Research Article

Evaluation of effervescent floating bed of Lafutidine in treatment of hyperacidity condition: Statistical design and *in-vitro* studies

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Abstract

Objective: The current study involves the development of oral effervescent floating bed of Lafutidine and the optimization of their *in-vitro* drug release. **Materials and methods:** A 3^2 Full factorial design was employed to systematically optimize the drug delivery containing two polymers. Inotropic gelation method was utilized to prepare floating beads. The proportions of Sodium Alginate and Sodium Bicarbonate were varied to be fitted in 3^2 full factorial design. Percent entrapment efficiency (M), drug release at 24h were taken as responses. Response surface plots were drawn and the optimum formulation was selected by desirability function. **Results:** *In-vitro* drug release study was carried out using simulated gastric fluid (SGF) pH 1.2. The experimental values of M, % Entrapment efficiency and % drug release at 1hr for check point batch were found to be 84.33%, and 22.05% respectively. The release profile indicated anomalous (non-Fickian) transport mechanism. **Conclusion:** The developed formulation was stable and provided sustained release of the drug over a period 12 hr. The optimized batch was passed stability test. It is concluded that the method attempted to formulate effervescent floating beads of lafutidine being simple and acceptable.

***Keywords*:** 3^2full factorial design, floating bed, ionotropic gelation, sweling index, entrapment efficiency

Introduction

The formulated multiparticulate increases the gastric residence time and provide the sustained release of drug. The formulated dosage forms will release the drug at the site of absorption- i.e., Upper GI tract, to optimize formulation by applying statistical design, to formulate sustain release multiparticulate system by using gas forming agent by ionotropic gelation method. Lafutidine is a H_2 receptor antagonist which used in to hyperacidity condition. The main drawback of lafutidine conventional dosage forms is short biological half-life, frequent administration and it has low water solubility. These criteria's makes lafutidine an ideal candidate for the development of multi-particulate formulation to release the drug at a sustain manner as well as reduce the dosage frequency. Lafutidine is least absorbed from lower part of gastrointestinal tract and better absorbed from the stomach (Vasava and Jha, 2011; Jassal et al., 2015).

By studying of Effervescent drug delivery for oral administration W0066089 (Pather et al., 2000) patent, we found that there is certain disease which require drug release after lag time and total floating from the time of administration. Lafutidine has low solubility and short half-life. It is available in form of sustained release dosage form release over long time. So, there is need to develop multiparticulate effervescent floating drug delivery. The aim of the present study is an evaluation of effervescent floating bed of Lafutidine in treatment of hyperacidity condition: Statistical design and *in-vitro* studies.

Materials and methods

Materials: Lafutidine was procured from Pure chem, Ankleshwar, Sodium alginate was obtained from Molychem, Mumbai, Pectin was procured from ACS chemicals, Ahmedabad, Calcium chloride, Hydrochloric acid and Sodium bicarbonate were procured from Finar Limited, Ahmedabad.

Methods of preparation of beads

Ionotropic gelation method

All the ingredients like drug, polymer and gas forming agent

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were accurately weighed and prepared by ionotropic gelation method. Required amount of sodium alginate, pectin and sodium bicarbonate were dissolved in 10 mL double distilled water with constant stirring at 250 rpm on magnetic stirrer. Accurately weighed amount of drug was than added. The resultant mixture was extruded drop by drop from 18G needle into 1% to 4% calcium chloride as cross-linking agent (100 mL) under magnetic stirrer at 300 rpm and the droplets were retained for 10 min in the cross-linking solution to complete the reaction. Then the prepared beads were filtered and dried at room temperature for 24 hrs (Malakar and Nayak, 2012; Singh and Kim, 2000).

Optimization of variables using full factorial design

From the preliminary studies it was concluded that Sodium bicarbonate and sodium alginate have the significant effect on entrapment efficiency as well as drug release also. A 3^2 randomized full factorial design was used in present research work. In this design 2 factors were evaluated, each at 3 levels and experimental trials were performed. The concentration of both the polymers Sodium alginate/ pectin (X_1) and Sodium bicarbonate concentration (X_2) were selected as independent variables, while entrapment efficiency (Y_1) and %drug release (Y_2) were selected as dependent variables (Fatima and Kakatum, 2015; Chinta et al., 2014; Elmashad and Ashmony, 2012).

The polynomial terms were used to evaluate the responses. Where, Y is the dependent variable. b_0 is the arithmetic mean response of 9 runs and b is estimated coefficient for the factor (Table 1).

$$Y= b_0+b_1X_1+b_2X_2+b_{11}X_1X_1+b_{22}X_2X_2+b_{12}X_1X_2$$

Evaluation parameters

Micromeritics Properties (Vishami and Laxmi, 2015; Reddy et al., 2012; Sayeh et al., 2014)

Angle of repose (θ)

The angle of repose of prepared beads will determine by glass funnel method, weigh required quantity of the prepared products using following equation:

$$\theta = Tan^{-1}h / r$$

Where, θ = angle of repose h = height of the pile and r = radius of the powder cone

Bulk density

The bulk density of prepared beads will be measured by using following equation:

Bulk density = Weight of products in gram / Bulk volume of products in cm^3

Tapped density

The tapped density of prepared beads will be measured by using following equation

Tapped density = Mass of products / Volume of micro products after tapping.

Carr's compressibility index

This is an important property in maintaining uniform weight. It is calculated using following equation.

% Compressibility Index = Tapped density – Bulk density X100 / Tapped density

Hausner's ratio

Hausner's ratio of prepared beads will calculated using following equation.

Hausner's ratio=Tapped Density X 100 / Bulk Density

Particle size determination

The size of micron sized multiparticulate is measured by compound microscope and optical microscopy, while larger size of multiparticulate is measured by digital vernier callipers e.g., beads.

Percentage yield

The yield of prepared beads was calculated using the following equation:

% Yield = (mass of prepared formulation)/(mass of drug+ mass of polymer)] × 100

Drug entrapment efficiency

Accurately weighed 100 mg of prepared beads from each batch were taken separately. Then beads were crushed using mortar and pestle. The crushed powder was placed in 50 ml 0.1 N Hydrochloric acid with pH 1.2. The polymer debris formed after disintegration of bead was removed filtering through 0.22 μm pore size Whatman filter paper. The drug content in the filtrate was determined spectrophotometrically using a UV–Visible spectrophotometer (Shimadzu, Japan) at 282 nm. The drug entrapment efficiency of beads was calculated by using this following formula:

% Entrapment efficiency = experiment drug content/ theoretical drug content x100

Swelling study

The swelling study of prepared beads was determined by water uptake study. An accurately weighed mass of beads was immersed in acidic media (0.1 N HCl, pH 1.2) for 2 hr. After removal of samples, the excess fluid was carefully removed from the surface with a filter paper. The swollen beads were weighted, dried until constant weight, and weighted again. Swelling index was calculated by the formula:

Swelling Index = W_t – W 0 X 100 / W

Where,

W_t = Weight of products after water uptake. W_0 = The initial weight of products.

In -vitro floating study

The *in-vitro* floating time of prepared beads was measured using 0.1 N HCl, pH 1.2. These beads were floated after being placed in the acidic medium. Here, Sodium bicarbonate in the beads was responsible for floating. Low-density bicarbonate can lower the density of the polymeric systems with incorporation.

Floating lag time and total floating time

The floating lag time is defined as the time taken by the beads to reach the top from the bottom of the dissolution flask. The floating lag time of beads was measured by visual inspection. The time for which the formulation float constantly on the surface of the medium is known as the duration of floating. Total floating time of beads was determined by visual inspection.

In vitro drug release studies

In vitro drug release of beads was carried out using USP II dissolution test apparatus in 0.1 N HCl (pH 1.2) as dissolution medium. The temperature was maintained at 37±0.5 °C with 50 rpm agitation speed. At appropriate time intervals 5 ml samples were collected and replaced with 5mL of fresh solution. The samples were assayed spectrophotometrically at 282 nm.

Kinetics analysis of drug release

The mechanism of drug release was analysed by fitting the dissolution data with different mathematical models (Korsemeyer–Peppas, Higuchi, First-order, Hixson– Crowell and Baker–Lonsdale). To analyze the mechanism of drug release from the formulations, the in vitro dissolution data was fitted to Zero-order, First-order, Higuchi, and Korsmeyer and Peppas release models (Dandang, 2013; Ashra, 2014; Kumar et al., 2011). In this by comparing the obtained r values, the best fit model (r value nearest to 1) was selected.

Zero order kinetics

Drug dissolution from pharmaceutical dosage forms that do not disaggregate and release the drug slowly, if the area does not change and no equilibrium conditions are obtained can be represented by the following equation.

$$Q_t = Q_o + K_{ot}$$

Where, Q_t = Amount of drug dissolved in time t, Q_o = Initial amount of drug in the solution and K_o = Zero order release constant.

First order kinetics: To study the first order release rate kinetics the release rate data were fitted to the following equation.

$$\text{Log } Q_t = \log Q_o + K_{1t}/2.303$$

Where, Q_t = Amount of drug released in time t, Q_o = Initial amount of drug in the solution and K_1 = First order release constant.

Higuchi model: Higuchi developed several theoretical models to study the release of water soluble and low-soluble drugs incorporated in semisolids and or solid matrices. Mathematical expressions were obtained for drug particles dispersed in a uniform matrix behaving as the diffusion media (Ashra, 2014).

The Higuchi equation is $Q_t = K_H$ x t 1/2 Where, Q_t = Amount of drug released in time t and K_H = Higuchi dissolution constant

Accelerated Stability study

The accelerated stability study was conducted as per ICH guideline. Accelerated stability was carried out under the condition 40º C ± 2º C 75%RH ± 5% for 1 month (Ashra, 2014).

Results and discussion

Optimization of 3^2 full factorial design

All factorial batches were studied for its floating lag time, there were no lag time for all formulations because of gas forming agent such as $NaHCO_3$ provide immediate floating of beads. The total floating time was >12 hr. for all floating beads formulation. They were remaining float still after complete drug release. The percentage entrapment efficiency of floating beads was carried out for all the

Table 1. Formulation Batches using 3^2 Full Factorial Design

Ingredients (mg)	B1	B2	B3	B4	B5	B6	B7	B8	B9
Lafutidine	10	10	10	10	10	10	10	10	10
Sodium Alginate	300	400	500	300	400	500	300	400	500
Pectin	500	600	700	500	600	700	500	600	700
$NaHCO_3$	600	700	800	600	700	800	600	700	800
CaCl2	2%	3%	4%	2%	3%	4%	2%	3%	4%
Water (ml)	10	10	10	10	10	10	10	10	10

Coded Value	Actual Value	
	Sodium Alginate:Pectin	$NaHCO_3$
-1	3:5	6
0	4:6	7
+1	5:7	8

batches. It was found that as increase in concentration of pectin and $NaHCO_3$ entrapment efficiency was increase. The highest entrapment was found in batch B9 (Table 1 and 2).

The *in-vitro* drug-release studies were carried out for all formulated Sodium bicarbonate entrapped sodium alginate/ pectin floating beads containing lafutidine (Figure 1).

From the results it was concluded that polymer concentration and amount of gas forming agent such as $NaHCO_3$ added can control the release behaviour of floating beads. It showed delay in drug release when increase in polymer concentration and $NaHCO_3$ concentration. It also showed reduction in amount of drug which was release at absorption site. The initial burst release was also reduced when increase in Sodium alginate/pectin proportion and concentration of Sodium bicarbonate. The batch B1 and B2 showed 97.16 and 97.38% drug release in after 6 hr. The batch B7, B8 and B9 showed drug release 97.40, 95.79 and 92.31% respectively up to 12 hr (Table 3 and 4).

Statistical analysis

The statistical model was incorporated and polynomial terms were used to evaluate the various responses (Ashra, 2014: Patel and Patel, 2015).

$$Y = b0 + b_1X_1 + b_2X_2 + b_{11}X_1X_1 + b_{22}X_2X_2 + b_{12}X_1X_2$$

The polynomial terms were used to considering the magnitude coefficients. The data were analyzed using Microsoft excel 2007.

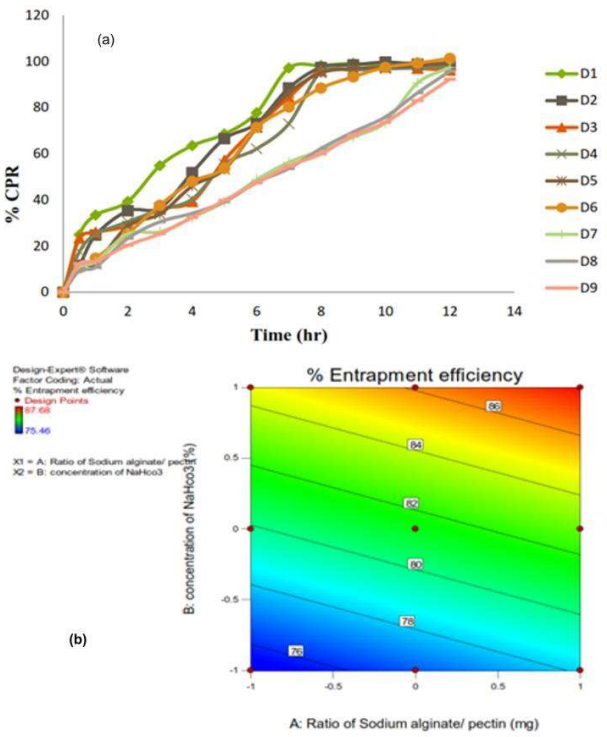

Figure 1. (a) *In-vitro* drug release of full factorial design batches **(b)** Contour plot depicting effect of polymer ratio and $NaHCO_3$ on % Entrapment efficiency

Table 2. Composition of various Factorial Batches and Actual vs Coded Value

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8	F9
Drug	10	10	10	10	10	10	10	10	10
Sodium Alginate	300	400	500	300	400	500	300	400	500
Pectin	500	600	700	500	600	700	500	600	700
$NaHCO_3$	600	700	800	600	700	800	600	700	800
$CaCl_2$	2	3	4	2	3	4	2	3	4
Distill Water	10	10	10	10	10	10	10	10	10

Table 3. Evaluation of factorial batches

Code	B_d (g/cm^3)	T_d (gm/cm^3)	Angle of Repose	%Yield	%Swelling Index at 2 (hr)	Particle Size (mm)
B1	0.455±0.004	0.498±0.009	30.43	73.55	11.33±1.2	1.37±0.06
B2	0.462±0.005	0.508±0.006	29.75	75.38	15.46±0.3	1.51±0.08
B3	0.466±0.006	0.555±0.007	27.58	79.80	12.41±0.2	1.58±1.67
B4	0.357±0.007	0.384±0.009	28.29	81.81	10.35±0.1	1.34±1.9
B5	0.358±0.005	0.382±0.046	30.04	82.6	7.73±0.5	1.40±0.09
B6	0.416±0.004	0.454±0.011	27.49	73.58	8.61±0.3	1.82±0.14
B7	0.454±0.006	0.5±0.006	28.78	79.98	7.74±0.1	1.40±0.15
B8	0.398±0.008	0.443±0.007	26.55	80.91	8.61±0.3	1.9±0.0075
B9	0.384±0.004	0.454±0.005	28.56	82.20	9.84±0.2	1.84±0.15

Results are (Mean±SD), n=3

The obtained results of ANOVA suggested that F calculated value of each dependent variable like %entrapment efficiency, % drug release at 12 hr as given in table 5 and 6. Tabulated F (5, 3) value was found to be 9.01 at a= 0.05. Calculated F values were greater than tabulated for all dependent variables therefore selected factors have significant effect on all dependent variables. From the results of regression analysis, it was found that both independent variables had statistically significant influence on all dependent variables as significance F value < 0.05.

Statistical analysis for % Entrapment efficiency (Y1)

The polynomial equation was generated from Microsoft Excel 2007.

$$Y = 82.91 + 1.53X_1 + 4.74X_2 - 1.0296X_1X_1 - 1.0266X_2X_2 + 1.345X_1X_2$$

For %entrapment efficiency as, seen from the equation and graph indicated that the concentration of Sodium bicarbonate increases the drug entrapment also increased. The pectin/ Sodium alginate also influenced the entrapment of drug. So, both factors have significant effect on entrapment of drug (Figure 2 and 3).

As seen from equation the coefficient of X_2 ($NaHCO_3$ concentration %) variable was lower than coefficient of X_1 (Ratio of sodium alginate/pectin) variable indicated that effect of X_1 variable was more significant than effect of X_2 variable. The positive sign of both the coefficient indicated that there was increase in the response Y_1 with increase in either of variables. It was observed that X_1, X_2, X_1X_1 were significant variables with p- value less than 0.05, while X_1X_2 variable was not significant.

Statistical analysis for % drug release at 2 hr (Y_2)

The polynomial equation was generated from Microsoft Excel 2007

$$Y = 29.71 - 0.03X_1 - 8.32X_2 - 0.61X_1X_1 + 0.87X_2X_2 + 0.1825X_1X_2$$

For the drug release at 12 hr, as seen from the equation and graphs the decrease in drug release initially when increase in Sodium alginate/ pectin and concentration of $NaHCO_3$. The negative sign indicates decrease the response with increase in level of independent variables. The coefficient of X_1 was higher than coefficient of X_2 which indicated that the effect

Table 4. Observed dependent variable of full factorial design

Code	Y_1 (%Entrapment efficiency)	Y_2 (%Drug Release at 2 hr)
B1	76.5±1.00	42.52
B2	76.88±1.54	30.21
B3	75.46±1.04	36.20
B4	78.45±1.09	33.57
B5	83.54±1.21	29.48
B6	84.15±1.06	27.30
B7	83.34±0.93	27.70
B8	86.26±0.97	22.18
B9	87.68±0.94	20.11

Results are (Mean±SD), n=3

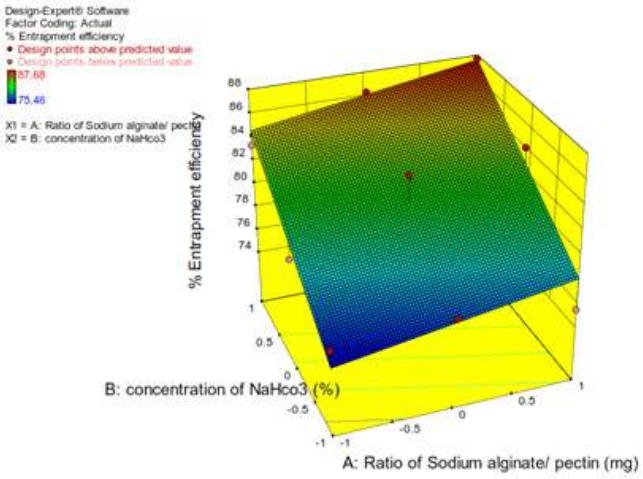

Figure 2. Surface response plot showing effect of $NaHCO_3$ and polymer ratio on % Entrapment efficiency

Table 5. Summary of results of full model regression analysis

Y_1 % Entrapment Efficiency							
(Y_1)	**B_0**	**B_1**	**B_2**	**B_{11}**	**B_{22}**	**B_{12}**	**R^2**
Coefficient	82.91	1.5	4.74	-1.296	-1.0266	1.345	0.961
p Value	4.94E-07	0.0859	0.0041	0.297	0.3923	0.161	
Y_2 Drug Release at 12 hr							
(Y_2)	**B_0**	**B_1**	**B_2**	**B_{11}**	**B_{22}**	**B_{12}**	**R^2**
Coefficient	29.71	-3.031	-8.32	0.38	0.61	0.87	0.998
p Value	9.01E-07	0.00013	6.72E06	0.061	0.3049	0.0255	

Table 6. Results of ANOVA

X_{21}variable was more significant as compare to X_2variable. From the equation it was concluded that only X_1 and X_2 variables were significant, while polynomial terms X_1X_1 and X_2X_2 were not significant because of higher p-value (> 0.05). The contour plot and surface response plot showed effect of sodium alginate/pectin ratio and concentration of $NaHCO_3$ on the drug release at 12 hr (Figure 4).

Optimization of batch from desirability function using Design expert version 10

The optimum formulation was selected based on the criteria of attaining value with the minimum and the maximum limit of formulation variables. An overall desirability function dependent on all the investigated formulation variables was used to predict the ranges of variables where the optimum formulation might occur. The desirable ranges are from zero to one (least to most desirable, respectively). The maximum value for entrapment of drug was selected 87.68 % for optimization, the value of drug release at 2 hr kept minimum 20.11 for selection of optimized batch.

From the graph (Figure 1 and 2), it was concluded that the F9 batch was selected as optimized batch which has composite desirability 0.997 as per given table 7. The predicted value of Y1, Y2 was 87.602 and 20.017 respectively. Optimized batch is given table 8 and figure 5.

Prediction of release mechanism for optimized batch

The dissolution profile of optimized batch was analyzed

Table 6. Results of ANOVA

Parameters	D_f	SS	MS	F Calculated	p-Value
		Y_1%Entrapment Efficiency			
Regression	5	161.01	32.20	15.17	0.0024
Residual	3	6.36	2.12		
Total	8	473.40			
		Y2 % Drug release at 12 hr.			
Regression	5	473.14	94.628	1082.86	4.42
Residual	3	0.2623	0.0874		
Total	8	474.40			

Table 7. Solution obtained from design expert Version 10

Batch	Polymer Ratio	NaHCO3 Concentration	%Entrapment efficiency	%Drug Release	Desirability
S1	1	1	87.602	20.17	0.997
S2	0.983	1	87.577	20.045	0.996
S3	1	0.983	87.520	20.129	0.993
S4	0.794	1	87.293	20.381	0.978
S5	0.779	1	87.271	20.408	0.997

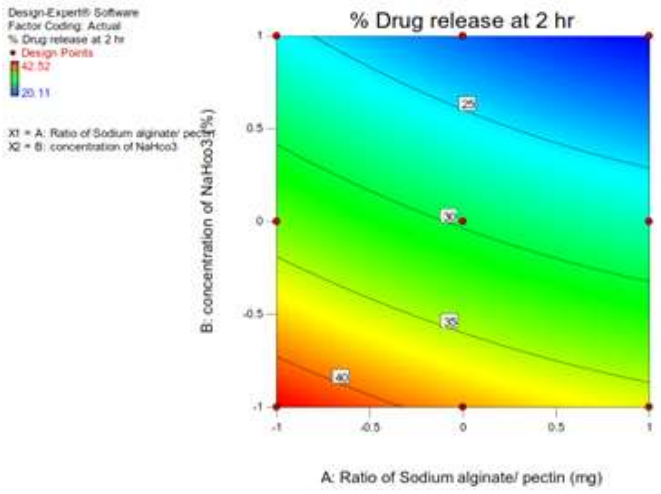

Figure 3. Contour plot depicting effect of polymer ratio and $NaHCO_3$ concentration on % drug release at 2 hr

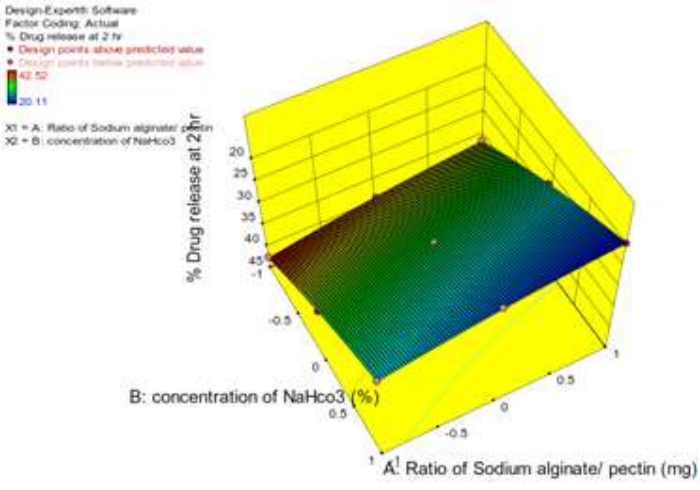

Figure 4: Surface response plot indicating effect of polymer ratio and $NaHCO_3$ concentration on %drug release at 2 hr

using kinetic model such as korsemeyer and Pappas to ascertain the kinetic drug release (Fule and Amin, 2014; Dween and Chimta, 2015). The diffusion coefficient n is the indicative the mechanism of drug release. The n value is used to characterize different release mechanisms, concluding for values for a slab, of $n < 0.5$ for Fickian diffusion mechanism, 0. 5 < n < 0.85 to non-Fiction (Anamolous) transport, values of n is 0.85-1.0 to Case-II transport (zero order), and n > 1.0 to super case II transport as per given in table 9.

Stability study

The stability study indicated that the formulation was physically and chemically stable with no significant changes in any of the evaluated parameters when stored at the 40 ± 2°C and 75 ± 5% RH conditions for 1 month. It was observed that there was a slight change in all parameters which have > ±5 % bias which was insignificance. Negligible difference was observed in results obtained from optimized batch and after the stability study (Table 10).

From the stability study f1 was found to be 2.99 and f2 was found to be 85.80 which ensured that the dissolution data for before stability and after stability of optimized batch was equivalent. Thus, from the f1 and f2 data it could be concluded that both dissolution profiles were similar and no significant changes observed in dissolution profile. From the stability study, it was concluded that the effervescent floating beads of Lafutidine was stable after 1-month stability period.

Conclusion

In this study of effervescent floating bead containing multi-particulate drug delivery system, the effervescent floating beads of Lafutidine was successfully formulated using Sodium alginate, pectin, and Sodium bicarbonate for the treatment of hyperacidity condition. The formulated dosage forms float over the 0.1 N HCl and provide the drug release for prolonged period (up to 12 hr). Among various batches of full factorial design, the batch F9 (5%:7% Sodium alginate/ pectin ratio) and (8% Concentration of sodium bicarbonate) was selected as optimized batch with 0.997 overall desirability, high entrapment efficiency and remain for extended period. The developed formulation was stable and

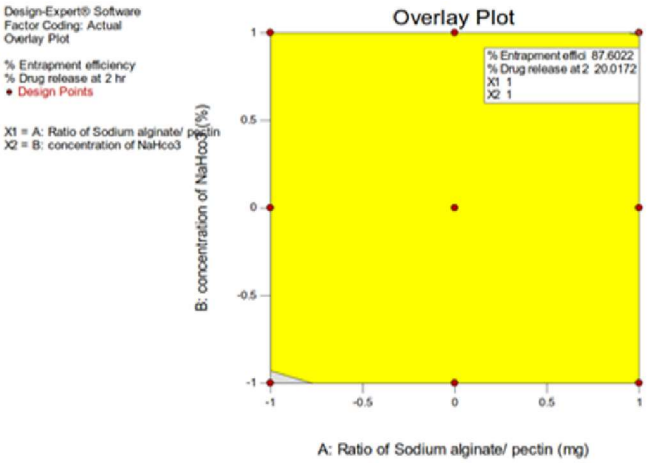

Figure 5. Optimization of batch from desirability function using design expert-10

Table 8. Formulation composition of optimized batch

Ingredients	Quantity
Lafutidine	10 mg
Sodium alginate	500 mg
Pectin	700 mg
Sodium bicarbonate	800 mg
Double distilled water	10 mL

Table 9. Model fitting for release profile of optimized batch

Code	Zero order	First Order	Higuchi	Korsemeyer Peppas	Hixon Model
Optimized Formulation	R^2	R^2	R^2	R^2	R^2
	0.9982	0.9750	0.9737	0.9789	0.9982

Table 10. Effect of stability testing on various parameters of optimized batch

Parameters	Before Stability Period	After Stability Period	%Bias
% Yield	82.20	80.54	-2.061
% Swelling Index	9.48±0.199	9.52±0.212	0.421
Particle size	1.48±0.15	1.80±0.23	-2.173
%Entrapment efficiency	87.68±0.94	86.45±0.124	-1.402
Floating Lag time	No Lag Time	No Lag time	-
Total Floating time	> 12 hr	> 12 hr	-

provided sustained release of the drug over a period 12 hr. The optimized batch was passed stability test as there were no significant change in all parameters after storage. It is concluded that the method attempted to formulate effervescent floating beads of Lafutidine being simple and acceptable.

Conflict of Interest: None

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