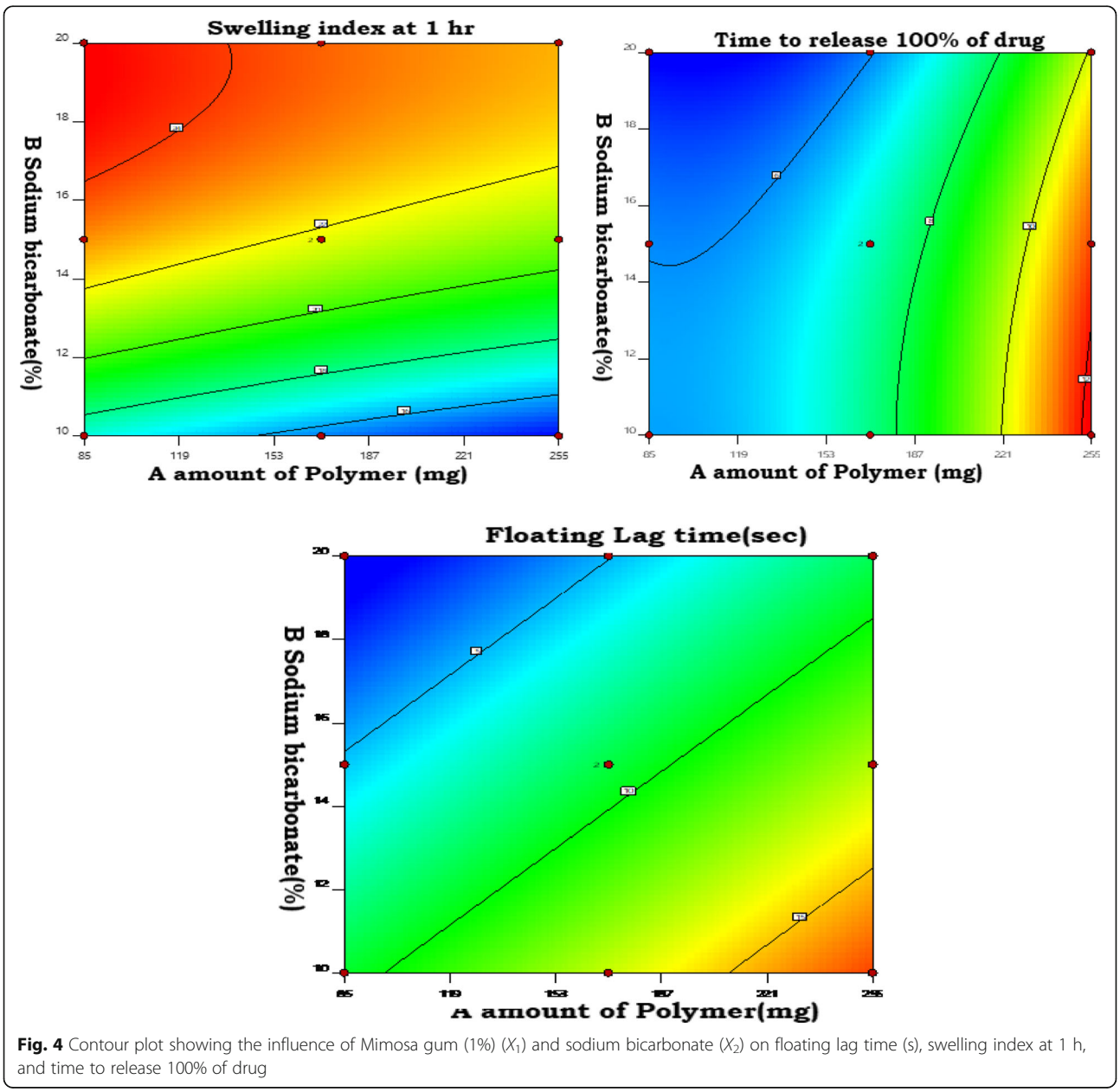


Fig. 4 Contour plot showing the influence of Mimosa gum (1%) (X_1) and sodium bicarbonate (X_2) on floating lag time (s), swelling index at 1 h, and time to release 100% of drug

$$T_{100} = 16.33 + 5.17X_1 - 1.17X_2$$

For Mimosa 1% based EGFMT:

$$\text{Floating lag time} = 6.9667 + 0.037255X_1 - 0.50000X_2$$

$$\text{Swelling index at 1 h} = 21.76 - 1.18X_1 + 4.02X_2 + 0.2500X_1X_2 + 0.1357X_1X_1 - 2.16X_2X_2 - 3.11$$

$$T_{100} = 7.21 + 2.83X_1 - 0.83X_2 - 0.25X_1X_2 + 1.57X_1X_1 - 0.43X_2X_2$$

where X_1 and X_2 are the coded values of the test variables of the polymer quantity and % w/w of sodium bicarbonate respectively.

The detailed summary of results of multiple regression analysis of dependant variables for both polymer grades is shown in Table 10.

The contour plots were built to evaluate the relationship between polymer content and % of sodium bicarbonate and their effect on formulation parameters such as FLT, SWI, and T_{100} for both Mimosa 2% and Mimosa 1% based EGFM T (Figs. 2, 3, and 4). Similarly, response surface plots were generated to determine the role of effect of polymer content and % of sodium bicarbonate on FLT, SWI, and T_{100} for both Mimosa 2% and 1% based EGFMT (Figs. 3 and 5).

Optimization

The higher desirability value indicates the more suitability of the formulation and the optimized formula can directly

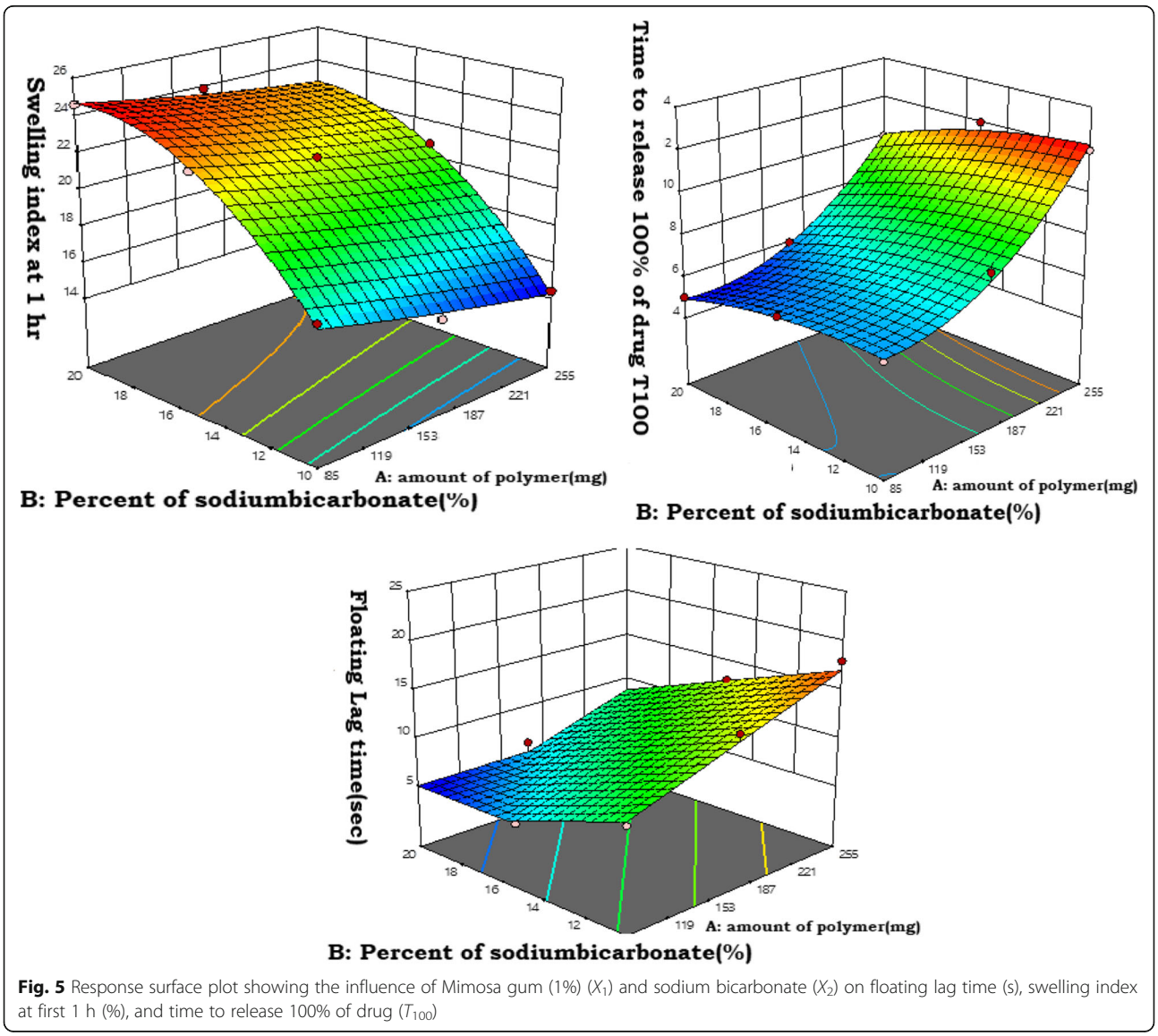


Fig. 5 Response surface plot showing the influence of Mimosa gum (1%) (X_1) and sodium bicarbonate (X_2) on floating lag time (s), swelling index at first 1 h (%), and time to release 100% of drug (T_{100})

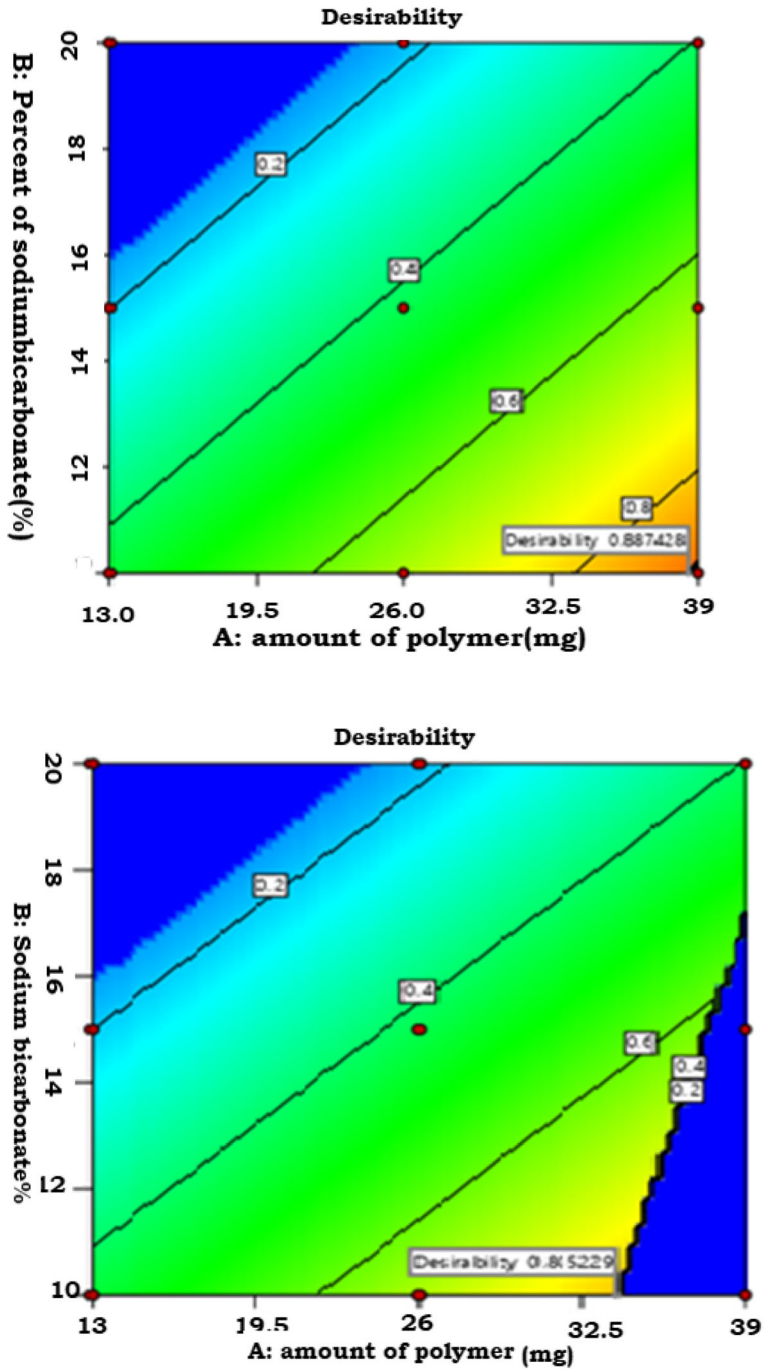


Fig. 6 Desirability plot for Mimosa gum (2%), (1%) based EGFMT

be obtained from the desirability function response surface plots and (or) overlay plots. The desirability function (as shown in Fig. 6) was found to be higher (near to 0.9) for the optimized formula indicating the suitability of the formulations. The optimal values of independent test variables were obtained from the overlay plots (Fig. 7).

Cross-validation of model

The model predicted that the formulation with floating lag time 9.1 s, swelling index at 1 h is 16.77% and T_{100} in 12 h can be obtained using the above optimum concentrations. Hence, formulations were prepared with the above optimized concentrations of polymer and sodium

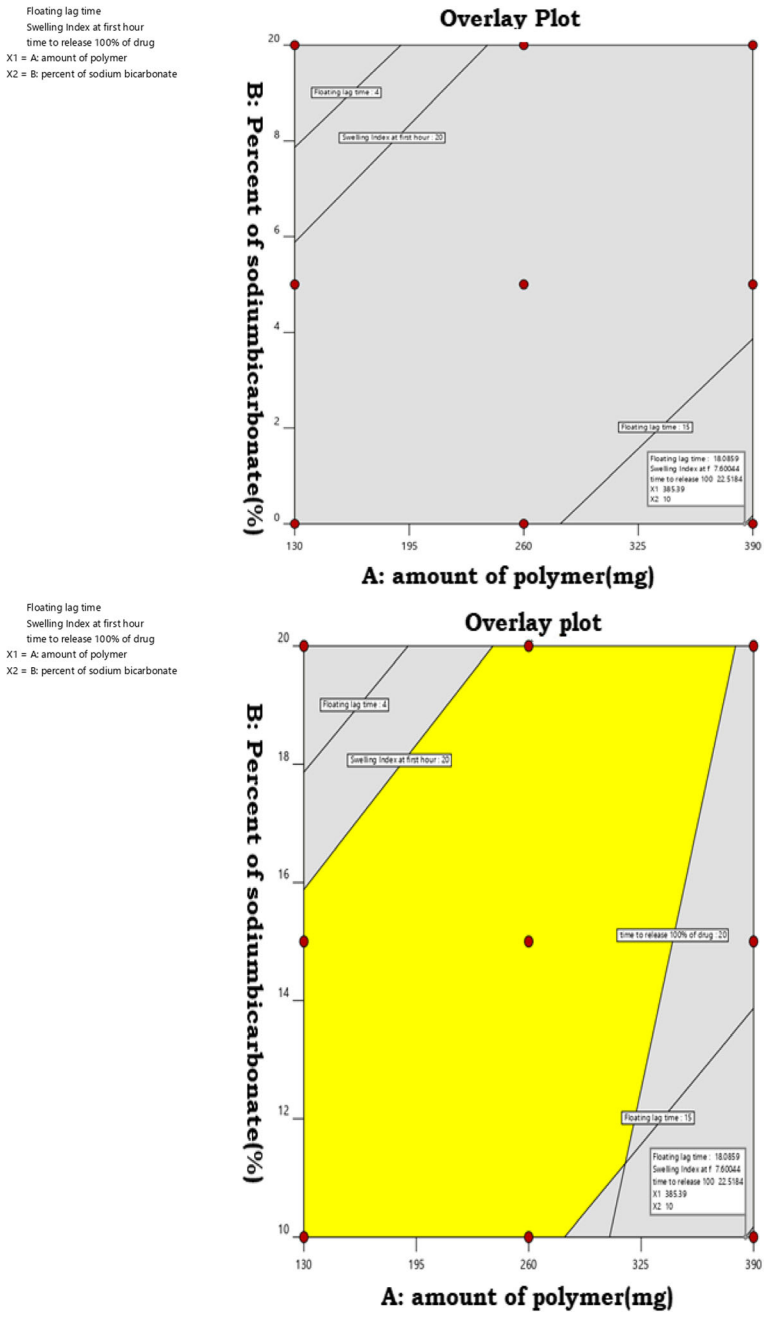


Fig. 7 Overlay plot for Mimosa gum (2%),(1%) based EGFMT

bicarbonate with other ingredients viz. Aerosil and magnesium stearate. The prepared optimized EGFMT fulfilled all the evaluation tests described and the results are shown in Table 11. The floating lag time for *M*(2%)opt was found to be 9.1 s and that of *M*(1%)opt was found to be 10.3 s. Both the optimized formulations floated up to 14 h and 13 h respectively for *M*2%opt and $M1\%_{opt}$.

The dissolution data of optimized EGFMT is represented and comparative dissolution profiles of the optimized EGFMT and theoretical release profile is shown in Fig. 8.

The correlation coefficient values of release order kinetics and release mechanism models along with f_1 and f_2 values are presented in Table 12.

Table 10 Model coefficients of EGFMT

Factor	Coefficient of estimate	*p* value	SE	95% CI Low	95% CI Low	VIF
Mimosa gum (2%)						
Response Y_1 (floating lag time): linear model						
Intercept	9.10 (β_0)	< 0.0001*	0.3063	8.38	9.82	
X_1-Mimosa (2%)	3.83(β_1)	< 0.0001*	0.3954	2.90	4.77	1
X_2-Sodium bicarbonate	− 4.17 (β_2)	< 0.0001*	0.3954	− 5.10	− 3.23	1
Response Y_2 (swelling index): linear model						
Intercept	16.77 (β_0)	< 0.0001*	0.2330	16.22	17.32	
X_1-Mimosa (2%)	− 3.92 (β_1)	< 0.0001*	0.3008	− 4.63	− 3.21	1
X_2-Sodium bicarbonate	4.20	< 0.0001*	0.3008	3.49	4.91	1
Response Y_3 (T_{100}): Linear model						
Intercept	16.30 (β_0)	< 0.0001*	0.16	15.92	16.68	
X_1-Mimosa (2%)	5.17 (β_1)	< 0.0001*	0.21	4.68	5.65	1
X_2-Sodium bicarbonate	− 1.17	0.0007	0.20	− 1.65	− 0.68	1
Mimosa gum (1%)						
Response Y_1 (floating lag time): linear model						
Intercept	5.80 (β_0)	0.0002	0.3767	4.91	6.69	
X_1-Mimosa (1%)	3.17(β_1)	0.0003	0.4863	2.02	4.32	1
X_2-Sodium bicarbonate	− 2.50 (β_2)	0.0013	0.4863	− 3.65	− 1.35	1
Response Y_2 (swelling index): Quadratic model						
Intercept	21.76(β_0)	< 0.0001	0.1889	21.23	22.28	
X_1-Mimosa (1%)	− 1.18(β_1)	0.0008	0.1290	− 1.54	− 0.8251	1.0000
X_2-Sodium bicarbonate	4.02(β_2)	< 0.0001	0.1290	3.66	4.37	1.0000
X_1X_2	0.2500(β_{12})	0.1888**	0.1580	− 0.1887	0.6887	1.0000
X_1X_1	0.1357(β_{11})	0.5477**	0.2069	− 0.4387	0.7102	1.03
X_2X_2	− 2.16(β_{22})	< 0.0001	0.2069	− 2.74	− 1.59	1.03
Response Y_3 (T_{100}): quadratic model						
Intercept	7.21 (β_0)	0.0001*	0.2088	6.63	7.79	
X_1-Mimosa (1%)	2.83(β_1)	0.0001	0.1426	2.44	3.23	1
X_2-Sodium bicarbonate	− 0.833 (β_2)	0.0043	0.1426	− 1.23	− 0.43	1
X_1X_2	− 0.2500 (β_{12})	0.2256**	0.1747	− 0.73	0.23	1
X_1X_1	1.57(β_{11})	0.0023	0.2287	0.93	2.21	1.03
X_2X_2	− 0.428 (β_{22})	0.1342**	0.2287	− 1.06	0.206	1.03

T_{100} time to release 100% of drug, *SE* standard error, *CI* confidence interval, *VIF* variance of inflation factor *Significant ($p < 0.05$); ** not significant ($p > 0.05$)

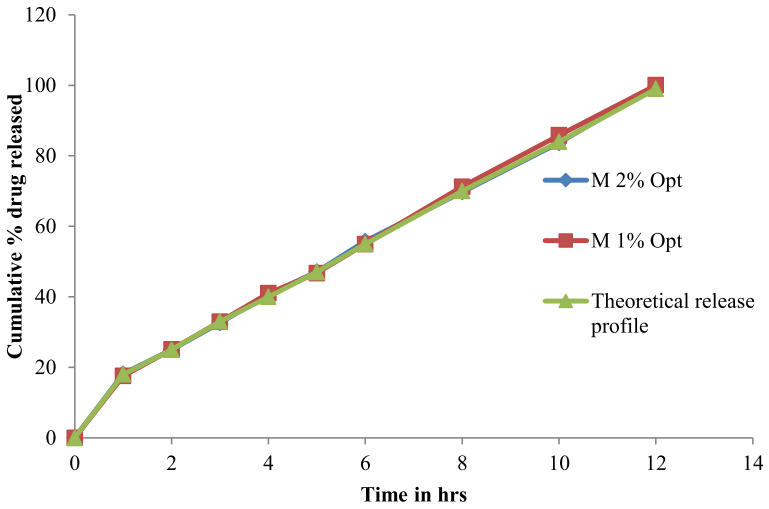


Fig. 8 Comparative dissolution profiles of $M2\%_{opt}$, $M1\%_{opt}$, and theoretical release profile

Upon comparison of the observed responses with that of the anticipated responses, the prediction error was lower than 5.0% (Table 13).

Drug-polymer interaction studies

FTIR The FTIR spectra of pure drug Nizatidine, pure polymers Mimosa (2%), and Mimosa (1%) and their optimized formulations $M2\%_{opt}$ and $M1\%_{opt}$ are shown in Fig. 9.

The FTIR spectrum of Nizatidine showed peak at 3503.74 cm^{-1} due to –OH; 3399.82–3372.73, 3236.89 cm^{-1} due to $-NH_2$ and –NH respectively, 1446.39–1599.98 cm^{-1} due to C=N, 694.88–608.86 cm^{-1} due to C-S, 1326.12 cm^{-1} due to $S(=O)_2$ asymmetric stretching, 1144.28 cm^{-1} due to $S(=O)_2$ symmetric stretching confirming the drug structure.

The FTIR spectrum of Mimosa (2%) showed hydroxyl stretching at 3440.82 cm^{-1}, C-O-C asymmetric stretching at 1289.33 $cm^{-1,}$ and C-O-C symmetric stretching at 1103.89 cm^{-1}.

Table 11 Formulae of optimized EGFMT

Quantity (mg/tablet) ingredients	$M2\%_{opt}$	$M1\%_{opt}$
Nizatidine	85.00	85.00
Mimosa (2%) (X_1)	170	–
Mimosa (1%) (X_1)	–	194.7
Sodium bicarbonate (X_2)	38.25 (15%)	29.08 (10.4%)
Aerosil	2.00	2.00
Magnesium stearate	1.00	1.00
Total	296.25	312
Characteristics		
FLT (s)	9.1	10.3
SWI	16.7	16.3
T_{100}	12	11.039
TFT (h)	14	13
Uniformity of weight[a] (mg)	296.5 ± 0.67	312 ± 1.24
Uniformity of content[b] (%)	100.09 ± 0.25	101.04 ± 1.09
Hardness[c] (kg/cm^2)	4.5	4.6
Friability (%)	0.09	0.01

[a]Mean ± % deviation, $n = 20$
[b]Mean ± s.d., $n = 10$
[c]Mean, $n = 5$

Table 12 Correlation coefficient, f_1, and f_2 values of optimized EGFMT

	$M2\%_{opt}$	$M1\%_{opt}$
Zero-order '*r*' value	0.9952	0.9956
First-order '*r*' value	0.8684	0.8789
Higuchi '*r*' value	0.9757	0.9749
Hixon–Crowell '*r*' value	0.9320	0.9041
Korsmeyer–Peppas '*r*' value	0.9932	0.9945
Korsmeyer–Peppas '*n*' value	0.70	0.71
f_1	0.75	1.30
f_2	97.84	93.58

The FTIR spectrum of $M2\%_{opt}$ showed all the characteristic peaks of Nizatidine with minor shifts indicating the undisturbed drug in the formulation. This spectrum showed alcoholic –OH stretch at 3504.37 cm^{-1}, –NH2 and –NH stretch at 3399.44 and 3236.45 cm^{-1} respectively; C=N stretch at 598.94 cm^{-1}, C-S stretch at 691.88 cm^{-1}, $S(=O)_2$ asymmetric and symmetric stretching at 1326.01 cm^{-1} and 1144.59 cm^{-1} respectively; and C-O-C asymmetric stretching at 1284.25 cm^{-1} and C-O-C symmetric stretching at 1113.43 cm^{-1}.

The FTIR spectrum of $M1\%_{opt}$ showed all the characteristic peaks of Nizatidine with minor shifts in its FTIR spectrum like alcoholic –OH stretch at 3493.82 cm^{-1}, primary and secondary amine (–NH2 and –NH) stretch at 3388.42 and 3237.67 cm^{-1} respectively, C=N stretch at 1589.05 cm^{-1}, C-S stretch at 684.45 cm^{-1}, $S(=O)_2$ asymmetric and symmetric stretching at 1306.26 cm^{-1} and 1132.15 cm^{-1} respectively, C-O-C asymmetric stretching at 1280.28 cm^{-1} and C-O-C symmetric stretching at 1109.16 cm^{-1} confirms the undisturbed drug in the formulation.

DSC analysis The DSC thermograms of pure drug Nizatidine, pure polymer Mimosa gum, and optimized formulations $M2\%_{opt}$ and $M1\%_{opt}$ are shown in Fig. 10.

Nizatidine showed a single sharp endothermic peak at 170.08 °C corresponding to the melting range of Nizatidine. Mimosa gum showed broad endothermic peaks at 77.35 °C and 73.43 °C respectively. Nizatidine melting peak was slightly shifted to left for $M2\%_{opt}$ and $M1\%_{opt}$ at 168.64 °C and to 165.71 °C respectively.

XRD studies X-ray diffractograms of pure drug Nizatidine, polymer Mimosa gum, and their optimized formulations $M2\%_{opt}$ and $M1\%_{opt}$ were shown in Fig. 11.

X-ray diffraction patterns revealed that pure Nizatidine was clearly in crystalline state as it showed sharp distinct peaks notably at 2θ diffraction angles of 5.8, 11.5, 15.8, 17.5, 18.1, 19.2, 19.5, 20.0, 20.5, 21.0, 22.4, 22.8, 23.2, 24.0, 24.5, 26.2, 26.6, 27.2, 30.2, and 32.2° (2θ).

Pure Mimosa gum showed two distinct sharp peaks at 19.2 and 23.4° (2θ) indicating the crystallinity of the polymers.

Formulation $M2\%_{opt}$ showed characteristic peaks of pure drug without shift at 15.8, 18.1, 19.5, 26.2, 27.2, 30.2, and 32.2° (2θ) and some new peaks were appeared at 10.6 and 22.3° (2θ). Intensity of the some of the observed peaks are reduced and shifted slightly.

$M1\%_{opt}$ formulation showed characteristic peaks of pure drug, Nizatidine without shift at 18.1, 21.0, 22.4, and 26.6° (2θ). One peak disappeared at 17.5° (2θ) and some peaks showed lower intensity or shifted slightly.

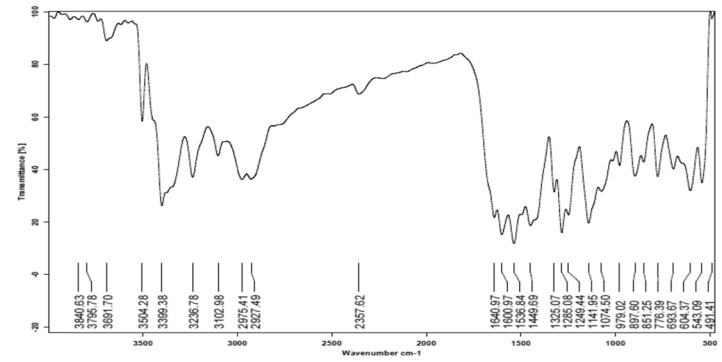
Discussion

The values of angle of repose [34], bulk density, and compressibility index indicated that the Mimosa gum powder has good flow properties and compressibility.

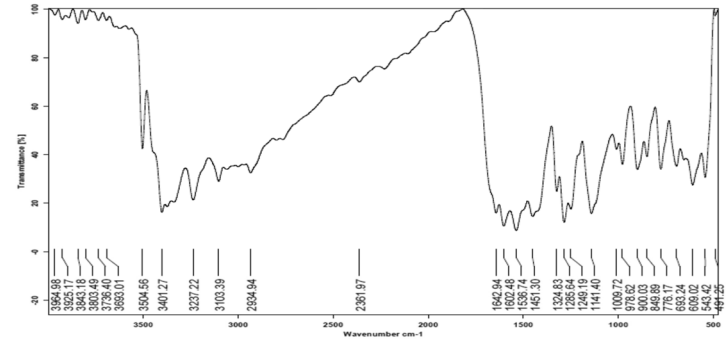
Table 13 Cross-validation of model obtained using experimental and predicted results of both optimized EGFMT

Optimized formulation	Response	Predicted value	Experimental value	% prediction error[a]
$M2\%_{OPT}$	FLT	9.1	9.3	− 2.19
	SWI	16.7	16.8	− 0.59
	T_{100} (h)	12	12.00	0
$M1\%_{OPT}$	FLT	10.3	10.34	− 0.38
	SWI	16.3	16.4	− 0.613
	T_{100} (h)	11.039	12.00	0.00

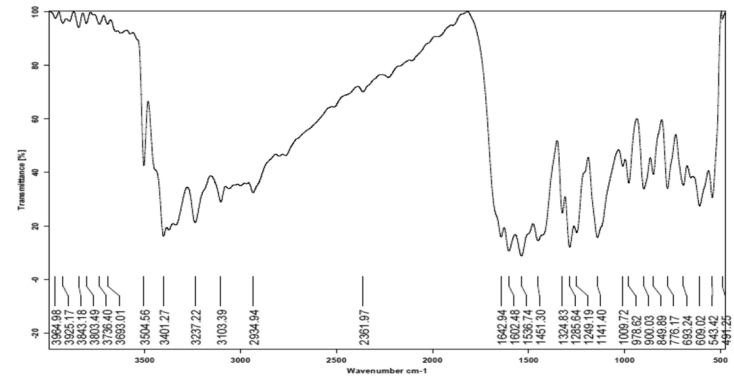
[a]Percent error was calculated using the formula: [(predicted value − experimental value)/predicted value] × 100



(a)



(b)



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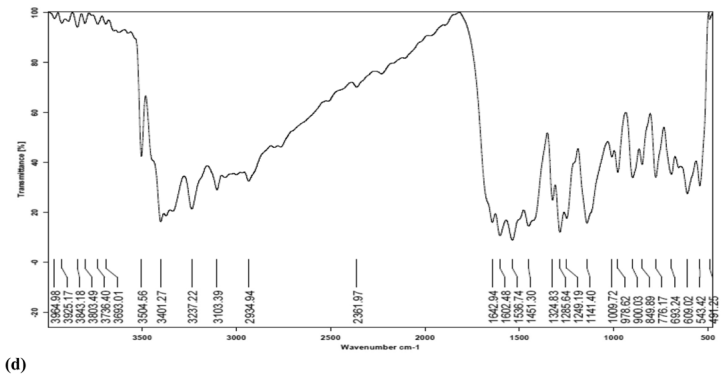

(d)

Fig. 9 FTIR spectra of **a** Nizatidine, **b** Mimosa, **c** M 2%$_{opt}$, and **d** M 1%$_{opt}$

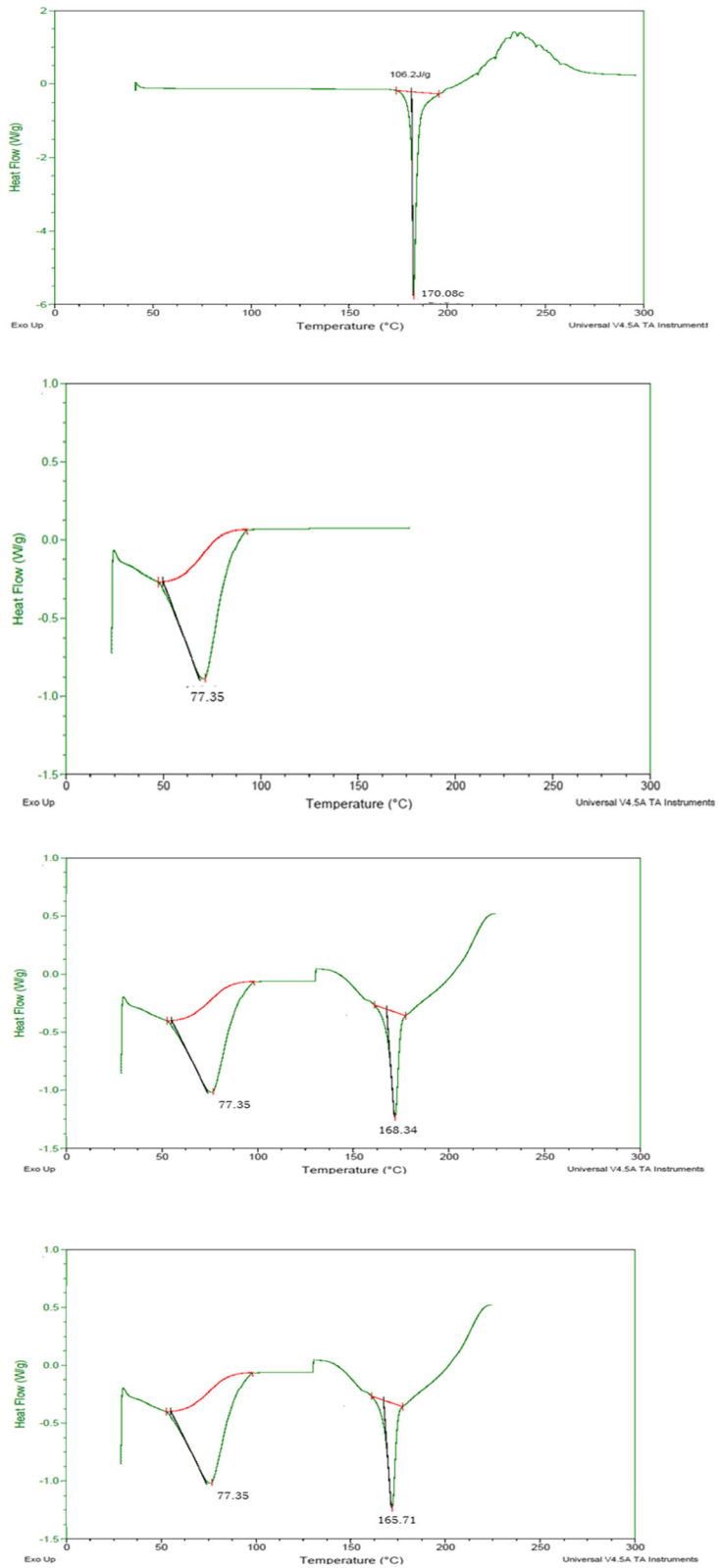

Fig. 10 DSC of **a** Nizatidine, **b** Mimosa gum, **c** M 2%$_{opt}$, and **d** M 1%$_{opt}$

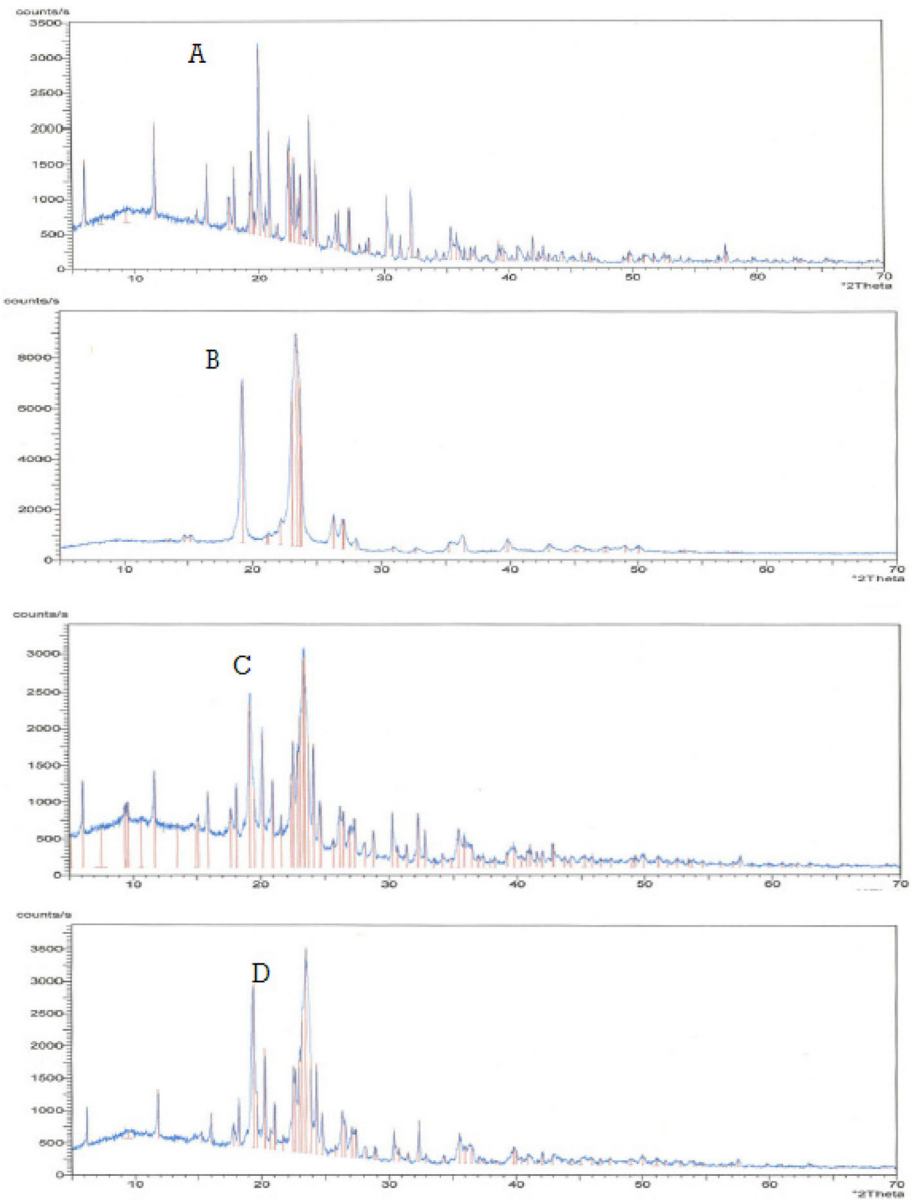

Fig. 11 X-ray diffractograms of **a** Nizatidine, **b** Mimosa gum, **c** M2%$_{opt}$, and **d** M1%$_{opt}$

High value of swelling index revealed the high swelling ability of Mimosa gum.

The swelling ability of any polysaccharide depends upon its water retention capacity [35]. The water absorption capacity of Mimosa gum was found to be 19 ml. The pH of the 1% w/v Mimosa gum solution was found to be 4.8 indicating the gum is weakly acidic in nature. Acidic nature of Mimosa gum may be due to the presence of acetyl groups, which is confirmed by the determination of volatile acidity of Mimosa gum. The volatile acidity of Mimosa gum was found to be 17.2%. It was reported that the viscosity of gum is directly proportional to the volatile acidity of gum. Hence, determination of volatile acidity is a useful tool in the evaluation of the quality of the gum with regard to its viscosity.

The angle of repose values of all drug-polymer physical mixtures were found to be 24–33° indicating the suitability of physical mixtures for direct compression. The floating lag time was increased with increase in the polymer content, whereas decreased with increase in the amount of sodium bicarbonate. This could be due to the entrapment of the generated gas in the polymer hydrogel enabling it to float. These results clearly indicated the influence of the viscosity of the polymer in maintaining the floating of the EGFMT.

The tablets prepared in each batch were found to have uniformity of weight and the percent deviation was found to be complied with compendial standard for uniformity of weight of the tablets. Hardness values for all the prepared tablets were found to be in the range of 4 to 5 kg/cm^2. Friability test is intended to determine the physical strength of the tablets. The friability values of all the prepared tablets were less than 1% which indicated that the test was complied with the official compendial tests for tablets as per IP. The content of each individual preparations was found to be within the limits of 85–115% of the average content indicating the uniformity of content test complies with the official compendial tests for tablets as per IP.

The most important factor influencing the rate of drug release from hydrophilic swellable matrices is drug to polymer ratio. An increase in polymer concentration results in increased viscosity, thicker gel layer with a longer diffusion path. This could cause a decrease in the effective diffusion coefficient of the drug and therefore a reduction in the drug release rate.

Dissolution data indicated that the higher viscosity (or molecular weight) Mimosa (2%) delayed the drug release for extended period of time up to 23 h when compared to lower viscosity (or molecular weight) Mimosa (1%), which controlled the release of the drug up to 12 h only. This behavior could be explained that polymer particles of increasing viscosity (or molecular weight) will swell rapidly and produce swollen particles of smaller volume. The matrices made of particles with higher viscosity grade will contain pores of smaller diameters due to formation of hydrogel with higher gel strength which will slower drug release than those made up of polymer particles with lower viscosity grade [36].

T_{100} values were found to be increased with increasing the polymer content and viscosity (or molecular weight) and decreased with increasing the amount of sodium bicarbonate. These findings indicated substantially slower release with increase in polymer's viscosity (molecular weight). The hydrogel formed during the penetration of dissolution media into the matrix structure consists of closely packed swollen particles. With further increase in polymer amount, thicker gel forms inhibiting dissolution media penetration resulting significant increase in the values of T_{100}.

Increased sodium bicarbonate resulted in relatively higher drug release rates indicated by decreased T_{100} values. The increased amount of sodium bicarbonate caused a large amount of effervescence, which in turn resulted in pore formation, which led to rapid hydration of the polymer matrix and thereby rapid drug release [37].

The significant parameters in the equations can be selected using a stepwise forward and backward elimination for the calculation of regression analysis. However, in the present study, full model having both significant and non-significant p values were used for obtaining dependent variables. Coefficients with one factor indicate the effect of that particular factor, while the coefficients with more than one factor and those with second-order terms represent the interaction between those factors and the quadratic nature of the phenomena, respectively. Positive sign of the term indicates positive (additive) effect, while negative sign indicates negative (antagonistic) effect of the factor on the response.

Main effects of all the selected independent variables like polymer quantity (X_1) and % w/w of sodium bicarbonate (X_2) are highly significant ($p < 0.05$).

Negative and additive effects were observed respectively for polymer (X_1) and sodium bicarbonate (X_2) in case of FLT indicating the increased time with increased polymer content and increased sodium bicarbonate concentration. Swelling index at 1 h indicating the decreased swelling with increased polymer content and increased sodium bicarbonate concentration, whereas reverse situation was observed for T_{100} values, i.e., additive and negative effects for respectively polymer and sodium bicarbonate. This indicated the influence of both polymer and sodium bicarbonate concentrations in achieving the desired drug release, floating lag time, and swelling index.

The variance of inflation factor 5 (VIF) measures the extent to which the variance of particular model coefficient is inflated by the lack of orthogonality in the design [38]. The VIF values for all the models were found to be one, indicating good estimation of coefficient.

From the contour plots, it was observed that increase in the polymer (X1) from 85 to 170 mg and later to 255 mg increased FLT, decreased SWI, and increased T_{100}, i.e., retarded the release of Nizatidine from matrix tablets. This could be due to the increase in resistance of the gel layer to drug dissolution and gel erosion. At a higher polymer level, formation of tightly swollen gel layer caused by more intimate contact in between the particles of Mimosa resulted in decreased mobility of insoluble drug particles in swollen matrices, which lead to decreased release rate.

Additionally, increasing the sodium bicarbonate (X_2) from 10 to 15% and then to 20% decreased FLT, increased SWI, and decreased T_{100}, i.e., enhanced the release of Nizatidine from matrix tablets. The increased amount of sodium bicarbonate caused a large amount of effervescence, which in turn resulted in pore formation, leading to rapid hydration of the polymer matrix and thereby decreased FLT.

The optimized formulation of Mimosa gum (2%) (*M*2%opt) contained 170 mg of polymer and 25.5 mg (15%) of sodium bicarbonate. Similarly, the optimized formulation of Mimosa (1%) (*M*1%opt) contained 255 mg of polymer and 34 mg (10%) of sodium bicarbonate.

The predicted formulations were prepared and compared their dissolution profile with the theoretical profile. The optimized formulations were very close to '0' (< 2) and f_2 values were more than '50' (> 90) indicating the similarity between the optimized formulations and theoretical profile. The results clearly indicated that the optimized formulations followed zero order release kinetics with diffusion mechanism as per the predicted theoretical release rate confirming the suitability of the predicted theoretical release profile.

Lower values of the relative error indicated that there was a close agreement of experimental values with predicted values for both the polymers. This proved the predictability and validity of model and ascertained the effects of polymer and the amount of sodium bicarbonate on drug release.

The FTIR spectra of $M2\%_{opt}$ and $M1\%_{opt}$ showed all the characteristic peaks of Nizatidine confirms the undisturbed drug in the formulation.

Compared to pure drug, the melting peak was broadened to some extent in the formulations which may be due to changes in crystalline form. In addition, the studied polymers were hydrophilic in nature with melting points less than that of Nizatidine. The low melting point of the polymers might have influenced the shift in the melting point of drug in the formulation.

Conclusion

GRDDS of Nizatidine was prepared using Mimosa gum 1% and 2% as rate retarding polymer. The results clearly indicated that the optimized formulations followed zero-order release kinetics with diffusion mechanism as per the predicted theoretical release rate confirming the suitability of the predicted theoretical release profile.

Abbreviations

GRDDS: Gastroretentive drug delivery systems; RSM: Response surface methodology; DSC: Differential scanning calorimetry; EGFMT: Effervescent gastric floating matrix tablets; FLT: Floating lag time; TFT: Total floating time; DE: Dissolution efficiency; MDT: Mean dissolution time; XRD: X-ray diffraction

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Authors' contributions

We declare that this work was done by the authors named in this article: MLS conceived and designed the study and carried out the laboratory work, analyzed the data, and drafted the manuscript. RBJ supervised the work assisted in the data analysis. All authors have read and approved the final manuscript.

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Competing interests

The authors declare that they have no conflict of interest.

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