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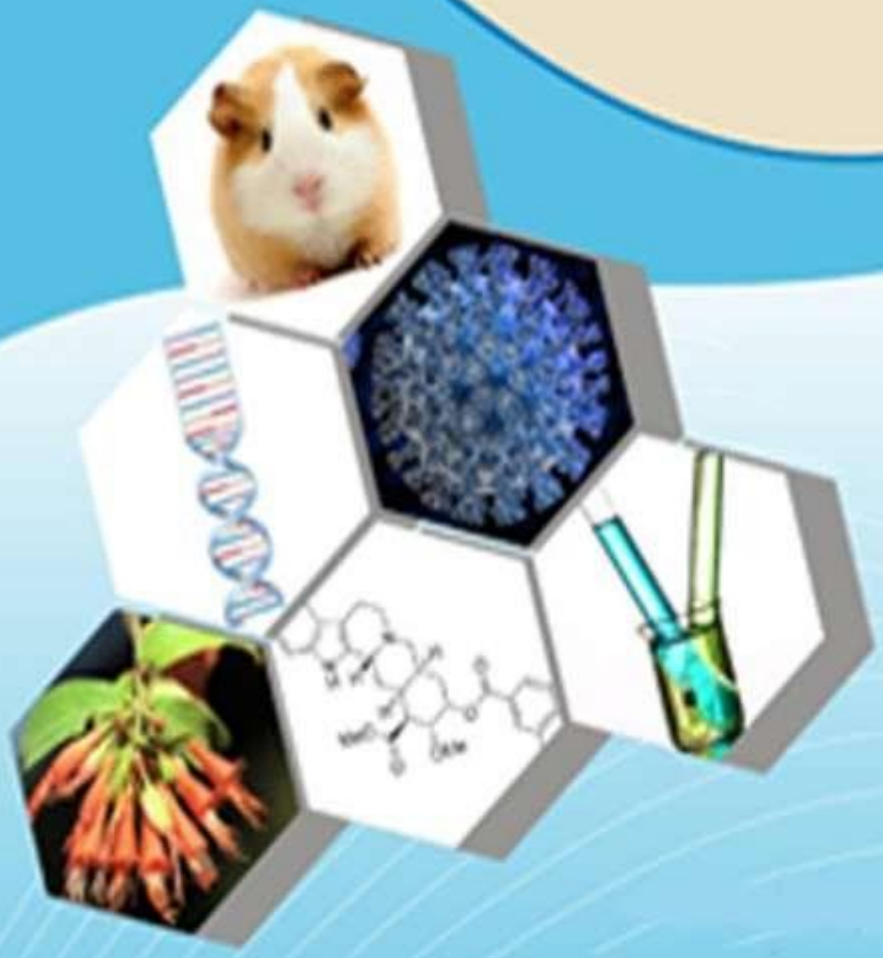

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Formulation and Optimization of Raft Forming Chewable Tablet Containing Lafutidine

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ABSTRACT

A novel histamine H2-receptor antagonist, lafutidine has a duration of action of 1.92 hours in the body. Because it is absorbed selectively from the upper section of the GI tract, the goal of using gastroretentive medication administration is to increase its bioavailability. The study's overarching objective was to develop lafutidine chewable tablets that also included an antacid, raft-forming agent, and gas-generating agent. In vitro drug release, weight variation, acid neutralization capability, raft strength, and percentage of drug content were some of the metrics used to assess the tablet formulation process that used the wet granulation technique. In the first round of testing, a number of raft-forming chemicals were used. The optimization strategy used in this work was a 32 complete factorial design. We used raft strength and acid neutralization capability as our dependent factors, and we employed sodium alginate to pectin ratio and calcium carbonate amount as our independent variables. Batch F8 was chosen as the optimal formulation because of its high acid neutralization capability and highest raft strength. There was no evidence of drug-excipient interactions in the research of drug-excipient compatibility. Optimal formulation stability testing revealed that, even under accelerated environmental conditions, tablets remained unchanged for a full month. An effective dosage form for the treatment of gastroesophageal reflux disease may be raft-forming chewable tablets made with the optimal amounts of sodium alginate, pectin, and calcium carbonate.

Lafutidine, sodium alginate, pectin, acid neutralization capability, RAFT strength, agents that create RAFT, and related terms.

INTRODUCTION

Gastro esophageal reflux disease (GERD) is a condition in which the contents of the stomach come back into the esophagus (the tube that carries food from the mouth to the stomach). Doctors call this as “acid reflux.” GERD often causes heartburn, a burning feeling in the chest and throat. Heartburn may happen many times a week, especially after eating or at night. GERD can also cause cough or have asthma symptoms. It can also make your voice sound hoarse and raspy. Various treatment options available for GERD are taking medicines like antacids, H2 antagonist, proton pump inhibitor, etc.; surgery to strengthen the barrier between the stomach and the esophagus may be a treatment option for acid reflux and endoscopic treatments help strengthen the muscle that keeps food and acid from going up into the esophagus. [1] Raft forming anti reflux preparation is generally used in the treatment of gastric acid related disorders, especially GERD, heartburn and oesophagitis. Raft forming anti reflux preparations forms a viscous, gelatinous neutral layer or barrier on the top of the gastric acid contents.

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The floating barrier

remains located at the lower oesophageal sphincter (LES) and prevents the acidic gastric content from getting refluxed into the esophagus and provides symptomatic relief to GERD patients.

Since this barrier floats on the surface of the stomach content like a raft on water, the barrier is called a raft and the formulations are called as "raft forming anti reflux preparations". The unique mechanism of action to provide relief in symptomatic GERD separates raft forming anti reflux preparations from traditional antacids and other therapeutic classes for treatment of GERD. A raft forming formulation requires sodium or potassium bicarbonate. In the presence of gastric acid, bicarbonate is converted to carbon dioxide, which becomes entrapped within the gel precipitate, converting it into foam, which floats on the surface of the gastric contents. The antacid component contained in formulations provide a relatively pH neutral barrier. [2] Calcium carbonate can be used as an antacid as well as a raft strengthening agent. It releases calcium ions, which react with alginate and form an insoluble gel. Various polymers, especially different polysaccharides have been used in various research works. Alginic acid, alginates and pectin are the most widely used raft forming agents. Other polysaccharides are also being used, which include guar gum, locust bean gum, carrageenan, pectin and isapgol.

All recent treatments available for GERD either have one or more problems like side effects, costly or painful. Hence the objective of the present investigation was to formulate and evaluate a chewable raft forming tablet containing Lafutidine. Lafutidine blocks the action of histamine on the H2 receptors present in the stomach and thereby decreases acid secretion. [3-6]

MATERIALS AND METHODS

Materials

Lafutidine was gift sample from Emcure Pharmaceuticals, Pune, India. Sodium alginate was purchased from Finar Chemicals Ltd., Ahmedabad, India. All other excipients used to prepare chewable tablets were of standard pharmaceutical grade and all chemical reagents used were of analytical grade.

Methods

Preparation of Raft Forming Chewable Tablets [7]

Drug, polymer and other ingredients were weighed accurately. All ingredients except the binder, volatile ingredients and lubricant were mixed thoroughly. PVP K30 M was dissolved in sufficient quantity of water and added to a powder mixture to prepare dough wet mass. The prepared wet mass was passed through a 22# sieve. The granules were allowed to dry in a hot air oven at 70oC for 1 h and then resifted through a 40# sieve. The granules were collected and other ingredients were added and lubricated. Granules were compressed to tablets using 12 mm diameter flat punch with the help of a rotary tablet compression machine.

Preliminary Screening for Selection of Raft Forming Polymer

Preliminary screening was carried out to select a good raft forming polymer, which has good raft strength. Six different raft forming agents, viz., sodium alginate, pectin, guar gum, xanthan gum, gellan gum and isapgol were used in the study. The formulations for tablets of preliminary batches (P1-P6) are shown in Table 1.

Table 1: Preliminary screening of raft forming polymers

Ingredients (mg)	P1	P2	P3	P4	P5	P6
Lafutidine	10	10	10	10	10	10
Sodium alginate	200	-	-	-	-	-
Pectin	-	200	-	-	-	-
Guar gum	-	-	200	-	-	-
Xanthan gum	-	-	-	200	-	-
Isapgol husk	-	-	-	-	200	-
Gellan gum	-	-	-	-	-	200
Sodium bicarbonate (5%)	40	40	40	40	40	40
Calcium carbonate	125	125	125	125	125	125
Polyvinyl pyrrolidone K30 (5%)	40	40	40	40	40	40
Mannitol	343	343	343	343	343	343
Menthol	2	2	2	2	2	2
Aspartame (2%)	16	16	16	16	16	16
Flavor	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Talc (2%)	16	16	16	16	16	16
Magnesium stearate (1%)	8	8	8	8	8	8
Total weight (mg)	800	800	800	800	800	800

Table 2: Coding of variables

Level	Factor X1: Ratio of sodium alginate to pectin	Factor X2: Amount of calcium carbonate (mg)
-1	0.5:1.5	100
0	1:1	125
+1	1.5:0.5	150

Drug- Excipients Compatibility Study

Drug- excipients interaction plays a vital role in the release of drug from the formulation. Fourier transform infrared (FTIR) spectroscopy has been used to study the physical and chemical interactions between drug and excipients. The FTIR spectra of Lafutidine and a mixture of Lafutidine with major excipients were recorded using the KBr mixing method using an FTIR instrument (FTIR-8400S; Shimadzu).

Optimization by 32 Full Factorial Design [8]

A 32 randomized full factorial design was used in the present investigation. In this design, two factors were evaluated, each at three levels, and experimental trials were performed at all night possible combinations. Amount of calcium carbonate and ratio of sodium alginate to pectin were chosen as independent variables in the 32 full factorial design, where as raft strength and acid neutralization capacity were selected as dependent variables (responses). Different levels and their respective values are depicted in Table 2. The formulation layout of the factorial batches (F1-F9) is shown in Table 3. Tablets of all the factorial batches were evaluated for weight variation, hardness, drug content, friability, raft strength, acid neutralization capacity and *in vitro* drug release. The polynomial equations can be used to draw conclusions after considering the magnitude of the coefficient and the mathematical sign it carries (i.e., negative or positive). Data were analyzed for regression using Microsoft Excel.

Evaluation of Raft Forming Chewable Tablets [9-10]

Weight variation test

Twenty tablets were selected at random, weighed and average weight was calculated. Not more than two of the individual weights should deviate from the average weight by more than 10%.

Friability

For each formulation, a pre-weighed tablet sample (six tablets) was placed in a Roche friabilator (Electrolab, Mumbai, India), which is then operated for 100 revolutions. The tablets were de-dusted and reweighed. Conventional compressed tablets that lose < 0.5 to 1% of their weight are considered acceptable.

Hardness

Hardness of tablets was determined using a Pfizer hardness tester (Campbell Electronics, Mumbai, India).

Content uniformity

Twenty tablets were weighed and powdered in a glass mortar. A quantity of powder equivalent to 10 mg Lafutidine was accurately weighed and transferred into a 10 mL volumetric flask. 0.1 N HCl was added up to 10 mL and shaken well. The solution was filtered through 0.45µ membrane filter and 1 mL of the above solution was transferred into a 100 mL volumetric flask and final volume in the flask was adjusted up to 100 mL with 0.1 N HCl. Absorbance of the resulting solution was measured at a λmax of 286 nm using UV-Visible spectrophotometer (Shimadzu 1800, Kyoto, Japan). The amount of the Lafutidine was calculated by using the equation of calibration curve.

Raft strength measurement by in-house method

A tablet powder equivalent to unit dose was transferred to150 mL of 0.1 N HCl maintained at 37°C in a 250 mL glass beaker. Each raft was allowed to form around an L-shaped wire probe (diameter: 1.2 mm) held upright in the beaker throughout the whole period (30 min) of raft development. Raft strength was estimated using the modified balance method. Water was added drop wise to the pan and the weight of water required to break the raft was recorded. A double pan dispensing balance was modified for raft strength measurement. One pan of the dispensing balance was replaced with an L-shaped wire probe as shown in Figure 1.

Table 3: Composition of the Factorial batches

Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9
Lafutidine	10	10	10	10	10	10	10	10	10
Sodium alginate	50	50	50	100	100	100	150	150	150
Pectin	150	150	150	100	100	100	50	50	50
Sodium bicarbonate (5%)	40	40	40	40	40	40	40	40	40
Calcium carbonate	100	125	150	100	125	150	100	125	150
PVP K30 (5%)	40	40	40	40	40	40	40	40	40
Mannitol	365	343	318	368	345	320	368	343	318
Menthol	2	2	2	2	2	2	2	2	2
Aspartame (2%)	16	16	16	16	16	16	16	16	16
Flavour	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Talc (2%)	16	16	16	16	16	16	16	16	16
Magnesium stearate (1%)	8	8	8	8	8	8	8	8	8
Total weight (mg)	800	800	800	800	800	800	800	800	800

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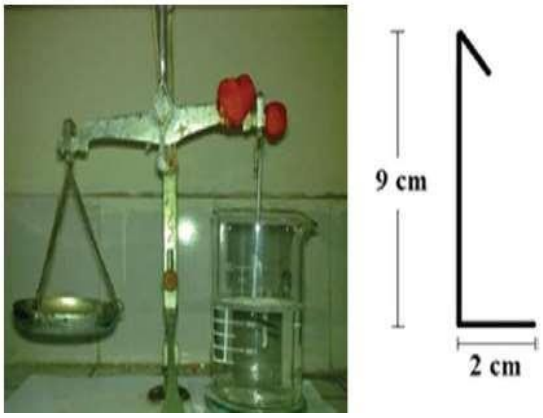

Fig. 1: (a) Modified balance method (b) Wire probe for raft strength measurement

Acid neutralization capacity

A tablet powder equivalent to unit dose was transferred to a 250 mL beaker; 50 mL of water was added to it and was mixed on a magnetic stirrer for 1 min. A 30 mL volume of 1.0 N HCl was added with continued stirring on the magnetic stirrer for 10 min after addition of the acid. Stirring was discontinued and the gum base was removed using a long needle without delay. The needle was promptly rinsed with 20 mL of water, and the washing was collected in the beaker; stirring was resumed for 5 min. Titration was begun immediately. Excess HCl was titrated against 0.5 N sodium hydroxide to attain a stable pH of 3.5.

The number of mEq of acid consumed by the tablet tested was calculated by using the formula:

Total mEq = (30 × N HCl) - (V NaOH × N NaOH) Where, N HCI is Normality of HCl; V NaOH is Volume of NaOH required; and N NaOH is Normality of NaOH.

***In vitro* drug release study [11]**

In vitro drug release study of Lafutidine chewable tablets (n=3) was performed using USP (United States Pharmacopoeia) apparatus II (TDT-08T; Electrolab, India) fitted with a paddle (50 rpm) at 37 ± 0.5°C using a simulated gastric fluid without enzymes (pH 1.2; 900 mL) as a dissolution medium. The tablet was crushed and then added to the dissolution medium. At predetermined time intervals, 10 mL samples were withdrawn, filtered through a 0.45µ membrane filter and analyzed at 286 nm using UV-Visible double beam spectrophotometer (Shimadzu 1800, Kyoto, Japan). Cumulative percentage drug release was calculated using an equation obtained from a calibration curve, which was developed in the range of 5-25 mg/mL for 0.1 N HCl.

Stability studies of the optimized formulation

Stability testing of drug products begins as a part of drug discovery and ends with the demise of the compound or commercial product. To assess drug and formulation stability, short term stability studies were done for 1 month. The stability studies were carried out on the most satisfactory formulations (batch F8). The most satisfactory formulations were sealed in aluminium packaging and kept in a stability chamber maintained at 40 ± 2°C/75 ± 5% relative humidity (RH) for 1 month. The optimized formulation sealed in aluminium foil was also kept at room temperature and humidity condition. At the end of the storage time, the samples were analyzed for raft strength, in vitro drug release and % drug content. The in vitro drug release profiles for both formulations (initial and after storage at 40 ± 2°C/75 ± 5% RH for 1 month) were compared by the similarity factor (f2).

Table 4: Evaluation of tablets of preliminary batches

Batch code	Raft forming agents	*Raft strength (gm)	*Acid neutralization capacity (mEq)
P1	Sodium alginate	5.86 ±1.814	6.86 ± 0.34
P2	Pectin	1.49 ±0.229	6.33 ± 0.493
P3	Guar gum	1.05 ± 0.166	5.21 ± 0.202
P4	Xanthan gum	1.28 ±0.194	0.00 ± 0.00
P5	Isapgol husk	1.08 ±0.118	4.95 ± 0.264
P6	Gellan gum	0.876 ±0.03	7.58 ± 0.475

*All values are mean ± SD (n=3)

RESULTS AND DISCUSSION

Results of Preliminary Screening

Tablets prepared using different raft forming agents were tested for raft strength in 0.1 N HCl. Among all six batches prepared with six different raft forming agents, tablets prepared using sodium alginate (batch P1) had maximum raft strength and acid neutralization capacity (Table 4). The alginate composition has been shown to form rafts over a narrow pH range of hydrochloric acid *in vitro* (pH 1 to 1.4). At higher pH (> pH 1.7) *in vitro*, it does not form good gel. It is known that the pH of human gastric juice is highly variable, commonly pH 1.4 to 2.1 for healthy volunteers. It would therefore be advantageous to formulate a composition capable of forming raft over a wider range of pH. Hence in present study attempt was made to formulate dosage form with combination of polymers which form raft over wider pH range. Therefore sodium alginate and pectin were used in further study.

Results of Drug- Excipients Compatibility Study

FTIR spectra of Lafutidine and Lafutidine with excipients are shown in Figure 2 and Figure 3, respectively. The FTIR spectra revealed that there were no changes in major peaks of Lafutidine when it was mixed with excipients indicating compatibility of drug and excipients.

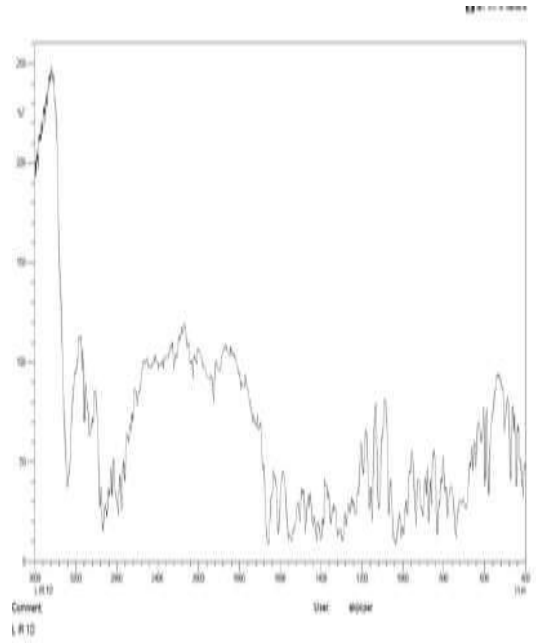

Fig. 2: FTIR Spectrum of Lafutidine

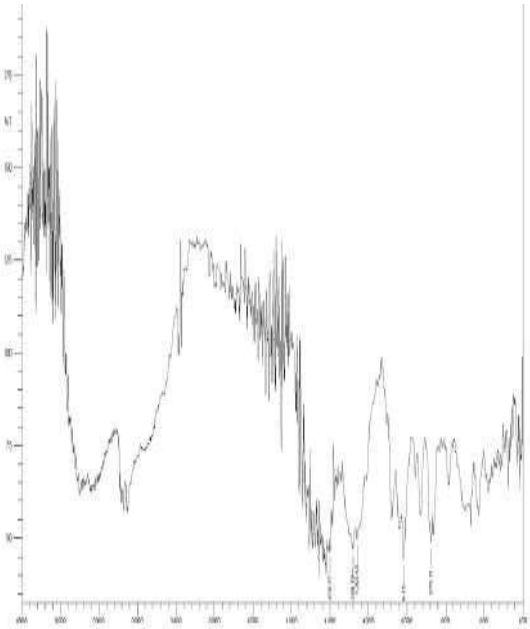

Fig. 3: FTIR Spectrum of Drug and Excipients

Evaluation of Factorial Batches F1 to F9

The factorial batches were evaluated for various parameters by the methods described in methodology section. The evaluation results are shown in Table 5 and Table 6. Thickness of tablets was found in the range of 5.18 to 5.20 mm. Average weight was found to be in the range of 799.3 to 800.4 mg. Hardness of tablets was in the range of 4.16 to 5.03 kg/cm2. All formulations showed good content uniformity (98.70 to 102.90 %). All tablet formulation showed acceptable friability (0.33 to 0.78 %). All the formulations showed good raft strength with a range of 10.75 to 13.76. Formulations exhibited wide variation in acid neutralization capacity ranging between 1.14 and 5.69. No significant difference in the drug content among the tablets indicated good content uniformity. *In vitro* dissolution study in simulated gastric fluid without enzymes, pH 1.2 was conducted as per method described earlier. The data for *in vitro* release are shown in Table 7 and are compared in Figure 4.

Table 5: Physicochemical properties of tablets of factorial batches

Batch Code	Diameter (mm)	*Thickness (mm)	*Average Weight (mg)	*Hardness (kg/cm²)	*% Drug content	%F
F1	12	5.20 ± 0.005	799.8 ± 1.68	4.25 ± 0.11	98.70 ± 0.98	0.47
F2	12	5.20 ± 0.005	800.9 ± 1.70	4.46 ± 0.15	102.90 ± 0.86	0.35
F3	12	5.20 ± 0.005	800.4 ± 1.07	4.16 ± 0.05	102.60 ± 0.69	0.58
F4	12	5.20 ± 0.000	799.8 ± 1.05	4.53 ± 0.05	100.90 ± 1.30	0.61
F5	12	5.20 ± 0.005	799.8 ± 1.68	4.65 ± 0.05	100.90 ± 0.60	0.52
F6	12	5.19 ± 0.005	800.2 ± 1.98	4.70 ± 0.00	102.20 ± 1.70	0.47
F7	12	5.18 ± 0.005	800.0 ± 1.15	5.00 ± 0.10	99.73 ± 0.65	0.40
F8	12	5.20 ± 0.010	799.3 ± 1.56	5.03 ± 0.05	101.30 ± 0.69	0.64
F9	12	5.20 ± 0.005	799.5 ± 1.43	4.98 ± 0.05	101.00 ± 1.39	0.78

*All values are mean ± SD (n=3), n=20, %F is % friability

Table 6: Raft strength and acid neutralization capacity of factorial batches

Batch Code	Raft strength (g)	Acid neutralization capacity (mEq)
F1	10.75 ± 0.10	1.14 ± 0.04
F2	11.15 ± 0.10	1.64 ± 0.03
F3	11.98 ± 0.076	1.32 ± 0.03
F4	12.33 ± 0.076	2.13 ± 0.05
F5	12.48 ± 0.028	2.79 ± 0.08
F6	12.75 ± 0.05	2.25 ± 0.07
F7	12.98 ± 0.02	3.45 ± 0.03
F8	13.45 ± 0.05	5.69 ± 0.06
F9	13.76 ± 0.07	3.95 ± 0.03

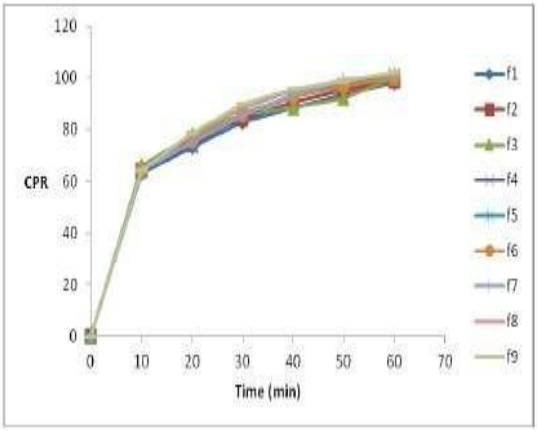

Fig. 4: *In vitro* drug release profile of factorial batches

Table 7: *In vitro* Drug Release Study in Simulated Gastric Fluid, pH 1.2

Time (min)	F1	F2	F3	F4	F5	F6	F7	F8	F9
10	60.15 ±0.0	64.22±0.0	65.9 ±0.0	64.22 ±0.0	64.21 ±0.0	64.2 ±0.0	64.21 ±0.0	64.21 ±0.0	64.21 ±0.0
20	73.00 ±1.32	76.39±0.61	78 ±0.00	73.57 ±0.00	74.98 ±0.52	75.69 ±0.00	75.16 ±0.00	78.16 ±1.05	76.91 ±0.00
30	82.97±1.92	84.11±0.00	85.97 ±1.06	85.38 ±0.61	86.05 ±1.21	86.23 ±0.00	85.52 ±0.00	88.20 ±1.33	89.79 ±1.33
40	88.52±0.55	90.52±0.92	88.44 ±1.06	92.79 ±0.61	93.16 ±0.52	92.64 ±1.05	93.51 ±0.92	95.51 ±0.92	95.89 ±1.05
50	93.69 ±0.78	95.19±0.55	91.96 ±1.10	97.14 ±0.92	97.52 ±0.00	96.82 ±0.52	99.29 ±0.28	98.84 ±0.27	98.69 ±0.81
60	98.4 ±0.78	99.0 ±0.28	1.00 ±0.02	100.65±0.52	100.52±0.53	100.1 ±0.60	101.5 ±0.92	101.49±0.51	102.39±0.30

All values are mean ± SD (n=3)

Table 8: Summary of Regression Analysis and ANOVA for acid neutralization capacity

	DF	SS	MS	F	P-value Prob > F
Regression	5	7.74	1.54	32.45	0.0081
Residual	3	0.14	0.047		
Total	8	7.88			Significant
Coefficient	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}
Coefficient value	12.47	0.40	1.05	-0.11	0.065	-0.18
P-value	0.004	0.019	0.0013	0.7021	0.339	0.378

Full Model: $Y1=12.47+ 0.40 X_1+1.05 X_2 - 0.11X_1X_2 + 0.065 X_1^2 - 0.18X_2^2$

Reduced Model: $Y_1 = 12.48 + 0.40 X_1 +1.05 X_2$

Table 9: Summary of Regression Analysis and ANOVA for raft strength

	DF	SS	MS	F	P-value Prob > F
Regression	5	16.05	3.21	9.55	0.046
Residual	3	1.00	0.33		
Total	8	17.06			Significant
Coefficient	b_0	b_1	b_2	b_{11}	b_{22}	b_{12}
Coefficient value	3.056	0.133	1.498	0.08	-1	0.47
P-value	0.0058	0.612	0.0079	0.092	0.33	0.800

Full Model: $Y1 =3.056 +0.133 X_1+1.498 X_2+0.08X_1X_2 -1.00 X_1^2 +0.47 X_2^2$

Reduced Model: $Y1 = 3.056 +1.498 X_2$

Statistical Analysis of Factorial Design Batches

Full and reduced model for acid neutralization capacity

The summary of regression analysis and ANOVA for acid neutralization capacity is shown in Table 8. The 3D surface plot is shown in Figure 5 (a). From the equation of full model, reduced model is drawn by rejecting insignificant factors on the basis of p value. it was found that variable X1 that is Ratio of Sodium alginate and pectin shows positive effect on acid neutralization capacity. Variable X2 that is amount of calcium carbonate shows positive effect on acid neutralization capacity more significant compare to variable X2. It can be qualitatively concluded that X1 and X2 had significant effect on response.

Full and reduced model for raft strength

The summary of regression analysis and ANOVA for raft strength is shown in Table 9. The 3D surface plot is shown in Figure 5 (b). From the equation of full model, reduced model is drawn by rejecting insignificant factors on the basis of p value. it was found that variable X1 that is Ratio of Sodium alginate and pectin shows positive effect on acid neutralization capacity. Variable X2 that is amount of calcium carbonate shows positive effect on acid neutralization capacity more significant compare to variable X2. It can be qualitatively concluded that X1 and X2 had significant effect on response.

In all batches F7, F8 and F9 showed almost similar acid neutralization capacity but batch F8 showed high raft strength compared to batch F7 and F9. So, batch F8 was selected as optimized batch.

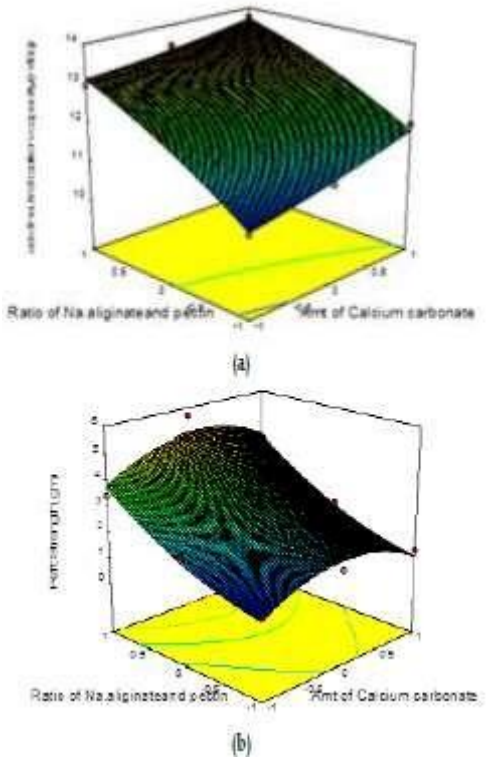

Fig. 5: Response surface plots showing effect Ratio of sodium alginate: pectin and amount of calcium carbonate on acid neutralization capacity (a) and raft strength (b)

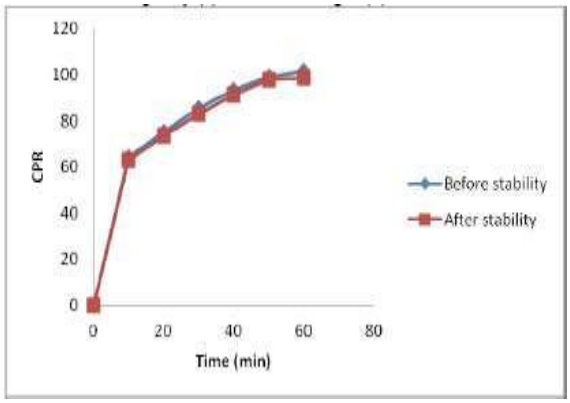

Fig. 6: Comparative Dissolution Profile of Batch F8 initially and after 1 month stability

Table 10: Evaluation of Optimized Batch F8 after stability study

After accelerated stability study 40 ± 2°C and 75 ± 5% RH		
Evaluation parameters	**0 days**	**30 days**
Hardness (Kg/cm²)	5.1	4.9
Friability	0.64	0.62
%drug content	101.1	100.5
Acid neutralization capacity (mEq)	13.45	12.96
Raft Strength (g)	5.69	5.23
In vitro drug release (1 h)	101.58	98.87

Results of Stability Study of Optimized Batch

After one month of accelerated stability study (40ºC ± 2ºC and 75 ± 5% RH) of optimized batch F8, all evaluation parameters and dissolution test were performed. The results are shown in Table 10 and comparison of drug release profile in Figure 6. Results of the accelerated stability study had shown no remarkable change in the release profile of Lafutidine from tablets after one month accelerated stability study. It was concluded that chewable tablet prepared by sodium alginate (raft forming agent) in combination with calcium carbonate (antacid) and sodium bicarbonate (gas generating agent) can form a floating raft in the presence of 0.1 N HCl. Raft strength was directly proportional to the amount of sodium alginate in the tablet. The amount of calcium carbonate and amount of sodium bicarbonate in the tablet were critical parameters in the formulation development. The optimized formulation had good raft strength, sufficient acid neutralization capacity and satisfactory in vitro drug release. The drug was also compatible with all excipients used in the formulation. The formulation was also stable at accelerated conditions of temperature and humidity for 1 month.

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