Formulation and evaluation of mucoadhesive tablets of furosemide by design of experiment

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Aim and objective
The present investigation concerns with the development and evaluation of mucoadhesive tablets of furosemide, which were designed to prolong the gastric residence time after oral administration.
Materials and methods
Mucoadhesive tablets of furosemide were formulated using different mucoadhesive polymers such as locust bean gum, tamarind gum, and chitosan in various ratios for treatment of hypertension by using design of experiment.
Results and discussion
The tablets were evaluated for various parameters such as compatibility studies, drug content, weight variation, hardness, thickness, friability, swelling studies, *in vitro* drug-release studies, *in vitro* mucoadhesion strength, *ex vivo* residence time test, and release rate kinetics. The *in vitro* release kinetics studies reveal that all formulations fit well with zero order, followed by Korsmeyer–Peppas, Higuchi, and the mechanism of drug release is erosion. After analysis of different evaluation parameters and drug-release kinetics, formulation code F16 was selected as a promising formulation for delivery of furosemide as a mucoadhesive gastroretentive tablet with best mucoadhesive strength and 98.76% cumulative percentage drug released at the 12th hour. Stability studies of the selected formulation were carried out to determine the effect of formulation additives on the stability of the drug and also to determine the physical stability of the formulation.
Conclusion
The stability studies were carried out at 40°C/75% RH for 90 days. There was no significant change in the physical property and weight variation, hardness, thickness, friability, *in vitro* drug-release studies, and *in vitro* mucoadhesion-strength drug content during the study period.

Keywords:
furosemide, gastroretentive tablet, mucoadhesive tablets, swelling index

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Introduction

One of the novel approaches for drug delivery system is gastroretentive delivery system. Prolonging the gastric retention of a delivery system is desirable for achieving therapeutic benefit of drugs that are absorbed from the proximal part of the gastrointestinal tract (GIT) or that are less soluble in GIT or are degraded by the alkaline [1]. Mucoadhesive controlled-release dosage formulations have gained considerable attention due to their ability to adhere to the mucous layer and release the drug in a sustained manner. Mucoadhesive delivery systems offer several advantages over other oral controlled-release systems by virtue of prolongation of residence time of drug in GIT, and targeting and localization of the dosage form at a specific site [2]. Furosemide, an antihypertensive agent, has been widely used for the treatment of hypertension, heart failure, and edema. Furosemide is acid-stable and completely absorbed in gastric pH. Furosemide's biological half-life is 2–3 h and bioavailability in the stomach is 60–64%. The pKa value is 3.5. Hence, as the pH increases, it becomes unstable and undergoes a degradation reaction, thus reducing its bioavailability. Water-soluble drugs are considered difficult to deliver in the form of sustained or controlled-release preparation due to their susceptibility to 'dose dumping phenomenon.' Attempts have been made to regulate their release process by use of mucoadhesive polymers in order to achieve a once-a-day dose treatment [3]. The current study aims at developing and evaluating oral mucoadhesive drug delivery system of furosemide, as it may prove to be more productive than the conventional controlled-release systems by virtue of prolongation of drug-residence time in the GIT. Furosemide

exhibits pH-dependent degradations and is more stable in acidic pH compared with neutral or alkaline pH conditions. Hence, an attempt was made to develop mucoadhesive tablets of furosemide, which would increase the bioavailability of furosemide. The prepared tablets were evaluated for physical properties (thickness, weight variation, friability, and hardness), swelling index, bioadhesion test, *in vitro* drug release, and accelerated-stability studies [4].

Materials and methods

Materials

Furosemide was obtained as a gift sample from Wockhardt Ltd (Aurangabad, India). Locust bean gum, tamarind gum, and chitosan were obtained from S.D. Fine (Hyderabad, India).

Method of preparation of mucoadhesive oral tablets

Mucoadhesive gastrointestinal tablets were formulated by direct compression method. All the ingredients of the formulation were passed through sieve no. 60 and were blended in a mortar with a pestle to obtain uniform mixing. The blended powder was then evaluated for precompression parameters. The blended powder of the core was compressed on 8-mm punch in a single-stroke multistation tablet punching machine that was removed [5] (Table 1).

The BBD matrix was generated using Design Expert software (Version 7.0, Stat-Ease Inc., Silicon Valley, California, USA), and the data obtained were analyzed by the same software. All responses were fitted to a second-order quadratic model by the Design Expert software. The second-order quadratic or polynomial equation can be approximated in the following mathematical model:.(1)

$$Y = \beta_0 + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_3 + \beta_4 X_1 X_2 + \beta_5 X_2 X_3 + \beta_6 X_1 X_3 + \beta_7 X_1^2 + \beta_8 X_2^2 + \beta_9 X_3^2$$

where Y is the level of the measured response, β_0 is the intercept, β_1–β_9 are the regression coefficients, X_1, X_2, and X_3 stand for the main effects, X_1X_2, X_2X_3, and X_1X_3 represent the interaction between the main effects, X_1^2, X_2^2, and X_3^2 are the quadratic terms of the independent variables that were used to simulate the curvature of the designed sample space. A backward-elimination procedure was adopted to fit the data to the quadratic model. The model adequacy was verified by analysis of variance (ANOVA), lack-of-fit and multiple correlation-coefficient (R^2) tests provided by the Design Expert software. The value of coefficients reflected the effect of independent variables and their interaction on the dependent variables. A positive coefficient indicates a synergistic effect; meanwhile, a negative one reflects an antagonistic effect. The significance of individual coefficients was determined by ANOVA test, and one was considered significant if the *P* value was less than or equal to 0.05. The quadratic models generated from the regression analysis were used to construct the three-dimensional graphs, in which the response parameter Y was represented by a curvature surface as a function of X. The effects of independent variables on the response parameters were visualized from the perturbation plots and two-dimensional contour plots. Further optimization was conducted with a desirability function [6] (Table 2).

Optimization using the desirability function

To optimize multiple responses, they should be highly correlated with each other. It is unlikely that the values desirable to optimize the effect of one response will have the same effect on the second response, thus a conflict can occur between them. Hence, the most favorable compromising zone must be sought for each of the responses without any bias. In the present study, all three responses were simultaneously optimized by a desirability function that uses the numerical optimization method introduced by Derringer and Suich in the Design-Expert software (Version 8.0, Stat-Ease Inc.). Recently, the desirability-function approach was reported in several articles for the optimization of multiple responses [7] (Table 3).

Table 1 List of dependent and independent variables in Box–Behnken design

Independent variables			Levels		
Variables	Name	Units	Low (−1)	Middle (0)	High (+1)
A	Locust bean gum	%	10	15	20
B	Tamarind seed gum	%	5	10	15
C	Chitosan	%	15	20	25
Dependent variable				Goal	
Y1	Ex vivo residence time	Hours		Maximize	
Y2	Mucoadhesive strength	Grams		Maximize	
Y3	Cumulative % drug released after 12 h	%		Maximize	

Table 2 Box–Behnken design with observed responses

Run	Amount of locust bean gum (%) (mg)	Amount of tamarind seed gum (%)	Amount of chitosan (%)	*Ex vivo* residence time (h)	Mucoadhesive strength (g)	Cumulative % drug released (%)
1	10	05	20	8	06.34±1.56	83.77±2.42
2	30	05	20	9	12.23±1.71	87.38±1.98
3	10	15	25	8	13.42±1.23	91.58±1.13
4	30	15	20	8	16.39±1.68	85.48±2.65
5	10	10	15	7	09.45±1.51	87.23±1.37
6	30	10	15	8	15.24±1.77	94.59±3.44
7	10	15	25	7	09.78±1.89	93.54±1.51
8	30	05	25	11	15.34±1.42	88.62±1.23
9	20	05	15	9	15.23±1.98	91.37±2.74
10	20	15	15	6	13.45±1.61	89.25±1.88
11	20	05	25	7	19.78±1.32	86.37±2.65
12	20	15	20	8	19.14±1.17	94.29±1.23
13	20	10	20	10	21.84±1.52	88.11±1.44
14	20	05	20	9	17.78±1.85	90.15±1.52
15	20	05	15	9	21.16±1.63	85.47±1.76
16	30	15	25	12	26.39±1.47	98.76±2.82
17	20	15	25	10	23.11±1.25	89.58±2.37

Table 3 Composition of furosemide mucoadhesive formulation by Box–Behnken design (weight in mg)

F.NO	Furosemide	LBG	TSG	CS	PVP K-30	DCP	Mg stearate	Aerosil	Total
F1	40	20	10	40	6	76	4	4	200
F2	40	60	10	40	6	36	4	4	200
F3	40	20	30	50	6	46	4	4	200
F4	40	60	30	40	6	16	4	4	200
F5	40	20	20	30	6	76	4	4	200
F6	40	60	20	30	6	36	4	4	200
F7	40	20	30	50	6	46	4	4	200
F8	40	60	10	50	6	26	4	4	200
F9	40	40	10	30	6	66	4	4	200
F10	40	40	30	30	6	46	4	4	200
F11	40	40	10	50	6	46	4	4	200
F12	40	40	30	40	6	36	4	4	200
F13	40	40	20	40	6	46	4	4	200
F14	40	40	10	40	6	56	4	4	200
F15	40	40	10	30	6	66	4	4	200
F16	40	60	30	50	6	06	4	4	200
F17	40	40	30	50	6	26	4	4	200

CS, chitosan; DCP, dicalcium phosphate; LBG, locust bean gum; TSG, tamarind seed gum.

Evaluation of mucoadhesive tablets

Physical parameters

Tablets were tested for hardness, friability, weight variation, and drug content. Hardness of the tablets was tested using a Monsanto hardness tester and friability of the tablets was determined in a Roche friabilator [8].

In vitro swelling studies

The degree of swelling of mucoadhesive polymer is an important factor affecting adhesion. For conducting the study, a tablet was weighed and placed in a petri dish containing 5 ml of 0.1 N HCl buffer, pH 1.2, in 6 h at regular intervals of time (1, 2, 4, and 6 h), the tablet was taken carefully by using filter paper. The swelling index was calculated using the following formula:.

$$\text{Swelling Index(S.I)} = (\text{Wt} - \text{Wo})/\text{Wo} \times 100$$

where S.I=swelling index, Wt=weight of the tablet after swelling at time t, Wo=weight of the initial tablet [9].

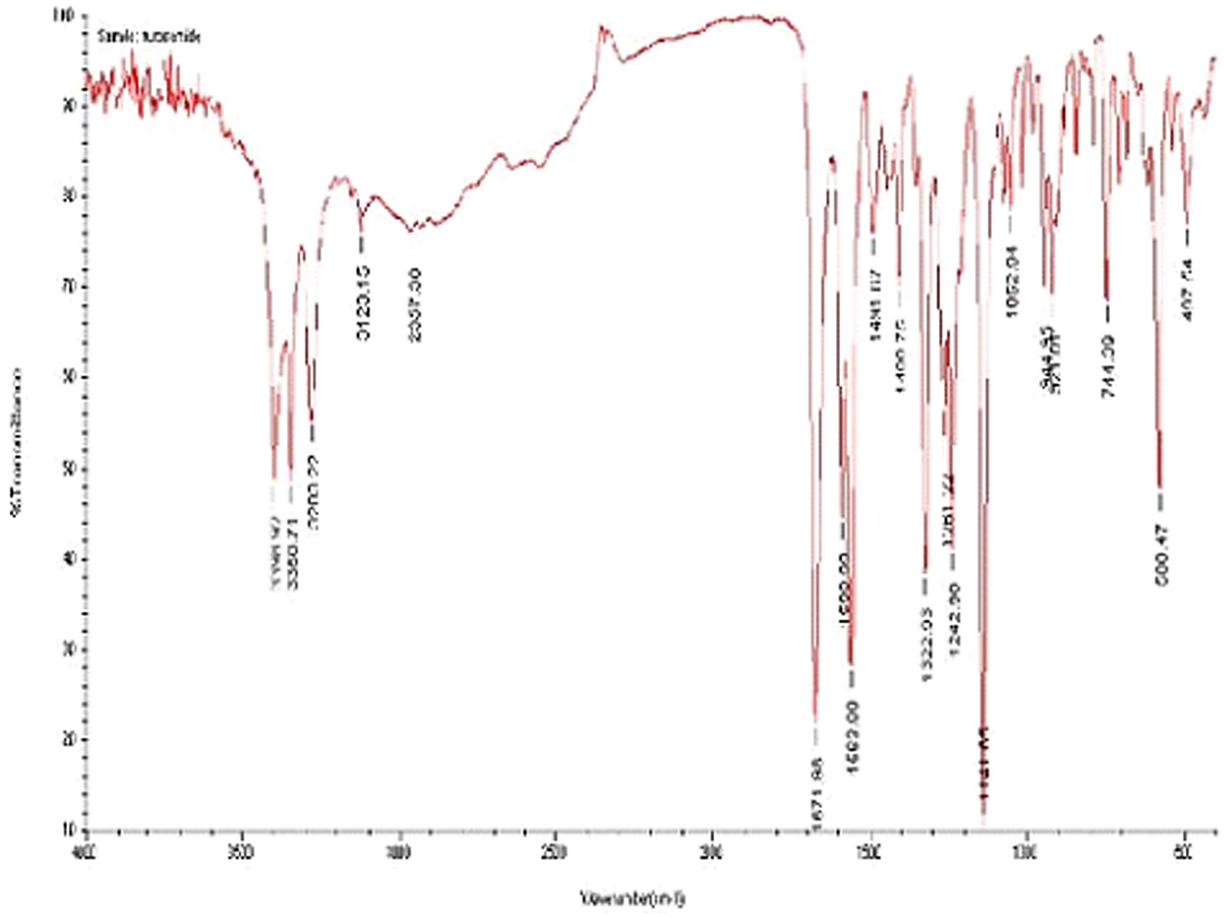
In vitro mucoadhesion study

Mucoadhesion strength of the tablets was measured on a modified two-arm physical balance. The sheep gastric mucosa was used as biological membrane for the studies. The sheep

Table 4 Postcompression evaluation tests

Formulation code	Hardness (kg/cm^2)	% Friability	Weight variation (mg)	Thickness (mm)	Content uniformity (%)
F1	4.8±0.5	0.426	199±0.2	3.11±0.13	98.24±0.8
F2	4.1±0.3	0.448	198±0.7	3.18±0.29	98.12±0.2
F3	4.9±0.1	0.513	200±0.5	3.23±0.34	97.28±0.9
F4	4.7±0.4	0.458	199±0.3	3.07±0.45	98.66±0.1
F5	4.8±0.6	0.484	200±0.4	3.42±0.76	98.25±0.5
F6	4.9±0.2	0.556	201±0.6	3.35±0.82	98.86±0.9
F7	4.9±0.3	0.462	199±0.2	3.18±0.12	97.78±0.8
F8	4.8±0.5	0.386	203±0.8	3.10±0.14	98.27±0.4
F9	4.7±0.4	0.539	199±0.5	3.01±0.17	98.96±0.9
F10	4.2±0.7	0.514	201±0.8	2.99±0.76	98.03±0.5
F11	4.8±0.3	0.486	202±0.3	3.15±0.31	98.27±0.4
F12	4.3±0.2	0.541	201±0.1	3.36±0.48	97.28±0.8
F13	4.6±0.4	0.413	198±0.4	3.27±0.55	97.33±0.7
F14	4.8±0.2	0.562	203±0.7	3.18±0.17	98.13±0.5
F15	4.4±0.5	0.442	201±0.9	3.45±0.29	98.35±0.8
F16	4.9±0.7	0.454	200±0.4	3.22±0.11	99.29±0.5
F17	4.0±0.2	0.456	198±0.9	3.17±0.17	97.65±0.3

Figure 1

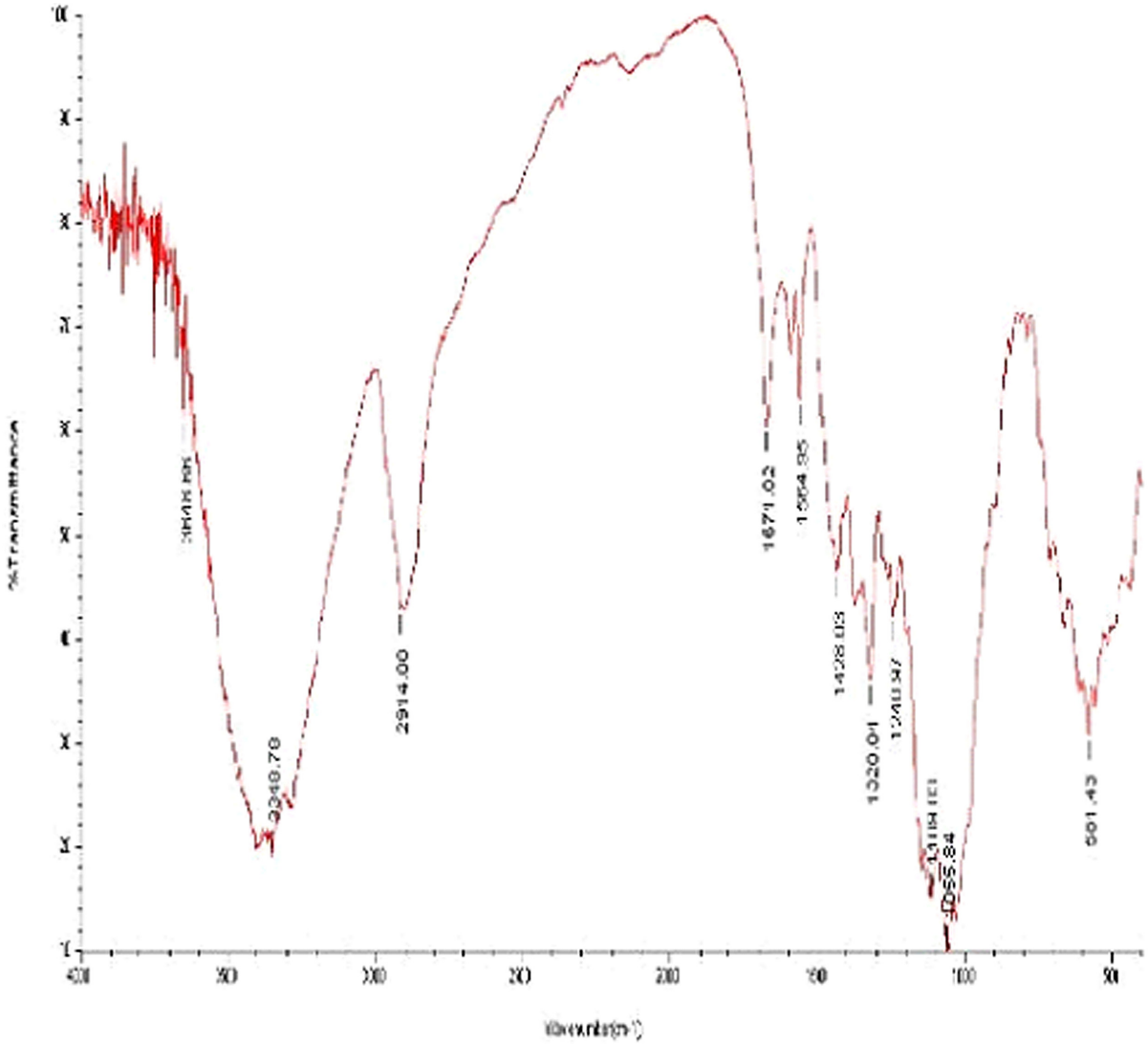


FTIR spectra of furosemide. FTIR, Fourier transform infrared.

gastric mucosa was obtained from the local slaughterhouse and was used within 3 h of procurement. The membrane was washed with distilled water and then with 0.1 N HCl buffer, pH 1.2, at 37°C.

The sheep gastric mucosa was cut into pieces and washed with 0.1 N HCl buffer, pH 1.2. The left pan of physical balance was removed. To the left arm of balance, a thick thread of suitable length was hung. To the free end of thread was attached a glass stopper of

Figure 2



FTIR spectra of optimized formulation. FTIR, Fourier transform infrared.

Table 5 Regression equations of the fitted models

Response	Equation
Ex vivo residence time $(Y1)$	$7+2\times1-3\times_2-1\times_3-3X^2{}_1+9X_1X_3+1X^2{}_2-3X_2X_3+3X^2{}_3$
Mucoadhesive strength $(Y2)$	$13.85+4.37\times_1+2.15\times_2+1.89\times_3+0.57X^2{}_1-2.16X_1X_3-2.55\ X^2{}_2-1.50\ X_2X_3-2.15\ X^2{}_3$
% Cumulative drug released (Y_3)	$83.26-3.52\times1+13.15\times2-9.39\times_3+1.82X^2{}_1-8.91X_1X_3+2.14\ X^2{}_2\ -14.15\ X_2X_3\ +2.53X^2{}_3$

Where Y_1, Y_2, and Y_3 are the predicted response and X_1, X_2, and X3 are the coded values of the test variables in the respective concentrations.

circular base (diameter 2.5 cm). A clean 250-ml beaker was placed below the glass stopper. A piece of gastric mucosa was tied to the glass vial, which was filled with 0.1 N HCl buffer. The glass beaker was tightly fitted into a glass beaker filled with 0.1 N HCl buffer, pH 1.2, at 37±0.5°C, so that it just touches the mucosal surface. The tablet was suck to the lower side of a rubber stopper. The two sides of the balance were made equal before the study. By keeping a 5-g weight on the right-hand pan, a weight of 5 g was removed from the right-hand pan, which lowered the pan along with the tablet over the mucosa. The balance was kept in this position for 1-min contact time. Mucoadhesive strength was assessed in terms of weight (g) required to detach the tablet from the membrane. The mean value of three trials was taken for each tablet. Mucoadhesive strength was measured as force of adhesion in Newtons [10]. The following formula was used and the results are shown in the table:.

$$\text{Force adhesion} = \text{Mucoadhesive strength}/100 \times 9.81$$

In vitro dissolution study

The USP dissolution test apparatus Lab matrix Manufacturing Ltd (Mumbai, India) (apparatus II paddle type), was used to study the drug release

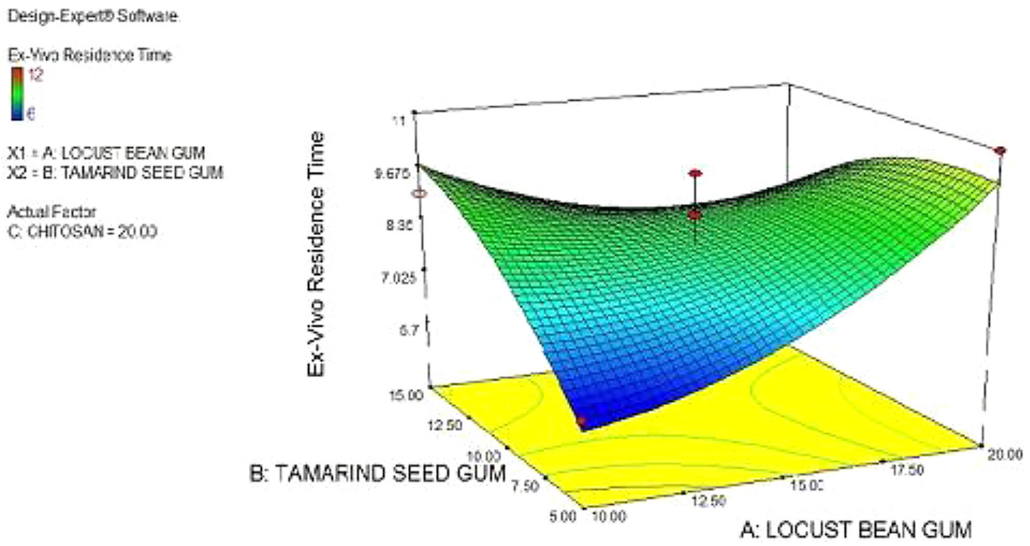
Table 6 Analysis of variance of the quadratic model for the response ex vivo residence time (Y1)

Source of variations	Sum of squares	Degree of freedom	Mean squares	*F* value	*P* value Prob>*F*	R^2
Model	2758.22	6	459.70	0.0181	<0.05	0.9994
A-amount of locust bean gum	93.15	1	93.15	0.0298	<0.05	
B-amount of tamarind seed gum	788.36	1	788.36	0.0342	<0.05	
C-amount of chitosan	19.55	1	19.55	0.0266	<0.05	
AB	2292.34	1	2292.34	0.0353	<0.05	
AC	1967.41	1	1967.41	0.0140	<0.05	
AB	2.19	1	2.19	0.0347	<0.05	
Residual	3452.21	6	575.37			
Lack of fit	3887.65	6	647.94	0.0261	<0.05	

Table 7 Analysis of variance of the quadratic model for the response mucoadhesive strength (Y2)

Source of variations	Sum of squares	Degree of freedom	Mean squares	*F* value	*P* value Prob>*F*	R^2
Model	1356.23	6	226.14	0.0135	<0.05	0.9997
A-amount of locust bean gum	23.89	1	23.89	0.0191	<0.05	
B-amount of tamarind seed gum	64.33	1	64.33	0.0322	<0.05	
C-amount of						
Chitosan	31.17	1	31.17	0.0178	<0.05	
AB	213.66	1	213.66	0.0296	<0.05	
AC	159.14	1	159.14	0.0323	<0.05	
AB	364.49	1	364.49	0.0251	<0.05	
Residual	569.20	9	63.21			
Lack of fit	489.37	6	81.15	0.0125	<0.05	

Figure 3



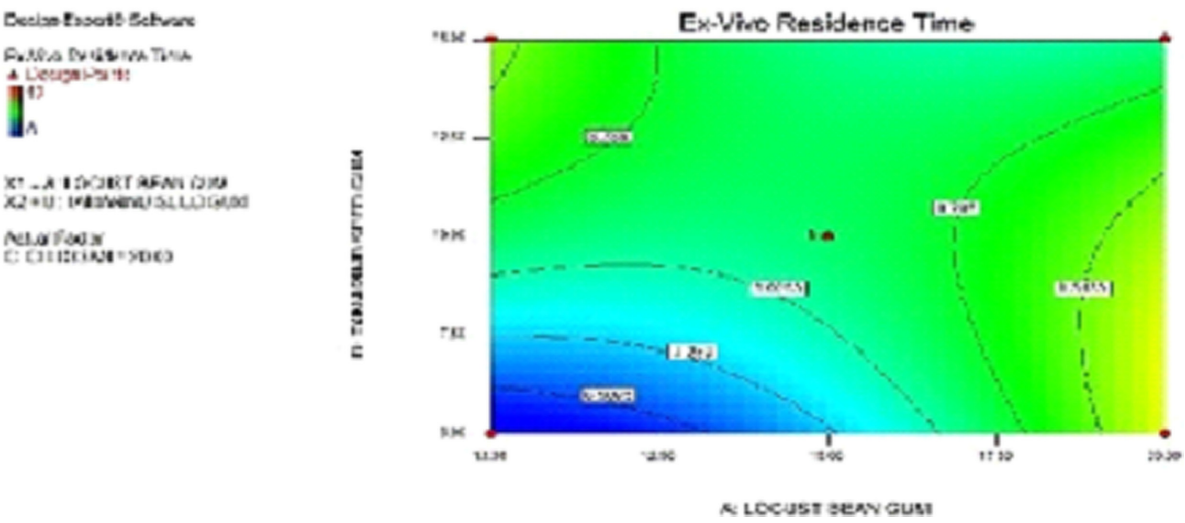
Response three-dimensional surface plot showing the influence of the amount of locust bean gum and amount of tamarind seed gum on ex vivo residence time fixed level of C.

from the tablets. The dissolution medium was 900 ml of 0.1 N HCl, pH 1.2. The release was performed at 37 ±0.5°C, with a rotation speed of 50 rpm. About 5-ml samples were withdrawn at predetermined time intervals and replaced with fresh medium. The samples were filtered through Whatmann filter paper and analyzed after appropriate dilution by ultraviolet spectrophotometer at 277 nm and drug release was determined from the standard curve [11].

Ex vivo residence-time test

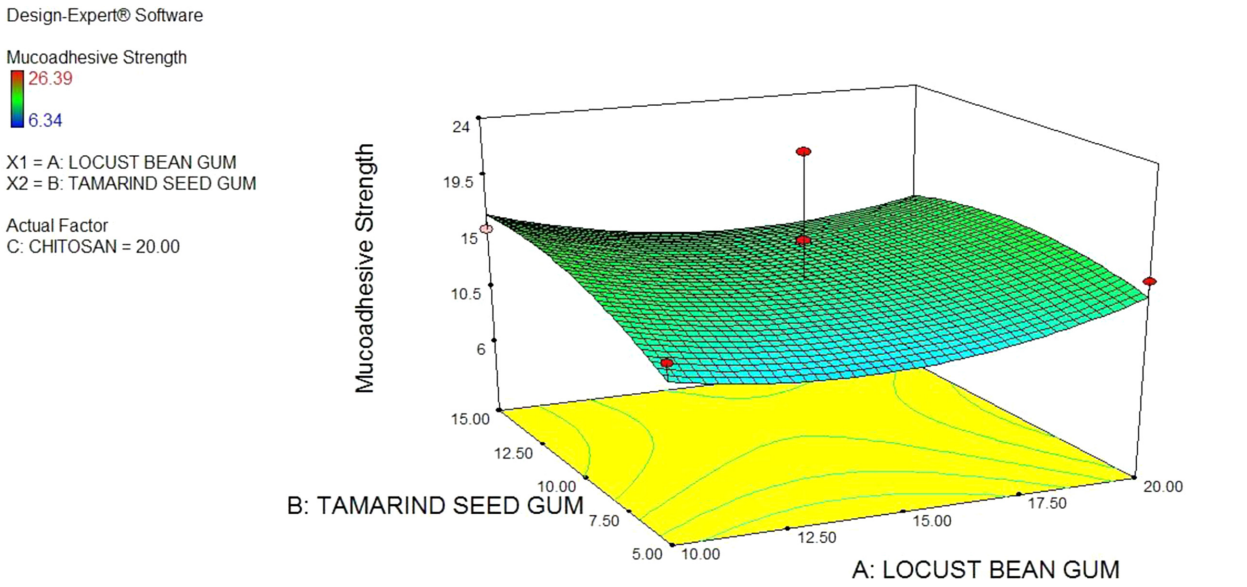
The disintegration test apparatus is used for the study of *ex vivo* residence time of tablets. The gastric mucosa is collected and is cut in to 2×2-size pieces. These pieces

Figure 4



Contour plot showing the influence of the amount of locust bean gum and amount of tamarind seed gum on ex vivo residence time fixed level of C.

Figure 5



Response three-dimensional surface plots showing the influence of the amount of locust bean gum and amount of tamarind seed gum on mucoadhesive strength fixed level of C.

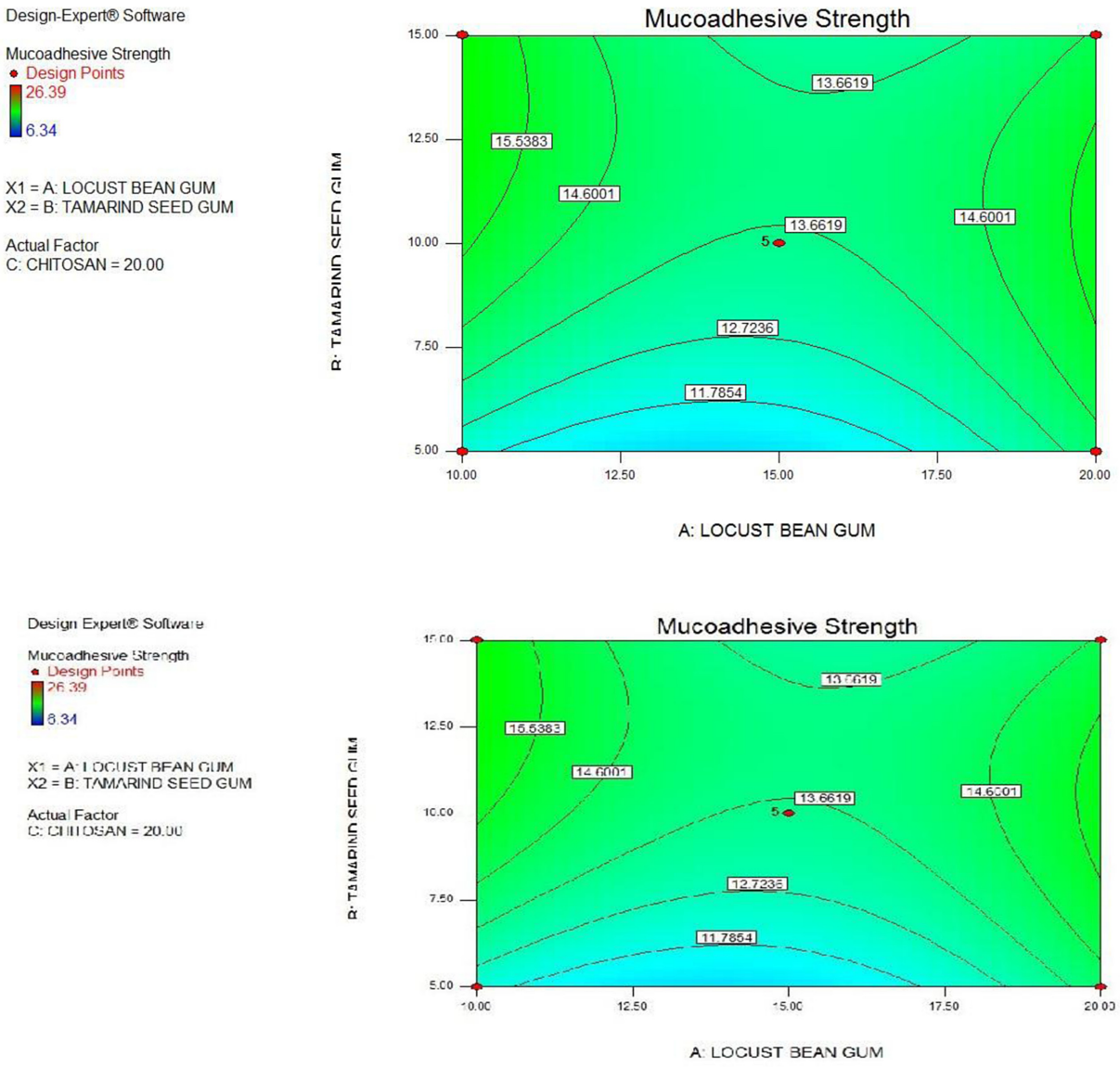
are placed on the glass sides and tied with rubberbands. The formulations are placed on the tissue and kept aside for a few minutes. Then all glass slides are fitted to the disintegration test apparatus and the apparatus is allowed to start, this process is continued for 12 h. The residence time of each formulation is noted as *ex vivo* residence time [12].

Results and discussion

It was desirable to deliver such drug in a gastroretentive dosage form or mucoadhesive drug delivery systems that would prolong the gastric residence time of drug delivery, thereby giving sufficient time for drug delivery system to release the drug and efficiently absorb the active moiety. It was suggested that mucoadhesive drug delivery systems are the easiest approach from the technical and logical point of view among gastroretentive drug delivery systems, so, for the present study, mucoadhesive drug delivery system was chosen. Mucoadhesive tablets were evaluated for their physical characteristics; the results are shown in Table 4.

All the values are represented as mean±SD (n=3).

Figure 6



Contour plot showing the influence of the amount of locust bean gum and amount of tamarind seed gum on mucoadhesive strength fixed level of C.

Fourier transform infrared studies

Fourier transform infrared studies were carried out on drug, excipients, and drug–excipient samples. No new peaks were found and hence compatibility between the drug and the excipients was found. It is shown Figs 1 and 2.

Design of experiments

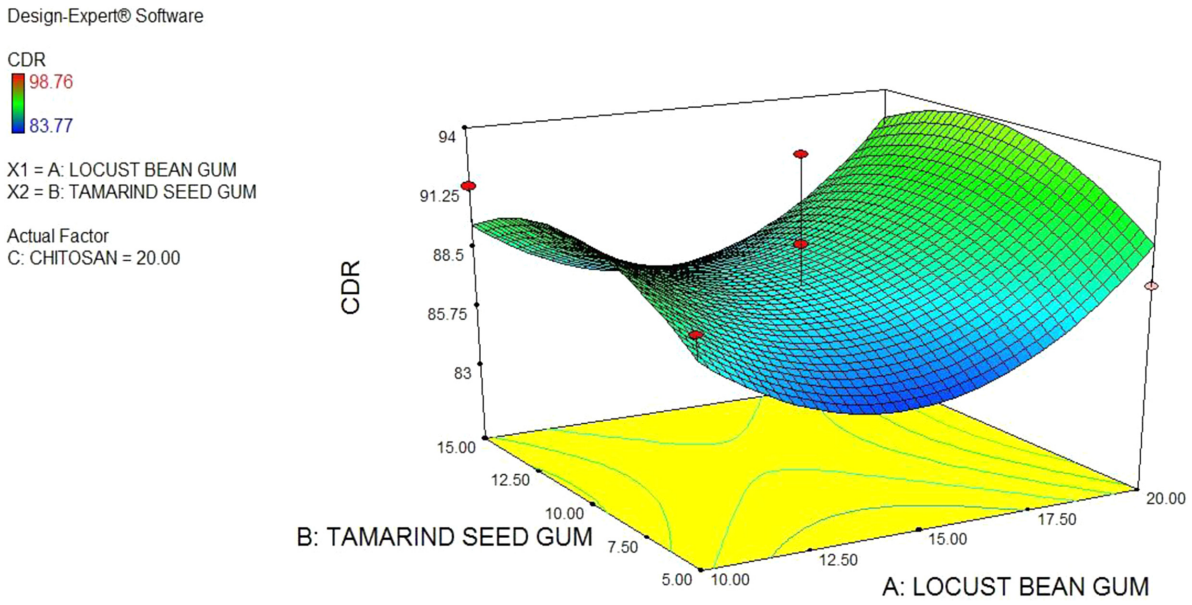
Design of experiments has been used as a powerful approach to reduce the variation in a process and, ultimately, to produce high product yield. Among various design approaches, the Box–Behnken design was used to optimize and evaluate the main effects, interaction effects, and quadratic effects of the process variables on the product yield. This design is suitable for exploring quadratic-response surfaces and constructing second-order polynomial models. The design consists of replicated center points and the set of points lying at the midpoint of each edge of the multidimensional cube. These designs are rotatable (or near rotatable) and require three levels of each factor.

These equations represent the quantitative effect of locust bean gum (A), tamarind seed gum (B) and chitosan (C) and their interaction on ex vivo residence time (Y1), mucoadhesive strength (Y2), and cumulative % drug released after 12 h (Y3). The values of the coefficients of A, B, and C are related to the effect of these variables on the responses Y1, Y2, and Y3. Coefficients with more than one-factor term and those with higher-order terms represent

Table 8 Analysis of variance of the quadratic model for the response cumulative percent drug released (Y3)

Source of variations	Sum of squares	Degree of freedom	Mean squares	*F* value	*P* value Prob>*F*	R^2
Model	2389.12	6	398.85	0.0418	<0.05	0.9996
A-amount of locust bean gum	38.43	1	38.43	0.0167	<0.05	
B-amount of tamarind seed gum	18.45	1	18.45	0.0298	<0.05	
C-amount of chitosan	93.17	1	93.17	0.0395	<0.05	
AB	62.38	1	62.38	0.0143	<0.05	
AC	84.57	1	84.57	0.0139	<0.05	
AB	73.70	1	73.70	0.0261	<0.05	
Residual	1102.30	9	122.85			
Lack of fit	789.01	6	132.16	0.0356	<0.05	

Figure 7



Response three-dimensional surface plot showing the influence of the amount of locust bean gum and amount of tamarind seed gum on cumulative percent of drug-released fixed level of C.

interaction terms and quadratic relationship, respectively. A positive sign represents synergistic effect, while a negative sign indicates antagonistic effect. A backward-elimination procedure was adopted to fit the data to the quadratic model. Both the polynomial equations were found to be statistically significant ($P>0.05$), as determined using ANOVA, as per the provisions of Design Expert software.

Determination of the second-order model

For estimation of coefficients in the approximating polynomial function applying coded values of factor levels, the least-square regression method was performed using the SAS System statistical software. By applying regression-analysis methods, the predicted responses have been obtained. The resultant equations are shown in Tables 5–7.

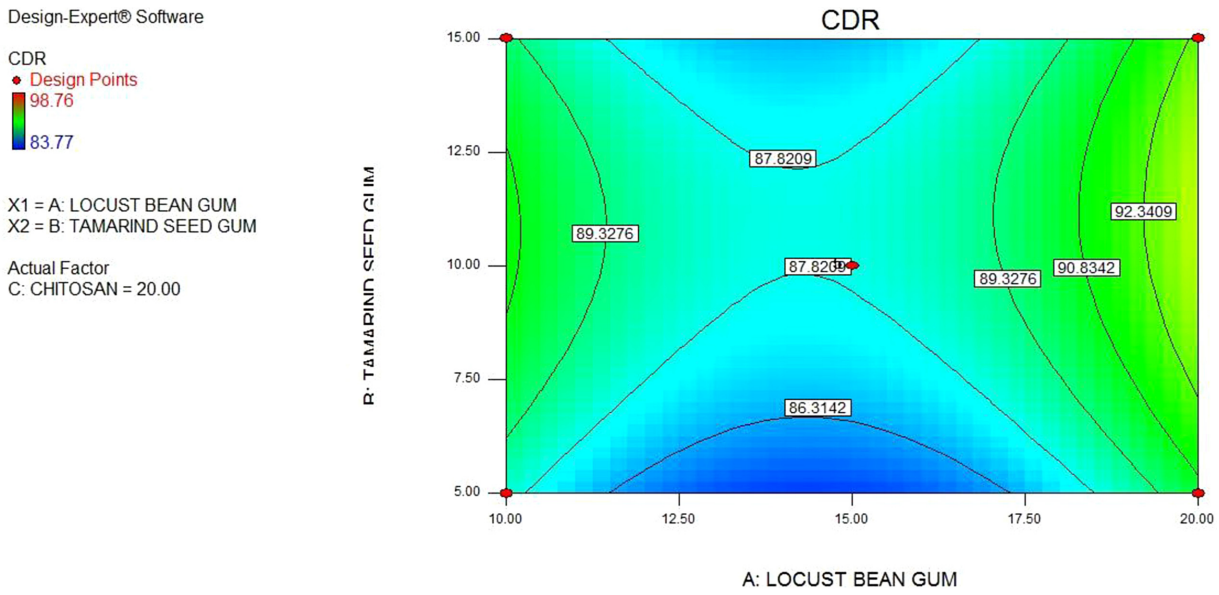
This method is mainly used to explain the effect of one factor on the other factor, whether this effect is significant or not, if significant, how does it influence the response. In this work, the effect of one factor (locust bean gum) on other factors (tamarind seed gum and chitosan) is explained and shown in Figs 3 and 4.

There is a small effect of locust bean gum on mucoadhesive strength of formulations. The formulations without chitosan have shown maximum mucoadhesive strength that is nearly 26. 39 g and shown in Figs 5 and 6, Table 8.

Response 3D surface plot showing the influence of the amount of locust bean gum and amount of tamarind seed gum on mucoadhesive strength fixed level of C and shown in Figs 7 and 8.

The effect of locust bean gum on % cumulative drug release is examined and it clearly indicates that there is a very significant effect of tamarind seed gum on %

Figure 8



Contour plot showing the influence of the amount of locust bean gum and amount of tamarind seed gum on cumulative percent of drug-released fixed level of C.

cumulative drug release. The formulations with all three factors show % drug release. But when tamarind seed gum is removed from the formulations, the maximum % CDR is near 81. This is the effect of factor (tamarind seed gum) on response.

Kinetic data/model fitting

The *in vitro* drug-release data were fit to different equations and kinetic models to explain the drug-release profiles. The coefficient of correlation of each of the kinetics was calculated and compared. The *in vitro* drug-release profile of the optimized formulation of mucoadhesive buccal tablets, that is, F16 fit to zero-order model. The data were further treated as per Korsmeyer's equation. The slope (n) values obtained by this equation indicated that the drug was released by Super case-II Transport dissolution (erosion) mechanism.

Conclusion

Furosemide mucoadhesive oral tablets could be formulated using the drug, locust bean gum and tamarind seed gum, and chitosan with different proportions. It can be seen that there is a synergistic effect when polymers are used in combinations. There is a significant effect of locust bean gum in formulations on drug-release rate from the tablets and mucoadhesive strength was also increased. The *in vitro* release kinetics studies reveal that all formulations fit well with zero order, followed by Korsmeyer–Peppas, Higuchi, and the mechanism of drug release is erosion. From the formulations F1–F17, the formulation F16 was selected as optimized formulation because it showed maximum release, and the other properties such as mucoadhesion strength were good, and the postcompression parameters were found to be within the pharmacopeial limits.

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Conflicts of interest

There are no conflicts of interest.

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