International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 14, Issue 2, 2022

Original Article

DEVELOPMENT AND EVALUATION OF RAFT FORMING GASTRO RETENTIVE FLOATING DRUG DELIVERY SYSTEM OF NIZATIDINE BY DESIGN OF EXPERIMENT

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Received: 30 Nov 2021, Revised and Accepted: 06 Jan 2022

ABSTRACT

Objective: The current research involves the formulation of a sustained-release gastro-retentive drug delivery system of nizatidine.

Methods: Using 3^3 Box-Behnken designs, about 17 experiments were performed and evaluated for various parameters like physical appearance, pH, *in vitro* gelling study, *in vitro* buoyancy study, measurement of viscosity, density measurement, gel strength, raft resilience, drug content, acid neutralization capacity, *in vitro* dissolution, release kinetics and stability studies.

Results: All the formulations exhibited good viscosity, density less than gastric fluid, gelling capacity retained, and buoyant for 12 h. Drug content ranges from 97.98 to 99.34 %, with a long neutralization period. The buoyancy lag time was found to be in the range of 15.34 to 26.12 sec and the % drug release at 12 h was between range from 85.67 to 99.45, with the highest release exhibited by F3. All formulations displayed zero order *in vitro* drug release>10 h with exceptional buoyancy properties. F3 was the optimized formulation and further subjected to FTIR and DSC study, concluding that compatibility of nizatidine with excipients in the formulation blend. Stability studies show no significant changes.

Conclusion: Results indicate that gastric-floating formulations of nizatidine have the prospective for superior gastric residence time and sustained drug release.

Keywords: Nizatidine, Histamine H2 antagonist, Box-Behnken design, Gel strength, viscosity, Release kinetics

DOI: https://dx.doi.org/10.22159/ijap.2022v14i2.43728. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

INTRODUCTION

Gastroretentive drug delivery systems (GRDDS) are the one that provides an opportunity for the formulation to remain buoyant for an extended time in the gastric region thereby increasing the bioavailability of drugs, especially for absorption window in the upper part of GIT such as the stomach or proximal part of the intestine [1]. Many technological approaches have been made to gastroretentive systems as a mucoadhesive, floating system, magnetic system, ion exchange resin, expandable, unfoldable system, and raft forming system [2].

It has been 50 y raft forming systems available in the market worldwide under various brand names such as Gaviscon. This raft forming system contains sodium alginate, which is the viscous solution at room temperature in a container. When administered orally upon contact with acidic pH of gastric juice, they get rapidly get converted into gel where each portion of liquid swell gets set as layers called raft which float on gastric content [3].

Sodium alginate a nontoxic polysaccharide biocompatible polymer can be successfully utilized in the preparation of gastroretentive systems. The polymer in contact with acidic pH (1.2) of the stomach swells and becomes a non-disintegrable matrix [4]. Xanthan gum a naturally occurring polymer has been added to these gastroretentive systems as it has the tendency to form viscous gel capable of entrapping CO2 bubbles in the matrix and also reduces chances of escaping these bubbles from polymer thus providing property and also drug diffusion channels [5]. Hydroxypropyl methylcellulose (HPMC) a hydrophilic polymer, which exhibit pH-dependent gelling property, can be utilized to make gastroretentive system. The polymer on exposure to acidic pH swells and from stable uniform porous network providing larger surface area contributing predictable and reproducible drug release [6].

Nizatidine belongs to the class of antihistaminic. An H2 receptor antagonist which has ulcer healing properties. The anti-ulcer property of the drug is due to decreased stomach acid secretion in parietal cells. Nizatidine is having an absorption window in the stomach as well as in the upper part of the intestine. The drug needs frequent dosing due to its short half-life (1-2h) due to which the drug is having only 37% percent oral bioavailability. Moreover, the drug is subjected to metabolism in the colonic region. These properties of the drug make it an appropriate choice for preparing a raft-forming gastroretentive system, where the drug release is confined to the gastric region for a longer time in a controlled manner. Thus, it helps to overcome the problem associated with conventional preparations [7, 8].

A 3^3 Box-Behnken Design (BBD) was employed as an experimental design to generate response surface methodology. Nizatidine was used as the model drug. BBD helped select variables and to know the interaction effect of polymers on drug release characteristics. Optimized formulation known as the best fit is obtained by generating quadratic effects polynomial model of formulation components on characteristics of GRDDS.

MATERIALS AND METHODS

Material used

Nizatidine was gifted by Dr. Reddy's lab Ltd., Hyderabad. The sodium alginate (SA) was obtained from Sisco Lab Pvt. Ltd., India. Hydroxypropyl methylcellulose (HPMC K4M) was obtained from ex-gratis by Himedia, India. Xanthan gum, Sodium bicarbonate, Calcium carbonate, and Calcium chloride were obtained from SD fine chem. India. Tri-sodium citrate and methyl and propylparaben were purchased from Gattefosse, Mumbai.

Optimization of formulation variables using box-behnken design

Design of experiments

Design of experiments were done using box Behnken design. It consist of a three-factor three-level design (table 1), which makes a total 17 experimental trial. The obtained responses (table 2) were subjected to a second-order quadratic model, which were confirmed by ANOVA, Lack of fit and multiple correlation coefficient tests furnished by design expert software Stat-Ease Design Expert ® software V8.0.1 [9].

Table 1: The BBD design

Independent variables			**Levels**		
Variable	Name	Units	Low	Middle	High
A	Amount of Sodium alginate	% w/v	1	1.5	2
B	Amount of HPMC K4M	% w/v	0.5	1	1.5
C	Amount of Xanthan gum	% w/v	0.25	0.75	1.25
Dependent variable			**Goal**		
Y1	Buoyancy lag time	Sec	Minimize		
Y2	% drug release at 1 h	%	Minimize		
Y2	% drug release at 12 h	%	Maximize		

Nizatidine: 150 mg/10 ml formulation

Table 2: BBD design and observed response

Run	Factor A alginate	Factor B K4M	Factor C	Response Y1	Response Y2	Response Y3
1	1	0.5	0.75	15.34	26.13	97.26
2	1.5	0.5	1.25	17.65	24.12	98.42
3	1	1	1.25	16.12	21.65	99.43
4	1.5	1	0.75	22.42	20.76	97.34
5	1	1	0.25	16.54	22.45	96.94
6	1.5	1.5	0.25	19.46	15.12	85.67
7	1.5	1	0.75	23.11	19.87	98.12
8	2	1	0.25	26.12	20.06	97.12
9	1.5	0.5	0.25	19.23	24.06	98.23
10	1.5	1.5	1.25	18.12	17.23	90.45
11	1	1.5	0.75	15.68	17.82	87.56
12	2	1	1.25	25.12	18.76	99.45
13	2	1.5	0.75	25.64	15.12	88.76
14	1.5	1	0.75	22.94	20.24	97.78
15	2	0.5	0.75	24.35	22.94	97.86
16	1.5	1	0.75	22.54	20.55	97.45
17	1.5	1	0.75	23.28	20.11	98.34

Preparation of in situ gel formulation of nizatidine

The dispersion of known quantity of sodium alginate and xanthan gum dispersed in deionized water along with tri-sodium citrate 0.3 % w/v and were mixed and maintained at 90 °C with constant stirring (Remi Magnetic Stirrer with Hotplate-1MLH) until a homogeneous viscous liquid was obtained. The contents cooled to 40 °C followed by $CaCl_2$ and Methyl and propylparaben were then added. The aqueous HPMC K4M solution was added to Nizatidine with continuous stirring. At 40 °C, both solutions were mixed followed by the addition of Calcium carbonate, sodium bicarbonate with continuous stirring. The mixture was sonicated for 15 min, pH adjusted to 5.5-6.5 using 0.1N NaOH solution [10].

Evaluation of nizatidine in situ gel RAFT formulation

Physical appearance and pH

All of the formulas were physically examined using a visual method against a dark and white background. The pH was measured at room temperature with a digital pH meter that had previously been calibrated [14].

***In vitro* gelling study**

The *in vitro* gelling study was carried out by placing 1 ml of the prepared formulation into a measuring cylinder containing 10 ml of the 0.1 N HCl, pH 1.2 as gelation solution maintained at 37±0.5 °C. The time taken for the formed gel to dissolve were observed visually. The experiment was repeated in triplicate [11, 14].

***In vitro* buoyancy study**

In order to conduct an *in vitro* buoyancy test, 10 ml of the raft formulation was placed in a watch glass. The solution and the watch glass were placed in a USP dissolution apparatus Type II containing 500 ml of dissolution media (0.1 N HCl, pH1.2) and kept at 37±0.5 °C and 50 rpm. The amount of time it takes the gelled mass to move upward (floating lag time) and the amount of time it stays afloat (total floating time) were recorded. The experiment was carried out three times [11, 14].

Measurement of viscosity

The viscosity of the prepared formulations was determined using Brookfield Digital Viscometer. The sample was sheared at a constant rate of 100 rpm using the spindle. The average of two readings was used to calculate the viscosity. The rheological data were analyzed by using Farrow's equation [11, 14].

Farrow's equation:

$$\log \log D = N \log \log S - \log \log \eta$$

Density measurement

The water displacement method was used to estimate the density of the generated in-situ gel. To transform the formulation into the gel, 10 ml of the formulation was taken and 20 ml of 0.1 N HCl, pH1.2 was added. The excess HCl was then removed, and the starting weight of the gel was recorded. Now, the gel was placed in a 50 ml measuring cylinder (starting volume), and water was added up to the 50 ml mark, with the volume of water in the presence of the gel being recorded. The volume of gel was calculated by comparing the volume of water with and without gel [14].

Gel strength

A modified rheometer was used to determine the gel strength. The formulations were placed in tubes, which were subsequently immersed in a beaker containing 0.1 N HCl at pH1.2 and kept at 37±0.5 °C. The rheometer was filled with the cylindrical gels, which rose gently as the probe was pushed through the gel. The load on the probe was determined as a function of the probe's depth of immersion beneath the gel surface [14].

Raft resilience

The goal of this test was to determine the raft's durability under more rigorous movement circumstances. Rafts were first created in glass jars by adding liquid product 0.1 M HCl and keeping the temperature at 37 °C. To replicate gastric agitation, the generated raft was transferred to jars that were capped and placed in a tumble

mixer set to revolve at 20 rpm. The rafts were visually inspected for gel size and coherence until no longer detectable rafts could be found. For visual inspection, a raft was defined as two or more floating gels with a diameter of at least 15 mm. The last time a raft was seen was used to determine raft resilience [12, 13].

Drug content

To determine the amount of nizatidine in the formulation, combine 10 ml in-situ gel (equal to 150 mg Nizatidine) with 30 ml methanol in a 100 ml volumetric flask and shake for 30 min on a rotary shaker. pH 1.2 was added to the 0.1 N HCl to get the final volume to 100 ml. After 15 min of sonication, the solution was filtered through Whatman filter paper and the absorbance was measured at 314 nm using 0.1 N HCl, pH 1.2 as a blank [14].

Acid neutralization capacity

The ability of the Nizatidine raft formulation to hold the antacid and provide an antacid reservoir property was determined by its acid neutralization capacity. Two flasks with a size of 500 ml were used. 1M HCL was added to one flask with deionized water, while 0.5M NaOH was added to the other flask. Both flasks were kept at 37 °C. To make a raft, 5 ml of the prepared formulation was poured in 0.1N HCL. The dried and powdered raft was centrifuged. Take a powdered raft that has been tittered against reagent B and placed in reagent A. The changes in pH were measured using a pH meter. The acid-neutralizing capability was calculated using the following equation [15].

$$\mathrm{ANC} = \mathrm{V} - \mathrm{T} \times 0.5 \times \frac{\text{total mass of the raft gel}}{\text{weight of the sample (mg)}}$$

Where V is the volume (ml) of HCl, and T is the volume (ml) of titer.

***In vitro* release studies**

The dissolution of Nizatidine from in situ gel raft system and the marketed formulation was estimated using USP dissolution test apparatus II, at 37 °C and 50 rpm speed using 900 ml of 1/10 N HCl corresponds to pH 1.2 as dissolution medium (DM). About 10 ml of the formulation was taken onto watch glass placed into a dissolution vessel without many disturbances. Samples were drawn at a preset time interval and the equivalent amount replenished with fresh DM. The samples were evaluated at 314 nm using the UV spectroscopic method [16].

Drug release kinetic analysis

The mechanism of drug release was analyzed by fitting dissolution data into various kinetic models. The release of Nizatidine from in situ gel raft system was evaluated by the curve fitting method [17, 22].

Fourier transformer infrared spectroscopy

Fourier Transform Infrared Spectroscopy (FTIR) spectra of pure drug, excipients, and physical form of raft system were recorded over a range of 4000-400 cm-1 to investigate any possible interactions between the drug and other excipients. Ingredients were combined with 500 mg of potassium bromide powder of IR grade and then compacted into a disc under pressure.

Differential scanning calorimetry (DSC)

To examine any possible drug-excipient interaction, differential scanning calorimetry tests of pure Nizatidine, sodium alginate, xanthan gum, HPMC K4M, physical mixture, and physical form of ideal raft system were done.

Short term stability

Stability studies were carried out at 3 different conditions (i.e., 25±2 °C, 60%±5; 30±2 °C, 65%±5; and 40±2 °C, 65%±5) and were inspected at regular time intervals [18].

Statistical evaluation

Statistical optimization of the formulation was done using Stat-Ease Design Expert ® software V8.0.1 (Stat-Ease, Inc., USA). [19]

RESULTS AND DISCUSSION

Design of experiments

Table 3: Regression equation of responses

Response	Regression equation
Y1	22.81+4.69 A+0.29 B–0.54 C-2.49 B^2–1.77 C^2
Y2	20.41–1.40 A–3.99 B
Y3	98.00–4.92 B+1.22 C+1.15 BC–4.97 B^2

The quantitative effect of the amounts of sodium alginate (A), HPMC K4M (B), and Xanthan gum (C) and their interaction on buoyancy lag time (Y1), percent drug release at 1h (Y2), and percent drug release at 12 h is shown by these equations (Y3). The effect of these factors on the replies Y1, Y2, and Y3 is related to the coefficients of A, B, and C. Interaction terms and quadratic relationships are represented by coefficients with more than one-factor term and those with higher-order terms, respectively. A synergistic effect is represented by a positive sign, while an antagonistic effect is represented by a negative sign. To fit the data to the quadratic model, a backward elimination approach was used. The statistical significance of all three polynomial equations was discovered. (P>0.005), (table 3 fig. 1).

Design Summary

File Version	8.0.1.0		
Study Type	Response Surface	Runs	17
Design Type	Box-Behnken	Blocks	No Blocks
Design Model	Quadratic	Build Time (ms)	48.95

Factor	Name	Units	Type	Subtype	Minimum	Maximum	-1 Actual	+1 Actual	Mean	Std. Dev
A	Amount of sodium alginate	% w/v	Numeric	Continuous	1.00	2.00	1.00	2.00	1.50	0.34
B	Amount of HPMC K4M	% w/v	Numeric	Continuous	0.50	1.50	0.50	1.50	1.00	0.34
C	Amount of Xanthan gum	%w/v	Numeric	Continuous	0.25	1.25	0.25	1.25	0.75	0.34

Response	Name	Units	Obs	Analysis	Minimum	Maximum	Mean	Std. Dev.	Ratio	Trans	Model
Y1	Buoyancy lag time	sec	17	Polynomial	15.34	26.12	20.8035	3.72619	1.70274	None	RQuadratic
Y2	% Drug release at 1h	%	17	Polynomial	15.12	26.13	20.4112	3.04232	1.72817	None	RLinear
Y3	% Drug release at 12 h	%	17	Polynomial	85.67	99.45	95.6576	4.45736	1.16085	None	RQuadratic

Fig. 1: The summary of box behnken design

Response 1: (Y1) buoyancy lag time

Buoyancy lag time is a crucial parameter for assessing the in situ gel raft systems. Effervescent preparations will have a better potential for improved buoyancy. The gas generating floating system of nizatidine show floating lag time ranging between 22-165 s [20].

A shorter lag time is preferred since a long lag time might lead to system failure due to unforeseen or inadvertent quick gastric clearance caused by the stomach's peristaltic action and forced gastric housekeeping waves. Using perturbation, contour, and 3D response surface plots, the influence of the primary and interacting effects of independent factors on the buoyancy lag time was

explained. The primary effects of A, B, and C on the buoyancy lag time are shown in the perturbation plot (fig. 2). (Y1). This diagram clearly illustrates that A has the greatest and most significant impact on Y1, followed by C and B, which have a little impact on Y1. 3D response surface plots and accompanying contour plots were used to further investigate the relationship between the dependent and independent variables. Fig. 3 depicts the effect of A and B on buoyancy lag time at a fixed level of C. The mathematical model for buoyancy lag time (Y1) was significant with an F-value = 363.29 implying that model is significant (fig. 2, 3, and 4).

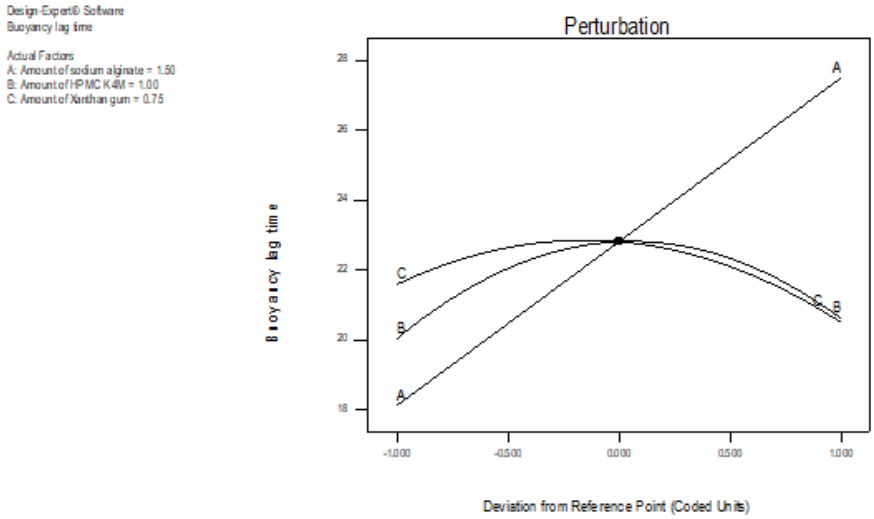

Fig. 2: Perturbation plot showing the effect of A, B, and C on buoyancy lag time

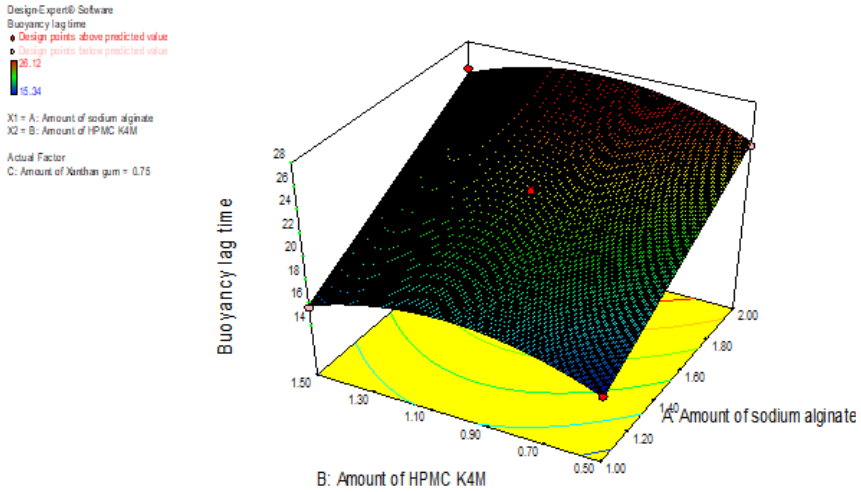

Fig. 3: Response surface plot indicating the effect of the amount of sodium alginate and amount of HPMC K4M on buoyance lag time at fixed C

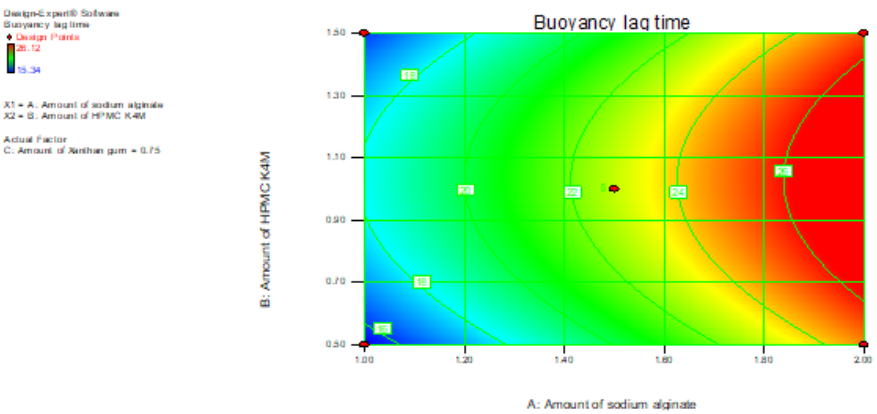

Fig. 4: Contour plot indication the influence of SA and HPMC K4M on buoyance lag time at a fixed level of C

Response 2: (Y2) Percent drug release at 1h

The quadratic model was generated to show that the amount of Sodium alginate (factor A) and amount of HPMC K4M (factor B) have a major effect on the percent drug released within 1h. The percent drug release by end of the first hour was between 15.12 to 26.13 %. The influence of the main and interactive effects of independent variables on percent drug release at 1h was elucidated using the perturbation, contour, and 3D response surface plots. (fig. 5, 6, and 7). The rapid release could be partially attributed to the fact that 0.1 N HCl (pH 1.2) would ensure a sink condition for the dissolution of Nizatidine. Among the two factors modeled, the effect of sodium alginate and HPMC K4M was found to have a negative influence on the burst effect, while xanthan gum was found to have a positive influence on the same. At low levels of A, Y2 increased from 17.82 to 26.13 %. Similarly, at high levels of A, Y2 increased from 15.12 to 22.94 %. At low levels of C, Y2 increased from 15.12 to 24.06 %. Similarly, at high levels of C, Y2 increased from 17.23 to 24.12 %. The theoretical (predicted) values and the observed values were in reasonably good agreement. The mathematical model generated for percent drug release at 1h (Y2) was found to be significant, with F value 208.29, implying that the model is significant [20].

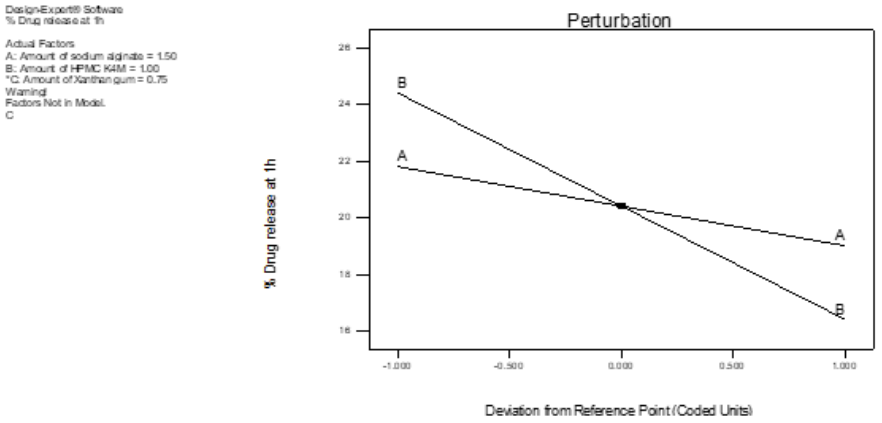

Fig. 5: Perturbation plot indicating the effect of A and B on % drug release at 1h

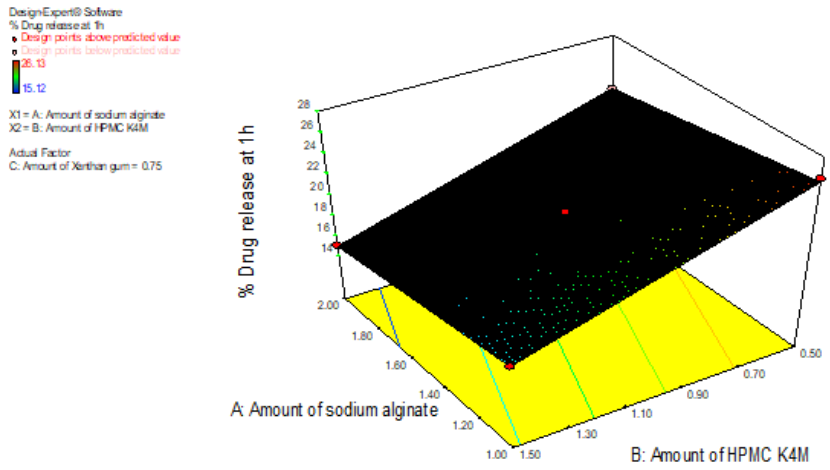

Fig. 6: Response surface plot showing the influence of the amount of sodium alginate and amount of HPMC K4M on percent drug release at 1h at fixed C

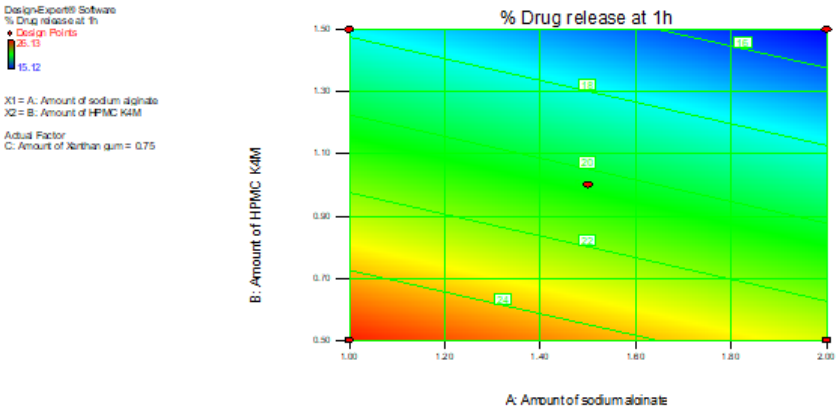

Fig. 7: Contour plots indicating the effect of the amount of SA and amount of HPMC K4M on % drug released at 1h at a fixed level of C

Response 3 (Y3) the percent drug release at 12 h

The percent drug released at 12 h ranged between 85.67 to 99.45 (table 2). The incorporated polymers can retard the release of the drug by the end of 12 h.). The influence of the main and interactive effects of independent variables on percent drug release by the end of 12 h was further elucidated using the perturbation, contour, and 3D response surface plots. The quadratic model revealed that the amount of HPMC K4M and amount of xanthan gum possess a significant effect on the percent drug released at 12 h. As increased concentration, these polymers lead to reduced free mobility and free assessable diffusional volume of the drug through raft structure and retarding release of the drug [21]

The predicted and obtained values were in close accord. The mathematical model was significant with an F-value = 356.64, indicating that the model is significant (fig. 8, 9, and 10).

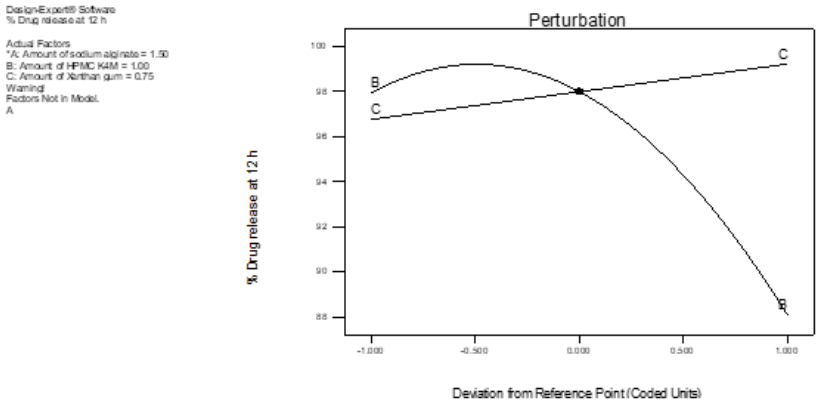

Fig. 8: Perturbation plot showing the effect of B and C on percent drug release at 12h (Y3)

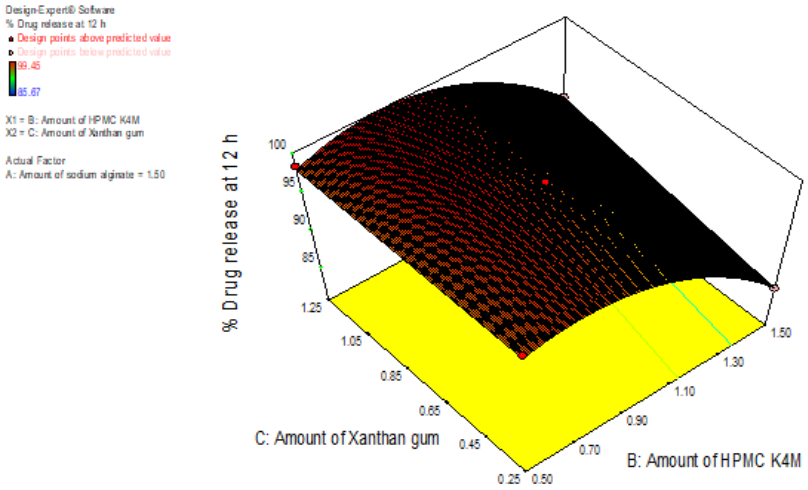

Fig. 9: Response surface plot showing the influence of the amount of HPMC K4M and xanthan gum on percent drug release at 12 h at a fixed level of A

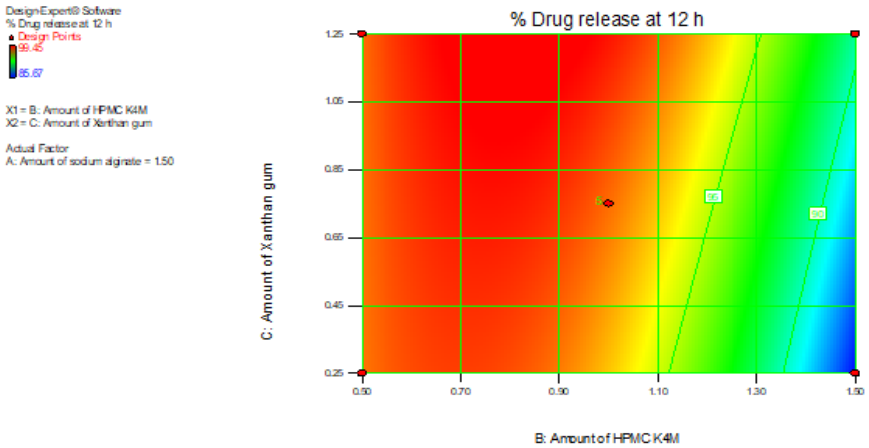

Fig. 10: Contour plot indicating the effect of HPMC K4M and xanthan gum on percent drug release at 12 h at a fixed level of A

Optimization by desirability function

To optimize the three responses at the same time, an optimization process was carried out using the desirability function. The responses were converted into the desirability scale as follows: buoyancy lag time (Y1), percent drug release at 1h (Y2), and cumulative percentage of drug release at 12 h (Y3). Y1 and Y2 needed to be lowered, while Y3 needed to be maximized. Individual desirability functions were generated using Ymax and Ymin as the highest goal function (D) for each response. Finally, the global desirability value was derived by using the Design-Expert programmer to combine the individual desirability function as the geometric mean of an extensive grid search and a feasibility search over the domain. At A: 1% w/v, B: 1.25 % w/v, and C: 1.25 % w/v, the maximum function value was reached, with a D value of 0.912. Three batches of formulations with the optimum composition were prepared, and the three responses for each formulation were analyzed to confirm the model's capability for prediction. The experimental values were found to be extremely near to the predicted values, showing that the Box–Behnken design combined with a desire function was successful in evaluating and optimizing the Nizatidine in situ gel raft system. Following three batches were taken as optimized formulations for further detailed study (table 4).

Table 4: Optimized values obtained by desirability function

Independent variable	Nominal values	Predicted			Observed			
		Buoyancy lag time (Y1) (sec)	Percent drug release at 1h (Y2)	Percent drug release at 12 h (Y3)	Batch	Buoyancy lag time (Y1) (sec)	%drug release at 1h (Y2)	% drug release at 12h (Y3)
Amount of Sodium alginate (A)	1 % w/v	15.3401±0.56	19.8344±1.24	96.1468±0.95	1	15.82±0.72	19.742±0.34	96.98±0.16
Amount of HPMC K4M (B)	1.25 % w/v				2	16.12±1.82	20.785±0.11	96.12±0.85
Amount of Xanthan gum (C)	1.25 % w/v				3	15.53±0.36	20.654±0.73	97.12±0.61

(All the measurements were performed in triplicate and values were expressed as mean±SD, n=3)

Evaluation

The formulations appeared off-white, with pH ranging between 7–8 (table 5). The gelling efficiency of formulations shows that the immediate gelation and gel structure were retained for about 12 h with gelation time<10 s (table 5). The *in vitro* buoyancy results show that formulations displayed minimum floating lag time and remained buoyant for about 12 h (table 5). A shorter lag time is preferred, as extended lag time would ultimately lead to failure of the system arising from unexpected and swift gastric clearance by the peristaltic action of the stomach.

The density of all formulations was<0.82 g/cm^3, which is the required value for gastric fluids (table 5). The gel strength ranged between 8.97 to 9.21 g/cm^2 (table 5). The rheological studies show noticeable amplification in viscosity with the rise in the number of polymers (table 5).

The percent drug concentration ranged between 98.96±0.37 to 99.55±0.19 %, which indicates uniform drug distribution.

Fourier transform infrared spectroscopy

The major IR peaks of Nizatidine were observed at 3502.85 cm^{-1} due to–OH; 3419.90–3369.75, 3244.38 cm^{-1} due to–NH2 and–NH respectively, 1446.66–1593.25 cm^{-1} (C=N), 688.61–597.96 cm^{-1} (C-S), 1317.43 cm$^{-1,}$ and 1155.40 cm^{-1} (SO2 stretching). In a physical mixture, the appearance of the major peaks of the drug without any vibration indicates the compatibility of the drug with excipients (fig. 11).

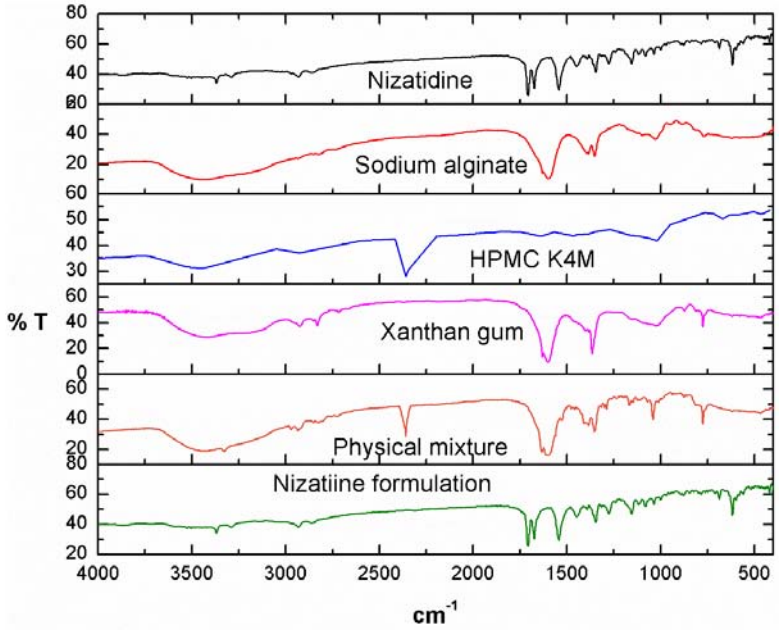

Fig. 11: FTIR spectra of pure Nizatidine, excipients, physical mixture, and Nizatidine raft system

Table 5: Evaluation of floating in-situ gel

Formulation	pH	Mean *in vitro* gelation time (sec)	Mean floating lag time (sec)	Floating duration (h)	Mean density (g/cm3)	Mean gel strength (g/cm2)	Viscosity (cps)	Drug content (%)
F1	7.12±0.56	6	15	>12h	0.812±0.11	9.13	143	99.34±0.13
F2	6.89±0.28	7	16	>12h	0.793±0.23	8.97	145	98.96±0.37
F3	7.34±0.73	6	17	>12h	0.762±0.17	9.21	139	99.55±0.19

(All the measurements were performed in triplicate and values were expressed as mean±SD, n=3)

Differential scanning calorimetry

The DSC curve of Nizatidine displayed a single sharp peak at 133.8 °C corresponding to the melting point (fig. 12). The DSC of sodium alginate displayed a broad endotherm at 71.4 °C, which is attributed due to water loss, and an endothermic peak at 345.5 °C. HPMC K4M exhibited a broad exothermic peak at 321.9 °C. Xanthan gum exhibited an exothermic peak at 71.4 °C and a broad endothermic peak at 345.5 °C. The physical mixture shows an endothermic melting peak of Nizatidine at 133.8 °C. The optimized formula does not show the characteristic endothermic peak of Lafutidine which might indicate that Lafutidine has formed an in-situ gel with the selected excipients.

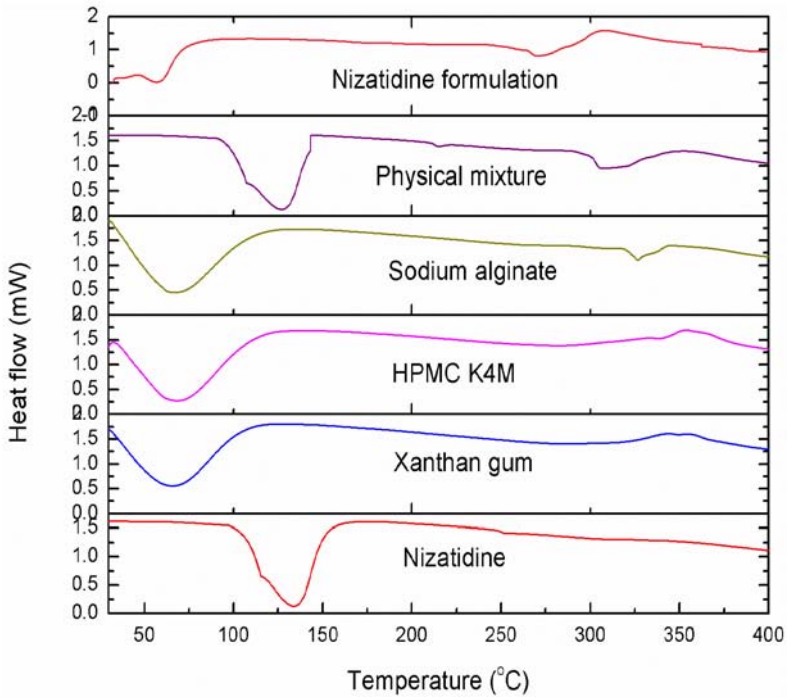

Fig. 12: DSC thermograms of pure nizatidine, excipients, physical mixture, and Nizatidine raft system

Table 6: Raft resilience measurements

S. No.	Formulation	Raft resilience (min)	
		Median	Range
1	F1	26	22-34
2	F2	25	20-31
3	F3	24	19-28

Raft resilience

Table 6 displays the median and range of the raft resilience values for all three formulations. As expected, all the formulations have shown the resistance to break up under the conditions of movement for a longer period. This information will be the basis for the raft strength.

Acid neutralization capacity (ANC)

All the formulations displayed similar ANC values (8). An efficient raft formulation must possess a higher ANC value and longer neutralization durations. The neutralization profile was used to test the raft forming system's ability to neutralize the acid passing through it. The neutralization period of each formulation was determined, and the results revealed that all formulations had the longest neutralization duration.

***In vitro* release studies**

The drug release of all three floating raft compositions was evaluated *in vitro*. The findings are summarized in table 7. (fig. 13). Increases in polymer concentration resulted in a considerable reduction in drug release rate and amount. This is due to the polymeric system's higher density, which causes the drug molecules to travel a longer diffusional path. It was also discovered that the drug release was rapid in the beginning, but that as time went on, the release became more moderate. Furthermore, when the amount of xanthan gum in the gelling system increased, so did the drug release. A rise in HPMC K4M concentration produced a similar effect.

Drug release kinetic analysis

The curve fitting method was used to determine the release of Nizatidine from the raft system. It is clear from the data that in the case of zero-order kinetics, the regression coefficient value is closer to unity (table 8). As a result, it can be concluded that the dissolution rate remains constant over time. Higuchi's model demonstrated good linearity in the drug release plot, indicating that the drug release is regulated by the matrix diffusion process (fig. 14).

Table 7: *In vitro* drug dissolution

Time in h	% Cumulative drug release nizatidine raft system			
	Marketed sample (mean±SEM)	F1 (mean±SEM)	F2 (mean±SEM)	F3 (mean±SEM)
0.5	59.54±2.26	8.98±0.98	7.79±0.86	8.64±0.92
1	73.54±1.18	15.56±2.13	14.93±0.76	15.98±1.12
2	91.74±2.18	23.21±0.66	24.78±1.17	24.34±1.74
3	98.99±1.74	32.72±1.23	33.36±1.63	33.12±1.43
4	99.12±1.68	42.87±1.79	43.65±2.28	43.12±2.11
5	99.34±1.44	55.34±2.11	56.87±1.15	54.23±0.72
6	99.45±1.26	67.86±0.96	66.86±2.06	67.12±2.02
9	99.65±0.93	83.35±1.33	84.98±1.66	84.83±1.72
12	99.78±0.34	98.76±2.11	97.98±0.94	99.34±1.88

(All the measurements were performed in triplicate.

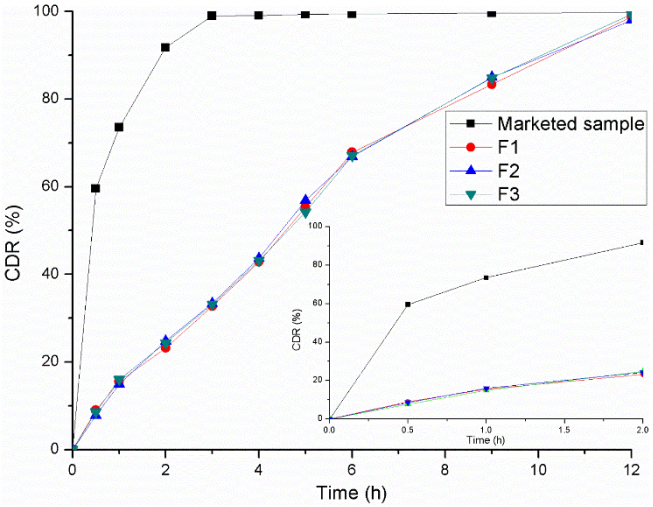

Fig. 13: The dissolution profile of optimized formulations

Table 8: Release kinetics of optimized formulation of nizatidine

Formulation code	Zero-order		First-order		Higuchi		Korsmeyer-Peppas	
	R2	N	R2	n	R2	n	R2	N
F3	0.97022	8.403	0.8124	-0.1544	0.9571	30.624	0.9121	80.622

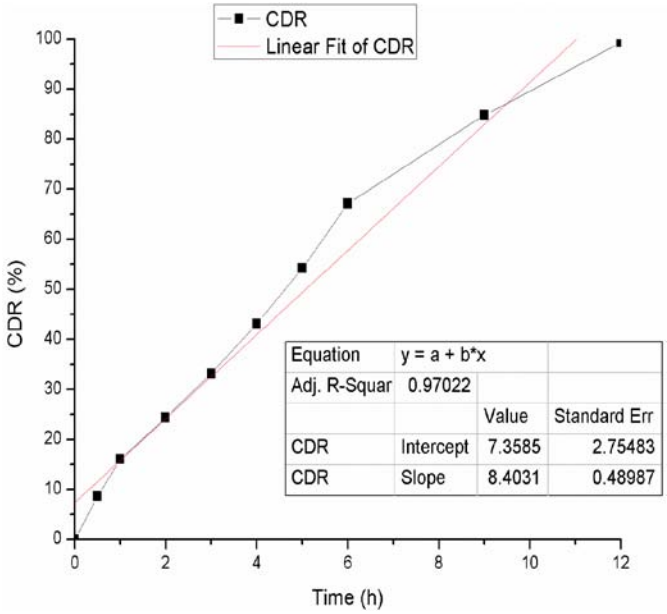

Fig. 14: Cumulative percent drug release of optimized formulation

Short term stability

The formulation F3 indicated no variation in physical appearance, floating behavior, and drug content during stability conditions.

CONCLUSION

In the current work, gastro-retentive in situ gel formulations of Nizatidine were successfully developed. All formulations showed good viscosity, gelling capacity with immediate floating property, extended drug release for 12h. With a drug release rate of 99.45 percent, the optimized formulation F3 was the most successful. In the combined action of drug diffusion and matrix erosion mechanism, the release behavior of the formulations was fitted to a zero-order model. F3 was further characterized for FTIR, DSC, and short-term stability studies, which revealed no interaction with excipients and formulation was stable. Thus, these results advocate that formulated nizatidine GRDDS indicated superior release and retentive properties that provide improved treatment for stomach ulcers.

FUNDING

Nil

AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors report no conflicts of interest in this work

REFERENCES

1. Eberle VA, Schoelkopf J, Gane PA, Alles R, Huwyler J, Puchkov M. Floating gastroretentive drug delivery systems: comparison of experimental and simulated dissolution profiles and floatation behavior. Eur J Pharm Sci. 2014 Jul 16;58:34-43. doi: 10.1016/j.ejps.2014.03.001, PMID 24704154.
2. Pahwa R, Saini N, Kumar V, Kohli K. Chitosan-based gastroretentive floating drug delivery technology: an updated review. Expert Opin Drug Deliv. 2012 May;9(5):525-39. doi: 10.1517/17425247.2012.673581, PMID 22444200.
3. Mandel KG, Daggy BP, Brodie DA, Jacoby HI. Review article: alginate-raft formulations in the treatment of heartburn and acid reflux. Aliment Pharmacol Ther. 2000 Jun;14(6):669-90. doi: 10.1046/j.1365-2036.2000.00759.x, PMID 10848650.
4. Arianto A, Bangun H, Yohana A, Silalahi J. Floating gastroretentive of amoxicillin using hard alginate capsules and its antibacterial activities. Asian J Pharm Clin Res. 2017;10(5 May):414-20.
5. Badhan AC, Mashru RC, Shah PP, Thakkar AR, Dobaria NB. Development and evaluation of sustained-release gastroretentive mini matrices for effective treatment of H. pylori infection. AAPS PharmSciTech. 2009;10(2):459-67. doi: 10.1208/s12249-009-9231-4, PMID 19381827.
6. Sathiyaraj S, Devi RD, Hari VB. Lornoxicam gastro retentive floating matrix tablets: design and *in vitro* evaluation. J Adv Pharm Technol Res. 2011 Jul;2(3):156-62. doi: 10.4103/2231-4040.85531, PMID 22171312.
7. Sanjay KM, Gupta MK. Characterization and evaluation of nizatidine floating microsphere-based drug delivery system for antiulcer activity. Int J Pharm Sci Res. 2019;10(10):4557-67. doi: 10.13040/IJPSR.0975-8232.10(10).4557-67
8. Darwish MKM, Abu El-Enin ASM, Mohammed KHA. Formulation, optimization, and evaluation of raft-forming formulations containing nizatidine. Drug Dev Ind Pharm. 2019 Apr;45(4):651-63. doi: 10.1080/03639045.2019.1569033, PMID 30638411.
9. Ranch KM, Maulvi FA, Naik MJ, Koli AR, Parikh RK, Shah DO. Optimization of a novel in situ gel for sustained ocular drug delivery using box-behnken design: *in vitro*, ex vivo, *in vivo* and human studies. Int J Pharm. 2019 Jan 10;554:264-75. doi: 10.1016/j.ijpharm.2018.11.016, PMID 30423418.
10. Abou Youssef NA, Kassem AA, El-Massik MA, Boraie NA. Development of gastroretentive metronidazole floating raft system for targeting Helicobacter pylori. Int J Pharm. 2015;486(1-2):297-305. doi: 10.1016/j.ijpharm.2015.04.004, PMID 25843757.
11. Abouelatta SM, Aboelwafa AA, El-Gazayerly ON. Gastroretentive raft liquid delivery system as a new approach to release extension for the carrier-mediated drug. Drug Deliv. 2018 Nov;25(1):1161-74. doi: 10.1080/10717544.2018.1474969, PMID 29792353.
12. Abbas G, Hanif M, Khan MA. pH-responsive alginate polymeric rafts for controlled drug release by using box behnken response surface design. Des Monomers Polym. 2017;20(1):1-9. doi: 10.1080/15685551.2016.1231046, PMID 29491774.
13. Abbas G, Hanif M, Shah S, Zaman M. Raft-forming system for pantoprazole and domperidone delivery: *in vitro* and *in vivo* study. Bioinsp Biomimetic Nano Biomat. 2019:1-10.
14. Karemore MN, Avari JG. *In situ* gel of nifedipine for preeclampsia: Optimization, *in vitro* and *in vivo* evaluation. J Drug Deliv Sci Technol. 2019 Apr;50:78-89. doi: 10.1016/j.jddst.2019.01.025.
15. Dettmar PW, Gil Gonzalez D, Fisher J, Flint L, Rainforth D, Moreno Herrera A, Potts M. A comparative study on the raft chemical properties of various alginate antacid raft-forming products. Drug Dev Ind Pharm. 2018 Jan;44(1):30-9. doi: 10.1080/03639045.2017.1371737, PMID 28836872.
16. Pashikanti S, BJ. Formulation and evaluation of floating *in situ* gel of ciprofloxacin. Int J App Pharm 2019;11(1). doi: 10.22159/ijap.2019v11i1.28603.
17. MSS, Priya S, Maxwell A. Formulation and evaluation of novel in situ gel of lafutidine for gastro retentive drug delivery. Asian J Pharm Clin Res. 2018;11:88-94. doi: 10.22159/ajpcr.2018.v11i12.29418',
18. Patel DM, Patel DG, Patel CN. Formulation and optimization of raft forming chewable tablet containing lafutidine. Int J Pharm Sci Drug Res. 2015;7:229-34.
19. Hao J, Fang X, Zhou Y, Wang J, Guo F, Li F, Peng X. Development and optimization of solid lipid nanoparticle formulation for ophthalmic delivery of chloramphenicol using a box-behnken design. Int J Nanomedicine. 2011;6:683-92. doi: 10.2147/IJN.S17386, PMID 21556343.
20. Orugonda K, Reddy V, Reddy SD. Pectin as a release retardant in gas generating floatable system of nizatidine-preparation and evaluation. J Glob Trends Pharm Sci. 2017;8(1):3554-63.
21. Alhamdany AT, Abbas AK. Formulation and *in vitro* evaluation of amlodipine gastroretentive floating tablets using a combination of hydrophilic and hydrophobic polymers. Int J Appl Pharm. 2018;10(6):126-34.
22. Mazumder R, Nath KL, Haque A, Maity T, Choudhuy KP, Shrestha B, Chakraborty M, Pal N. Formulation and *in vitro* evaluation of natural polymers based microspheres for colonic drug delivery. Int J Pharm Pharm Sci. 2010;1(2):211-9.