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Original Article

DESIGN, OPTIMIZATION, AND EVALUATION OF RAFT FORMING GASTRO RETENTIVE DRUG DELIVERY SYSTEM OF LAFUTIDINE USINGBOX–BEHNKEN DESIGN

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ABSTRACT

Objective: The current research was aimed to formulate and evaluate raft forming gastro retentive floating drug delivery systems of Lafutidine for improving gastric residence time and sustained drug release for an extended time.

Methods: Using Box–Behnken experimental design 17 formulations of lafutidine GRDDS were designed and evaluated for various parameters like physical appearance, pH, *In vitro* gelling study, *in vitro* buoyancy study, measurement of viscosity, density measurement, gel strength, drug content, acid neutralization capacity, the profile of neutralization, *in vitro* dissolution, release kinetic and stability studies.

Results: All the evaluations were performed and observed that the values were within range, and the buoyancy lag time ranged within 14.76 to 25.84 sec and the formulations remained buoyant for more than 8h with the gelling time of 12h, the drug content was ranging from 98.96 to 99.55 %, and *in vitro* release was 86.86 to 99.34% by the end of 12h. The release kinetics followed zero-order with Higuchi's model that indicating that drug release was found to be followed by the matrix diffusion process.

Conclusion: Out of all formulations F3 was the optimized formulation and it was further characterized for FTIR, DSC, and stability studies, which exposed that there were no interactions amongst drug and excipients and no major change in the formulation and found to be stable.

Keywords: Lafutidine, Anti-ulcer, Gastro-retentive, Box–Behnken design (BBD), Buoyancy lag-time, Zero-order release

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INTRODUCTION

Oral administration is the preferred method of delivering drugs to the systemic circulation. Its convenience and flexibility have led to the increasing interest in the development of new drug delivery methods. The concept of a controlled release gastroretentive dosage form (GRDF) was developed to provide continuous distribution of formulation to the upper GI tract while minimizing the limitations of poor colon absorption. These dosage forms are designed to stay in the stomach for an extended amount of time while releasing their contents in a steady and controlled manner. By stopping the dosage form from flowing through the pyloric sphincter, gastric retention is achieved. The gastroretentive drug delivery system (GRDD) stays in the stomach for a long time to improve drug bioavailability. High and low density, bio-adhesive, expansion, magnetic, and floating ion exchange resins and raft forming systems are all examples of GRDD [1].

The raft forming system is a viscous preparation that forms a gel network termed raft whenever it comes into touch with an acidic medium in the stomach. They contain a gel-forming ingredient along with alkaline bicarbonates or carbonates that are involved in carbon dioxide production. One of the mechanisms involved in raft formation is the formation of a viscous cohesive gel upon contact with stomach contents, where each portion of the liquid expands to form a continuous layer known as a raft. This raft floats on stomach fluids and acts as a barrier between the stomach and the esophagus, preventing gastric contents from refluxing into the esophagus. As a result, these systems have gained a lot of interest for antacid delivery and drug delivery for gastrointestinal infections [2]. The principle involved in the in situ gel formulation is pH-induced ionic gelation. The trisodium citrate incorporated into the formulation helps to maintain the formulation in liquid form until it reaches the stomach [3].

Alginate is a non-toxic gel-forming material that can be mainly used as a liquid gel-forming material due to its unique physical properties. Alginate is a non-toxic, naturally occurring macromolecule that can be used as a biodegradable scaffold. It is stable in an acidic environment and can be cross-linked to other chemicals. It is composed of linear copolymers that are linked by-D-mannuronic acid and-L-guluronic acid [4, 5].

Lafutidine is a newly developed antiulcer drug, it prevents the secretion of gastric juices. It promotes stomach lining to generate more mucin, inhibit neutrophil activation, which prevents injury due to inflammation, blocking the bonding between H. pylori to gastric cells. It is practically insoluble in water with a log p = 3.8and belongs to BCS class II. It is selectively absorbed through the upper session small intestine (absorption window) [6, 7].

The present research work is an attempt to prepare the formulations which reduce the cost and time involved for formulation with experimentation that utilizes computational modeling predominates. This is accomplished by the development and optimization of formulation using Design of experiments (DoE) and Quality by Design (QbD). These methods reduce the periodicity of drug dosage that augment the acceptability of patients, hence the current research was intended at developing a Lafutidine GRDDS system to sustain the plasma drug concentration for longer periods and alleviate the swallowing.

MATERIALS AND METHODS

Material used

Lafutidine was a gift sample from Sun Pharmaceuticals, Gujarat. Sodium alginate (SA) was obtained from Sisco Lab Pvt. Ltd., India. Hydroxypropyl methylcellulose (HPMC K4M) was obtained from Himedia, Mumbai. Xanthan gum, Sodium bicarbonate (SBC), calcium carbonate(CC), and calcium chloride were purchased from SD fine chem. India. Trisodium citrate and methyl and propylparaben were procured from Gattefosse, Mumbai.

Preliminary experiments

Box Behnken design with 3 factors (A, B, and C) and levels(-1, 0,+1) and 17 runs including 12 factorial points at the midpoint of the edges and five replicates at the center points were employed to choose the best model among the linear and two-factor interaction,

the impact of factors on various responses as listed in table 1. Further, optimization of GRDDS composition of raft formulation was carried out by numerical optimization method using desirability approach [8].

The raft formulations containing varying amounts of sodium alginate, HPMCK4M, and xanthan gum were taken as independent variables and dependent variables are buoyancy time, percent drug release at 1h, and percent drug release at the end of 12 h.

Table 1: List of dependent and independent variables in BBD

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

Lafutidine: 20 mg/10 ml formulation

Table 2: BBD experimental design and observed responses

Run	**Factor A amount of sodium alginate**	**Factor B amount of HPMC K4M**	**Factor C amount of xanthan gum**	**Response Y1 buoyancy lag time**	**Response Y2 % drug release at 1h**	**Response Y3 % drug release at 12h**
1	0.5	1.5	0.5	16.13	21.56	97.13
2	1.5	1.5	1	24.76	18.79	99.23
3	1.5	2	0.75	25.84	14.56	89.72
4	1	1.5	0.75	21.34	19.87	98.78
5	1.5	1	0.75	23.74	23.74	98.12
6	1.5	1.5	0.5	25.76	19.76	97.43
7	0.5	1	0.75	15.12	25.67	97.63
8	1	2	0.5	19.78	15.34	86.86
9	1	1.5	0.75	22.27	20.13	99.12
10	1	1	1	17.36	23.98	98.78
11	1	2	1	17.71	16.76	89.73
12	1	1.5	0.75	20.96	19.54	98.54
13	1	1.5	0.75	21.73	20.56	99.34
14	1	1	0.5	19.45	24.45	98.05
15	1	1.5	0.75	21.96	20.95	98.93
16	0.5	1.5	1	15.34	21.34	99.22
17	0.5	2	0.75	14.76	17.12	88.73

Formulation of lafutidine in situ gel

The Lafutidine was sieved through sieve no. 60 while other ingredients were sieved through 40. Weighed amounts of SA and xanthan gum was dispersed in deionized water, followed by the addition of trisodium citrate 0.3 % w/v and mixed to Sodium Alginate solution and controlled at 90 °C with stirring on a magnetic stirrer (Remi Magnetic Stirrer with Hotplate-1MLH) until a homogeneous viscous liquid was formed. The mixture was allowed to cool to 40 °C and calcium chloride and methyl and propylparaben were then added.

An aqueous solution of HPMC K4M was prepared in deionized water. Lafutidine was added gradually to the above mixture with constant stirring to attain homogeneous drug dispersion while stirring on magnetic stirrer disperse the known amount of gas-forming agent Calcium carbonate, buoyancy enhancer sodium bicarbonate slowly in the resulting solution with continuous stirring. The obtained formulation was then subjected to sonication for 15 min, the pH adjusted to 5.5-6.5 with 0.1N NaOH solution [9].

Evaluation of lafutidine in situ gel RAFT formulation

Evaluations were performed for physical appearance, pH, FTIR compatibility study, in vitro gelling studies, in vitro buoyancy studies, measurement of viscosity, density measurement, gel strength, drug content, acid neutralization capacity, and profile of neutralization according to the referred procedures mentioned in reference [10-13].

***In vitro* drug dissolution studies**

The dissolution of Lafutidine from in situ gel raft system and the marketed formulation was estimated using USP dissolution test apparatus II, at 37 °C and 50 rpm peddle speed using 0.9 L of 1/10 N HCl corresponds to pH 1.2 as dissolution medium (DM). About 0.01 L of the formulation taken onto watch glass was placed into a dissolution vessel. Samples were withdrawn at a preset time interval and the equivalent amount replenished with fresh DM. The samples were evaluated at 279 nm [14].

Drug release kinetic analysis

The mechanism of drug release was analyzed by fitting dissolution data into various kinetic models. The release of Lafutidine from in situ gel raft system was evaluated by the curve fitting method [15].

Short term stability

Because of potential efforts made in the preparation of formulation, stability studies were carried out storing the optimized formulation F3 in the amber-colored bottle with a rubber cap and aluminum covering. The sample was stored at three different conditions of temperature and humidity conditions corresponding to 25±2 °C, 60%±5;30±2 °C, 65%±5; and 40±2 °C, 65%±5 and were inspected at regular interval of time [16].

Statistical evaluation

All experimental data is provided as a mean standard deviation (SD). The One Way analysis of variance was used to compare the different groups (ANOVA). At $p<0.05$, differences between the groups were considered significant. Stat-Ease Design-Expert ® software V8.0.1 was used to do statistical formulation optimization (Stat-Ease, Inc., USA).

RESULTS AND DISCUSSION

Design of experiments

All the formulations were evaluated for buoyancy lag time, percent drug release at 1hour, and percent drug release at the end of 12hour. Results are shown in fig. 1. Quadratic polynomial model equations for three dependent parameters has been given in table 3 According to the Design-Expert software, all three equations were statistically significant (P>0.01), as evaluated by ANOVA [17].

Response 1: (Y1) buoyancy lag time

The buoyancy lag time ranged between14.76 to 25.84 sec. The quadratic models generated show that factors A has a major effect followed by C and B have a significant influence on buoyancy lag time. It has been reported a decrease in buoyancy lag time with a concomitant decrease in sodium alginate. This phenomenal effect is due to the higher amount of alginate forming a high-density structure thereby delaying buoyancy lag time. The relationship between these dependent and independent factors was further depicted using 3D and contour plots. The mathematical model obtained for buoyancy lag time (Y1) was significant with an F-value = 181.56 implying that model is significant. (fig. 2, 3, and 4)

Table 3: Regression equations

Response	Regression equation
Y1	21.68+4.84 A+0.30 B–0.74 C+0.61 AB–1.85 B^2–1.22 C^2
Y2	20.24–1.11 A–4.26 B
Y3	98.64–4.69 B+0.94 C–5.18 B^2

Design Summary

Study Type	Response Surface	**Runs**	17
Design Type	Box-Behnken	**Blocks**	No Blocks
Design Model	Quadratic	**Build Time (ms)**	0.77

Factor	Name	Units	Type	Subtype	Minimum	Maximum	-1 Actual	+1 Actual	Mean	Std. Dev.
A	Amount of Sodium alginate	% w/v	Numeric	Continuous	0.50	1.50	0.50	1.50	1.00	0.34
B	Amount of HPMCK4M	% w/v	Numeric	Continuous	1.00	2.00	1.00	2.00	1.50	0.34
C	Amount of Xanthan gum	% w/v	Numeric	Continuous	0.50	1.00	0.50	1.00	0.75	0.17

Response	Name	Units	Obs	Analysis	Minimum	Maximum	Mean	Std. Dev.	Ratio	Trans	Model
Y1	Buoyance lag time	sec	17	Polynomial	14.76	25.84	20.2359	3.69304	1.75068	None	RQuadratic
Y2	% drug release at 1 h	%	17	Polynomial	14.56	25.67	20.2424	3.14339	1.76305	None	RLinear
Y3	% drug release at 12 h	%	17	Polynomial	86.86	99.34	96.1965	4.33984	1.14368	None	RQuadratic

Fig. 1: The summary of box behnken design

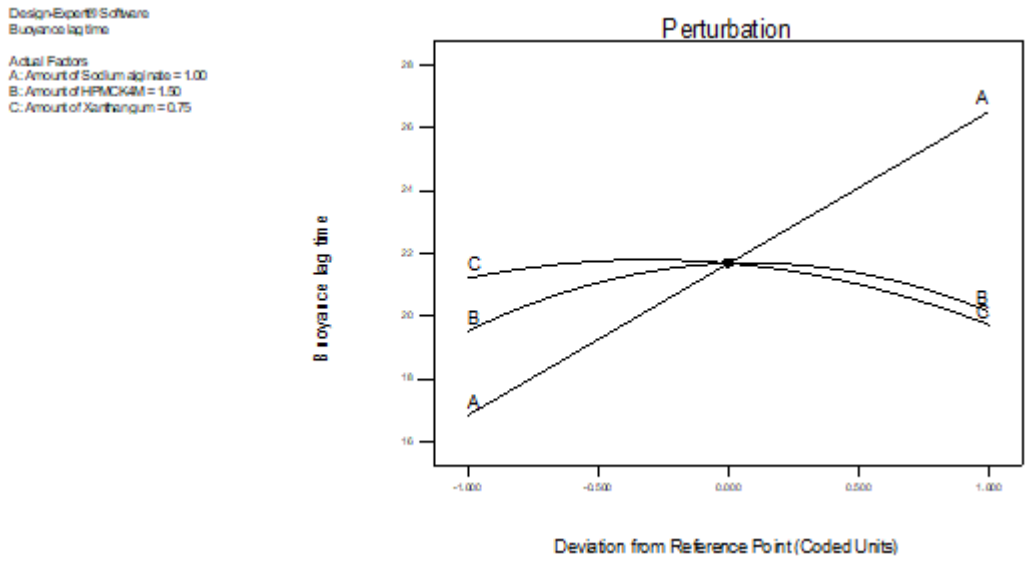

Fig. 2: Perturbation plot depicting the influence of variables A, B, and C on buoyancy lag time

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

The percent drug release within 1h ranged between 14.56 to 25.67 %. The quadratic generated revealed that sodium alginate and HPMC K4M have a significant effect on percent drug release at 1h. The speedy release might be because HCl would create sink conditions for the release of Lafutidine. The effect of A and B are negative while C was found to be positive on the initial burst. The influence of the main and interactive effects of independent variables on the percent drug release at 1h was further elucidated using the contour and 3D response surface plots. The mathematical model generated for percent drug release at 1h (Y2) was found to be significant with an F value 326.75implies that the model is significant. (fig 5, 6, and 7)

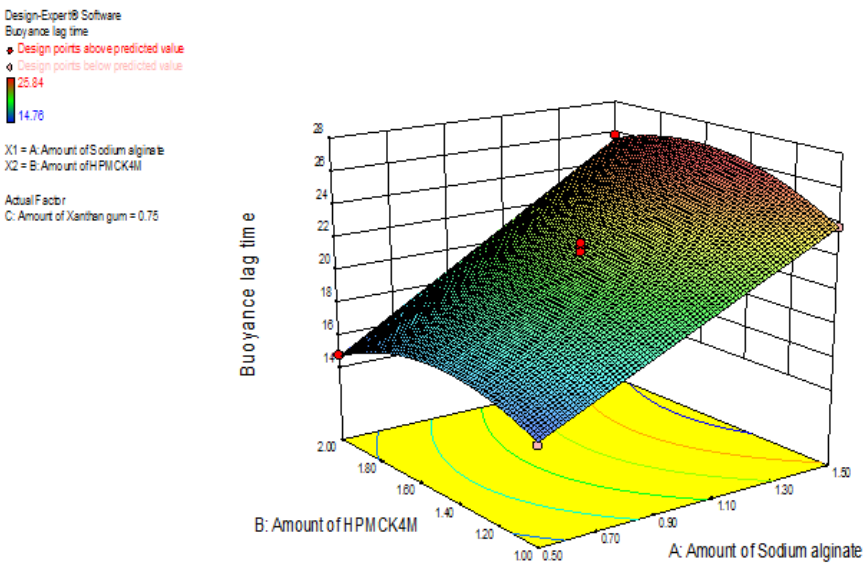

Fig. 3: Response surface plot depicting the influence of the amount of sodium alginate and amount of HPMC K4M on buoyance lag time at a constant level of C

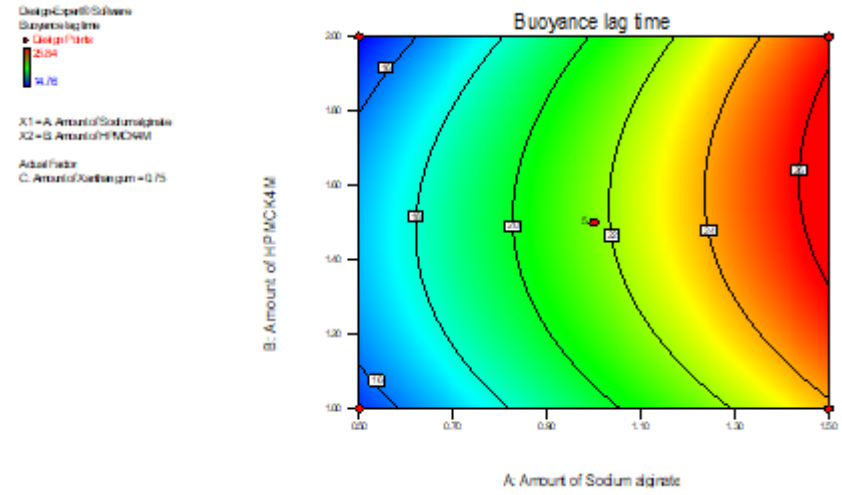

Fig. 4: Contour plot depicting the effect of SA and HPMC K4M on buoyance lag time at a constant level of C

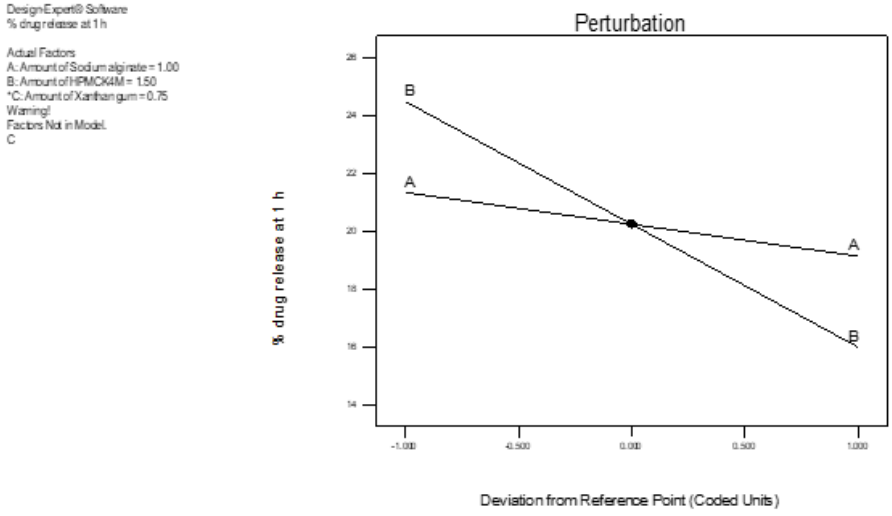

Fig. 5: Perturbation plot depicting the effect of A and B on percent drug release at 1h

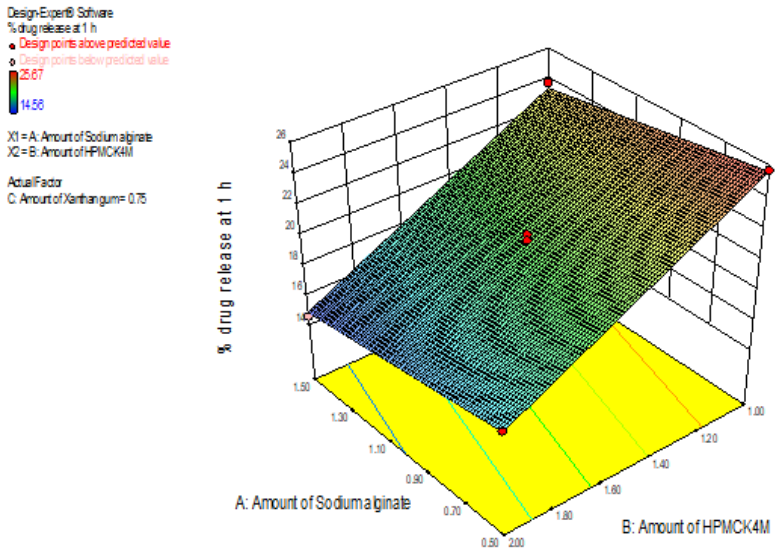

Fig. 6: Response surface plot depicting the effect of SA and HPMC K4M on percent drug release at 1h at a fixed level of C

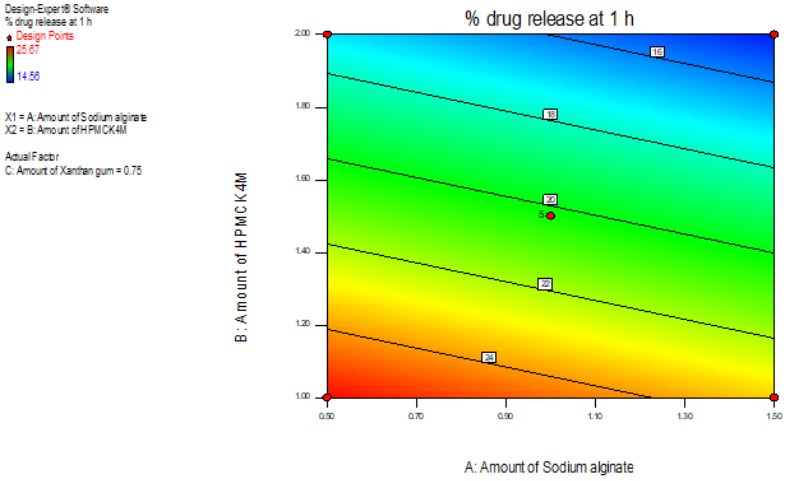

Fig. 7: Contour plots depicting the effect of SA and HPMC K4M on B at 1h at a constant level of C

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

At 12 h, the percent drug release ranged from 86.86 to 99.34. (table 2). According to the quadratic model, the amount of HPMC K4M and xanthan gum has a significant impact on Y3. Using contour and 3D response surface plots, the influence of the main and interacting effects of independent variables on % drug release at 12h was further explained. Observed and theoretical (predicted) values were nearly identical. The mathematical model for Y3 was significant, with an F-value of 292.34, indicating that the model is significant. (fig 8, 9, and 10)

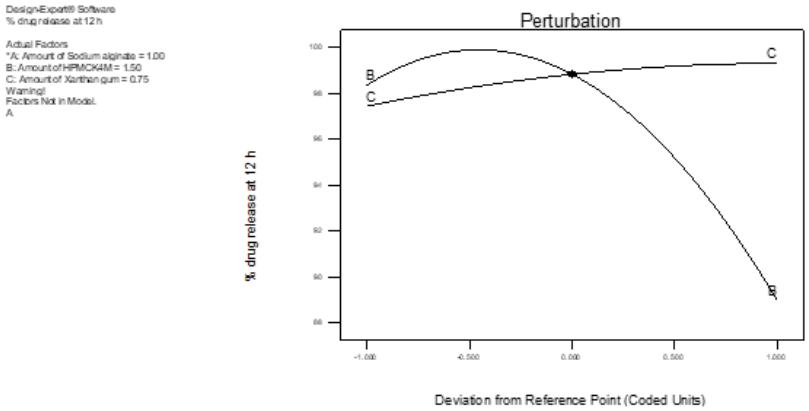

Fig. 8: Perturbation plot depicting the influence of B and C on Y3

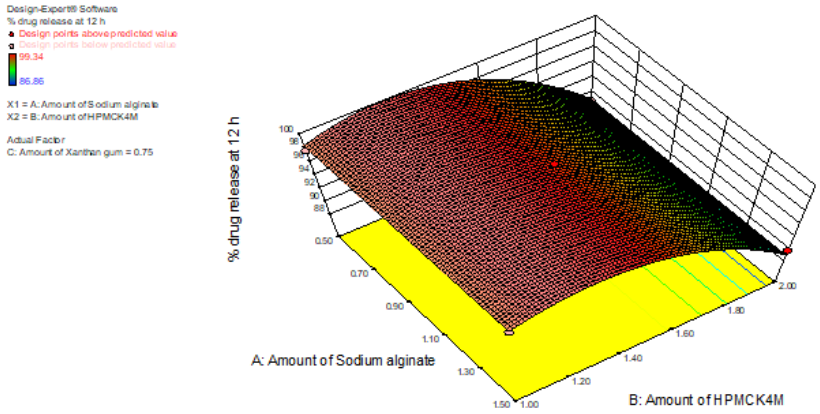

Fig. 9: Response surface plot depicting the effect of A and B on percent drug release at 12 h at a constant level of C

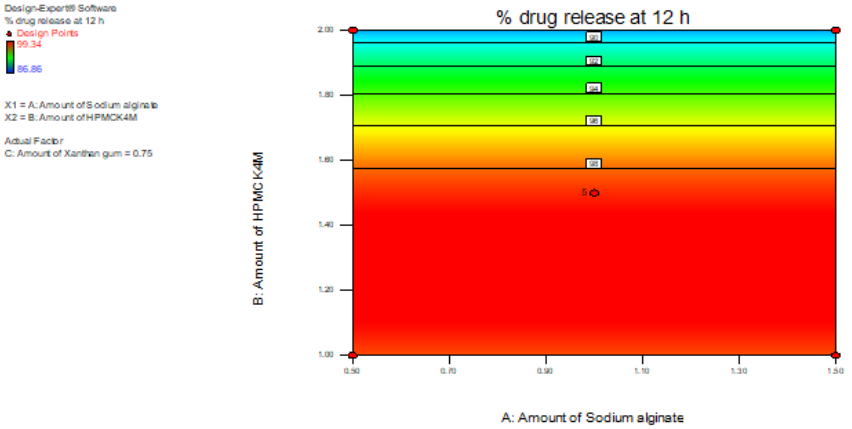

Fig. 10: Contour plot displaying the effect of the amount of A and B on percent drug release at 12 h at a fixed level of C

Optimization using desirability function

An optimization procedure using a desirability function was used to optimize all of the responses at the same time. The responses were translated 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. At A: 0.52 % w/v, B: 1.67 % w/v, and C: 1.0 % w/v, the highest 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 expected values, showing that the Box–Behnken design combined with the desired function was successful in evaluating and optimizing the Lafutidine in situ gel raft system (table 4).

Table 4: Optimized values obtained by the constraints apply on Y1, Y2, and Y3

Independent	Nominal	Predicted values			Observed values			
Variable	Values	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)	0.52 % w/v	14.76±0.24	19.8354±0.76	97.32±0.85	1	15.12±0.83	20.208±0.78	97.88±0.62
Amount of HPMC K4M (B)	1.67 % w/v				2	14.34±0.37	19.228±0.24	98.12±0.59
Amount of Xanthan gum (C)	1% w/v				3	15.81±0.63	19.516±0.42	97.20±0.42

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

Evaluation of formulations [18]

The formulations (F1-F3) were off-white creamy in color. The pH is within the tolerable range of 7–8 (table 5) which is appropriate for oral consumption.

The three formulations displayed instant gelation and retention of gel structure for above 12 h. The gelation time<10 sec indicates the release of Ca^{+2} ions when in contact with an acidic environment. These divalent ions bind with sodium alginate and xanthan gum to form a complex network which leads to the formation of a strong gel. This rigidity of gel is responsible for sustained delivery of drug as the drug molecules have to travel through the complex three-dimensional structures of polymer chains to reach the physiological environment [19]. All formulations displayed the least floating lag time and were

found to be buoyant for more than 12h (table 5) due to evolving CO_2 gas. The evolution of CO2 is directly related to the amount of sodium bicarbonate and is responsible for variation in floating lag time. Further, Ca^{+2} ion undergoes complexion with gums to fabricate a cross-linked 3D network to stay buoyant for more than 12h [20]

The density of all the formulations was<0.82 g/cm^3, which is due to the swelling of polymers that enhance gel volume. Moreover, the trapped CO2 gas in the swollen gel matrix also contributes to further decline in the density.

All three formulations exhibited gel strength ranging between 8.97-9.21 g/cm^2 (table 5). The results show that sodium alginate and xanthan gum combination lead to the creation of strong gel. The rheological study results show a mark-able enhancement in viscosity with raise in polymer concentration (table 5). The values of all 3 formulations are within the preferred range. The % drug concentration of all formulations ranged between 98.96 to 99.55 %, indicating homogeneous drug distribution. All the results were in agreement with the reference [18].

Table 5: Evaluation of floating in-situ gel

Formulation	pH	*In vitro* gelation time (sec)	Floating lag time (sec)	Floating duration (h)	Density (g/cm^3)	Gel strength (g/cm^2)	Viscosity (cps)	Drug content (%)
F1	7.12±0.56	6	15	>12h	0.812±0.11	9.13±0.12	143±0.79	99.34±0.13
F2	6.89±0.28	7	16	>12h	0.793±0.23	8.97±0.82	145±0.49	98.96±0.37
F3	7.34±0.73	6	17	>12h	0.762±0.17	9.21±0.64	139±0.26	99.55±0.19

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

Table 7: The dissolution profile of optimized formulations

	% Cumulative drug release			
Time (h)	Marketed sample	F1	F2	F3
0	0	0	0	0
0.5	68.34±0.56	5.12±0.73	4.79±0.96	5.77±0.88
1	81.46±0.39	8.43±0.26	7.86±0.45	9.56±0.75
2	98.74±0.67	15.21±1.24	14.78±0.37	16.34±0.68
3	99.06±0.63	30.72±0.84	29.36±0.16	31.12±0.18
4	99.43±0.27	46.87±0.29	45.65±0.54	47.12±0.47
6	99.5±0.25	60.34±0.94	58.87±0.39	61.23±0.50
8	99.62±0.43	77.86±0.39	76.86±0.64	78.12±0.16
10	99.73±0.82	97.35±0.18	96.98±0.19	97.83±0.26
12	99.77±0.26	99.12±0.59	98.86±0.73	99.73±0.59

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

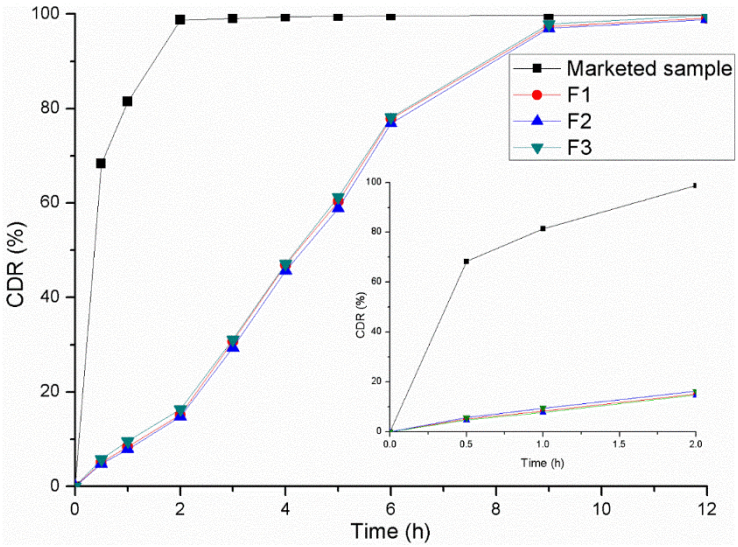

Fig. 11: Dissolution profile of optimized formulations, (All determinations were performed in triplicate and values were expressed as mean±SD, n=3)

Acid neutralization capacity

All the formulations displayed comparable acid neutralization capacity value 8. This value depends on the amount of sodium bicarbonate. All formulations display the longest neutralization duration of 30 min without many fluctuations. The constant amount of sodium bicarbonate may be the main contribution to such results [21].

***In vitro* release studies**

The *in vitro* release studies data is shown in the table: 7. the release of lafutidine is carried out 0.1N HCL to evaluate drug release profile. The optimized formulation was able to release more than8%, more than45%, and more than 99% of drug release at 1hour, 4hour, and 12 h respectively. This indicates the selected polymers were able to

control the drug release in an acidic medium and these findings agree with the studies as mentioned in reference [22].

Drug release kinetic analysis

Leon Shargel, Susanna Pong, Andrew B. C., Applied

Biopharmaceutics and Pharmacokinetics, Modified-Release

Drug Products, Fifth Edition, 2004: 515

Leon Shargel, Susanna Pong, Andrew B. C., Applied

Biopharmaceutics and Pharmacokinetics, Modified-Release

Drug Products, Fifth Edition, 2004: 515

The result obtained from regression coefficient value r^2 (table 8) found closure to unity in the case of zero-order kinetics. Hence it can be concluded that dissolution is constant over some time indicating zero-order as the best fit model. As per release plot fig. 11 of optimized formulation, Higuchi's Model showed good linearity with slope value n≤0.45 indicating drug release is governed by matrix diffusion which agrees also with drug release kinetics as mentioned in reference [23].

Table 8: Release kinetics of optimized formulation of lafutidine

Formulation code	Zero order		First order		Higuchi		Korsmeyer-peppas	
	R^2	N	R^2	n	R^2	N	R^2	N
F3	0.96609	13.7294	0.72711	-0.21063	0.91413	39.69109	0.89398	100.1048

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectra obtained from the analysis demonstrated that the drug and excipients had no physical interaction (fig. 12). Lafutidine main IR peaks were observed at 3328 cm-1 for N–H stretching in aliphatic, 2933 cm-1 for–C–H stretching in aromatic, 1658 cm-1 for–C=N stretching, 1610 cm-1 for N–H bending, 1350 cm-1 for C–H bending, and 1278 cm-1 for C–N stretching. The IR spectra of the formulation revealed all of the drug's characteristic peaks.

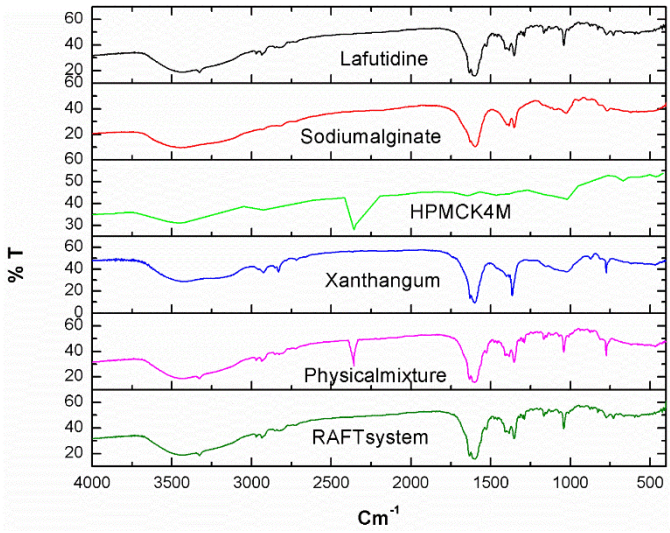

Fig. 12: FTIR spectra of pure lafutidine, excipients, physical mixture, and lafutidine raft system

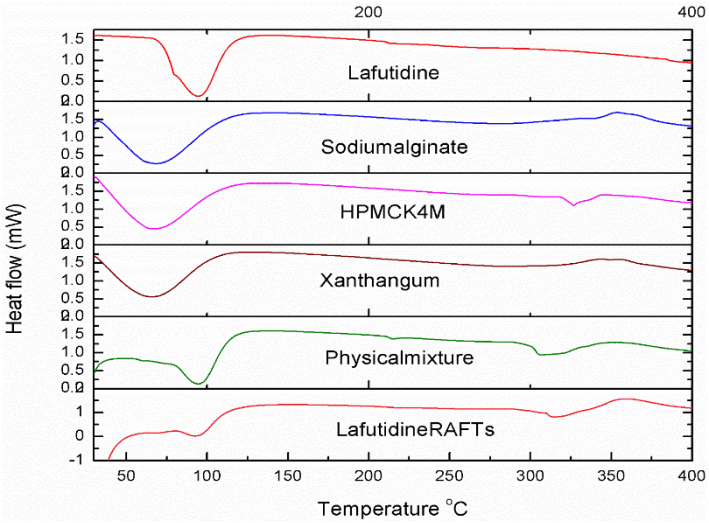

Fig. 13: DSC thermograms of pure lafutidine, excipients, physical mixture, and lafutidine raft system

Differential scanning calorimetry(DSC)

The DSC curve of Lafutidine displayed a sharp endothermic peak at 94.8 °C corresponding to melting transition temperature (fig. 13). The DSC thermogram of sodium alginate displayed a broad endotherm at 68 °C, which is due to water loss, and an exothermic peak at 352 °C. HPMC K4M exhibited a broad endothermic 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 optimized formula shows the characteristic endothermic peak of Lafutidine which might indicate that Lafutidine has formed an in-situ gel with the selected excipients.

Short term stability data

The optimized formulation F3 subjected to stability study indicates no considerable alteration in the stability of formulation concerning the physical appearance, floating behavior, and drug content at the end of one month compared to the beginning.

CONCLUSION

Formulation of lafutidine GRDDS was successfully done with all the evaluation tests performed and all the formulations were able to float instantaneously and kept floating for more than 12 h and all the tests values were observed within range with sustained release up to 12 h. The buoyancy lag time of F1, F2, and F3 ranges from 14.76 to 25.84 sec, the drug content was ranging from 98.96 to 99.55 %, and *in vitro* release was 86.86 to 99.34%. The release mechanism followed zero-order with Higuchi's model declaring matrix diffusion process. The best formulation optimized was F3, which showed no interactions between drug and excipients and no significant change in the formulation by FTIR and DSC studies. The final formulation was found to be stable for one month in short-term stability studies conducted. Hence it is proved that GRDDS formulation is a better choice for drugs like lafutidine which enhanced the drug release for a prolonged time by remaining buoyant in the stomach for 12 h which is useful in the treatment of gastric ulcers.

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AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

CONFLICT OF INTERESTS

The authors report no conflicts of interest in this work.

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