Preparation, Characterization and Optimization of Mucoadhesive Domperidone Tablets by Box Behnken Design

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ABSTRACT: In pharmaceutical industry, statistically valid experimental design can be utilized to optimize data in order to provide an economic and effective formulation, which could overcome several product and process development problems. Domperidone is a BCS Class II drug and has wide range of use, but has very poor bioavailability when administered orally because of degradation in intestinal fluid. The present study was focused on formulation, evaluation and optimization of mucoadhesive tablets of domperidone using a four-factor, three-level Box-Behnken design (BBD) so as to retain the prepared optimized formulation in gastric fluid for a prolong period of time in order to have better bioavailability and to get a sustained action. Physicochemical properties of the prepared formulations were determined according to the USP pharmacopeia official method and found satisfactory, except friability which was optimized to get the acceptable value. *In-vitro* dissolution study was performed for 8 hours for all the prepared formulations using USP II (paddle type) dissolution tester having 0.1N HCl (pH 1.2) as dissolution medium. Obtained data was further analyzed by means of quadratic response surface models so as to find out an optimize formulation in terms of desirable condition of dissolution rate after 1 hour, after 8 hours, total mucoadhesion time and tablet friability. Optimized formulation was further evaluated and it was found that, it was almost similar to the proposed optimized data. The formulation can provide a high degree of patient compliance, as sustained release formulation reduces the side effects and the cost of the formulation will be minimal as lesser amount of effort will be needed employing statistical model instead of conventional trial and error method.

Key words: Box-Behnken Design, mucoadhesive tablets, domperidone, response surface model.

INTRODUCTION

Oral administration is considered as the most convenient route for both conventional and novel drug delivery system. This is why; tablets are the most popular oral solid formulations available in the market which are preferred by both patients and physicians. So, it has advantages on immediate release to site specific delivery.[1] In case of oral administration, many therapeutic agents go extensive pre-systemic elimination by various reasons like gastrointestinal degradation or first pass hepatic metabolism. These make the formulation less bioavailable and toxic effects to the patients. Besides, rapid gastrointestinal transit may cause incomplete drug release from the device above the absorption zone which leads to the diminishing efficacy of the administered dose. Different approaches have been taken under considerations to solve these problems by prolonging the residence time of dosage form in stomach. Bio-adhesive systems, floating drug delivery systems, swelling and expanding systems are some of the techniques that can be adopted.[2,3]

Mucoadhesive drug delivery system is one of the most modern means which may be taken under consideration to solve these problems. This type of drug delivery system is capable to prolong the retention time of a dosage form in the stomach which is helpful to enhance the bioavailability of drugs by improving the solubility or other means. Mucoadhesive dosage forms extend the period of time and drug may be released for a prolong period of time and patient compliance can be achieved.[4]

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This system is very much important for those drugs which are degraded in the intestine. It can ensure the improvement of oral sustained delivery of drugs that have an absorption window in a particular region of the gastrointestinal tract.[5]

Domperidone, which is actually a benzimidazole derivative having molecular weight of 425.9, is a BCS Class II drug candidate. This is why it has very poor solubility and high permeability. Although, domperidone is a weak base and it has good solubility in acidic pH but in alkaline or higher pH the solubility of domperidone is reduced dramatically which may be a possible cause of its low bioavailability of around 17%.[6,7]

Thus, the aim of this present study is to prepare gastroretentive controlled release mucoadhesive tablets of domperidone. Another important issue is to design the formulation in an optimized way with an appropriate dissolution rate and other parameters. Response surface methodology (RSM) using Box-Behnken design (BBD) is very much accepted in this issue.[8] This statistical technique requires less experiment and time rather than traditional trial and error base methods. In addition, BBD is slightly more efficient than the central composite design but much more efficient than the three-level full factorial designs in terms of cost when the number of factor is more than two. This is why they are also very much effective in terms of efficacy and cost.[9,10] Another advantage of BBD lies in the fact that it does not contain combinations for which all factors are simultaneously at their highest or lowest levels. Thus, it is useful in averting unnecessary experiments performed under extreme conditions that may cause unsatisfactory results.

Under such circumstances, the development of mucoadhesive sustained-release or controlled-release formulations of domperidone in the form of tablet using Box-Behnken Design is of therapeutic relevance and has attracted the attention of the pharmaceutical industries. These extended release formulations can improve medication compliance, modify pharmacokinetics, and provide clinicians with greater ability to individualize therapy.

MATERIAL AND METHODS

Materials. Domperidone was obtained as gift sample form ACI Pharmaceuticals Ltd., Bangladesh. Methocel K100M and starch 1500 were obtained from Colorcon, USA. CP Kelco and Loba Chemie Pvt Ltd, India were the sources of gellan gum and sodium alginate respectively. Other chemicals and excipients used in this experiment were of analytical grade.

Formulation development by Box-Behnken Design. A 4-factor, 3-level BBD was used to explore and optimize the main effects, interaction effects, and quadratic effects of the formulation ingredients on the performance of the mucoadhesive tablets. A 4-factor, 3-level BBD requires 29 experimental runs with three central points to determine the experimental error and the precision of the design.[11] A total of 29 experimental runs were generated and evaluated using Design-Expert software (V. 7.0.0.1; Stat-Ease Inc., Minneapolis, Minnesota). The significant response factors used to assess the quality of the tablets formulation, including friability (Y1), mucoadhesion time (Y2), drug release after 1 hour (Y3) and drug release after 8 hours (Y4) were determined. The selected factors with the actual and coded levels as per the design are represented in Table 1. For the sake of convenience, later throughout the manuscript “Run 1” to “Run 29” have been denoted as “D-1” to“D-29”.

Preparation of mucoadhesive domperidone tablet. Tablets were prepared by direct compression method.[12] Drug, polymer and other excipients were weighed according to proposed formulations generated by Box Behnken design, which is represented in Table 2. The amount of drug and one excipient namely magnesium stearate was fixed in amount but others were changed according to the generated formula by BBD. Drug and other excipients were blended properly and taken in the hopper and the die and punch were adjusted to get desired weight of the tablet according to the proposed formulation.[13,14]

Physical parameters evaluation of mucoadhesive domperidone tablets. Diameter as

well as thickness of tablets were measured by using slide calipers. Other physical parameters like weight variation, hardness and friability were also determined according to the official method. [15]

Evaluation of dissolution parameters. The USP dissolution test apparatus USP type II (paddle type) was used to study the drug release from the

Table 1. Experimental variables used in the Box-Behnken Design (BBD).

	Levels, Actual (Coded)		
Independent Variables	Low (-1)	Medium (0)	High (+1)
A: Amount of Gellan Gum (mg)	25	30	35
B: Amount of Sodium Alginate (mg)	30	35	40
C: Amount of Methocel K 100M (mg)	40	45	50
D: Amount of Starch 1500 (mg)	50	57.5	65
		Goals	
Dependent Variables			
Y1: Friability (%)		Below 1%	
Y2: Mucoadhesion Time (hr)		8 hours	
Y3: Drug Release (after 1hr)		Maximize	
Y4: Drug Release (after 8 hr)		Maximize	

The results obtained for each response were fitted to a quadratic polynomial model. The models were validated by analysis of variance (ANOVA), lack of fit, and multiple correlation coefficient (R^2) tests.

Table 2. Formulation of mucoadheive domperidone tablets.

Formulation	Domperidone (mg)	Gellan Gum (mg)	Sodium Alginate (mg)	Methocel K100M (mg)	Starch 1500 (mg)	Magnesium Stearate (mg)	Total Weight (mg)
D-1	10	30	40	50	57.5	0.2	187.7
D-2	10	35	35	45	65.0	0.2	190.2
D-3	10	35	35	45	50.0	0.2	175.2
D-4	10	35	35	50	57.5	0.2	187.7
D-5	10	35	40	45	57.5	0.2	187.7
D-6	10	35	35	40	57.5	0.2	177.7
D-7	10	25	40	45	57.5	0.2	177.7
D-8	10	30	35	45	57.5	0.2	177.7
D-9	10	25	30	45	57.5	0.2	167.7
D-10	10	30	35	45	57.5	0.2	177.7
D-11	10	25	35	40	57.5	0.2	167.7
D-12	10	25	35	45	65.0	0.2	180.2
D-13	10	25	35	45	50.0	0.2	165.2
D-14	10	30	35	45	57.5	0.2	177.7
D-15	10	30	30	45	65.0	0.2	180.2
D-16	10	30	40	45	50.0	0.2	175.2
D-17	10	30	35	45	57.5	0.2	177.7
D-18	10	30	40	40	57.5	0.2	177.7
D-19	10	30	35	45	57.5	0.2	177.7
D-20	10	30	35	50	50.0	0.2	175.2
D-21	10	30	35	40	65.0	0.2	180.2
D-22	10	30	40	45	65.0	0.2	190.2
D-23	10	30	30	45	50.0	0.2	165.2
D-24	10	25	35	50	57.5	0.2	177.7
D-25	10	30	30	40	57.5	0.2	167.7
D-26	10	30	30	50	57.5	0.2	177.7
D-27	10	30	35	50	65.0	0.2	190.2
D-28	10	35	30	45	57.5	0.2	177.7
D-29	10	30	35	40	50.0	0.2	165.2

mucoadhesive domperidone tablet. For this, 900 ml of 0.1N HCl having pH 1.2 was considered as dissolution medium where the temperature was set to 37 ± 0.5°C, with a rotation speed of 50 rpm. After placing the mucoadhesive tablet in dissolution medium, 10 ml of samples were withdrawn at predetermined time intervals and replaced with fresh medium. After filtering the samples through Whatman filter paper, it was analyzed by UV spectrophotometer at 283.5 nm.[16,17]

Measurement of *ex-vivo* mucoadhesive strength. Mucoadhesive strength was determined by using fresh goat intestinal mucosa. Mucosal membrane was separated by removing the underlying fat tissues. After cleaning the mucosa with distilled water, it was cut into pieces and one piece was pasted to petridish by the help of adhesive and wetted with 3-6 drops of 0.1N HCl. The test was carried out then by using modifying holder and weight system.[5]

Measurement of force of adhesion. Force of adhesion was calculated from mucoadhesive strength by using following formula[5]-

Force of adhesion (N) = (mucoadhesive strength × 9.81) ÷ 1000

Measurement of *ex-vivo* mucoadhesion time. *Ex-vivo* mucoadhesion time was calculated by modifying the USP disintegration apparatus.[15] Time required to complete the erosion or detachment of the tablet from the mucosal surface was recorded as the mucoadhesion time.

Drug polymer compatibility study. Drug compatibility study was carried out by using Fourier Transform Infrared Spectroscopy (FTIR). FT-IR spectra were recorded with FT-IR 8400S Shimadzu spectrophotometer in the range of 4000-400 cm^{-1} for 30 times for pure drugs and physical mixtures of pure drug and polymers.[18] By comparing these spectra, compatibility was analyzed.

RESULTS AND DISCUSSION

Evaluation of physical properties of domperidone mucoadhesive tablets. It was found that all formulations showed uniform diameter and thickness. The average percentage of deviation of all tablet formulations was found to be within limit. Hardness was found satisfactory in terms of in-house specifications. In case of friability, some batches (D-9, D-19 and D-23) failed to meet the limit specified in the United States Pharmacopoeia (USP) (friability should be not more than 1%). Figure 1 presents the maximum and minimum values of thickness, diameter and hardness whereas Figure 2 represents the % values of friability.

Evaluation of dissolution parameters. Release profile of domperidone from mucoadhesive tablets is represented in Figure 3 (a, b, c). It has been found that the rate of drug release from the mucoadhesive tablets depends on the polymeric concentration and indicated that the release rate decreased with the increasing concentration of polymer, due to hindrance of swelling and disintegration of gellan gum and sodium alginate.[19,20] The increase in polymer concentration caused an increased viscosity of the polymer matrix and thus reduced the diffusion of the drug. Another reason used to explain this incident was that as the amount of uncoated drug and the amount of drug present close to the surface decrease with the increasing of polymer concentration, the rate of drug release decreases.

Measurement of *ex-vivo* mucoadhesive strength. The data for mucoadhesive strength for all the batches are reported in Table 3. The range for mucoadhesive strength of formulations D-1 to D-29 was found to be 28.30 gm to 21.50 gm. Formulation D-1 had the highest mucoadhesion strength, force of adhesion and mucoadhesion time whereas formulation D-25 showed the lowest mucoadhesion strength, force of adhesion and mucoadhesion time. The results revealed that, the higher the concentration of polymeric concentration, the higher the mucoadhesion strength, force of adhesion and mucoadhesion time. Among those polymers, Methocel K100M and sodium alginate played the vital role. The order of mucoadhesion strength, force of adhesion and mucoadhesion time can be shown by (D-1>D-22>D-5>D-18>D-19>D-7>D-27>D-13>D-21>D-8>D-12>D-17>D-24>D-4>D-14>D-20>D-6>

D-2>D-3> D-10>D-26>D-15>D-28>D-29>D-9> D-23>D-25).

Drug Compatibility Studies. Fourier Transform Infrared Spectroscopic studies were performed for checking the interaction between drug and polymer, if any. For this purpose, FTIR study was conducted for pure drug (domperidone) and physical mixture of pure drug and polymers. From the Figure 4 (a, b), it can be seen that physical mixture of domperidone, gellan gum, sodium alginate and Methocel K100M had shown almost similar type of spectrum in comparison to the spectrum of pure domperidone. Characteristic bands observed in pure domperidone and physical mixture were: -NH stretching vibration, - C-H stretching vibration, -CO-R-vibration and C-N stretching vibrations. By analyzing the principal peaks, it can be said that no major chemical interaction or changes took place during preparation and hence the drug was found to be stable in the formulation.

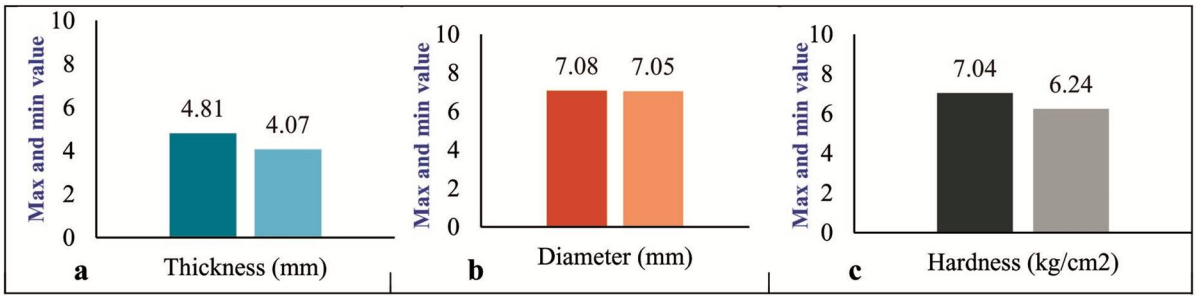

Figure 1. Evaluation of domperidone mucoadhesive tablets; a. Thickness, b. Diameter and c. Hardness.

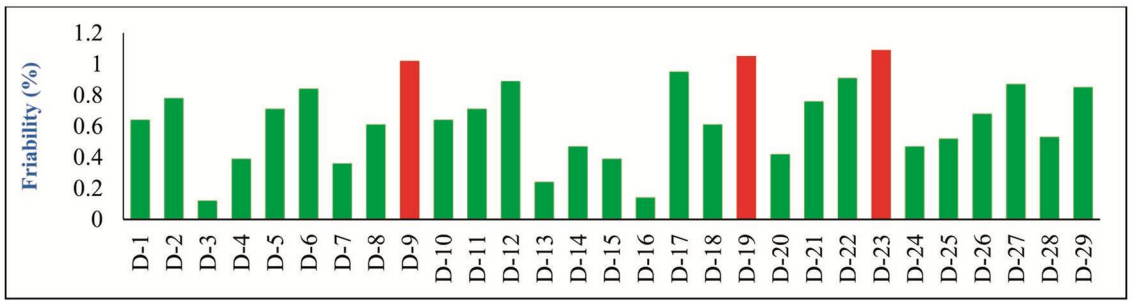

Figure 2. Values of friability of prepared mucoadhesive tablets (%).

Statistical analysis of dependent variables. For all the four responses- friability (Y1), mucoadhesion time (Y2), drug release after 1 hour (Y3) and drug release after 8 hours (Y4), obtained data were analyzed by ANOVA, lack of fit and coefficient estimation tests. The obtained data are presented in Table 4 and 5. The Model F-value for Y1 (3.49), Y2 (8.47), Y3 (4.10) and Y4 (12.84) imply that the model is significant. In the ANOVA test, values of "Prob>F" less than 0.05 indicate model terms are significant. For all the four responses, the p values of F-statistic of the model were 0.0103, 0.0002, 0.0113 and <0.0001, respectively. As the 'p value' for all this model is less than 0.05, it indicates that all these responses fitted the model well. Additionally, a model with non-significant lack of fit is good and desirable. A model with p values greater than 0.10 indicate the model terms are not significant. For all the responses, the "Lack of Fit- p value" is greater than 0.10, which imply that the responses fitted in the model. The "Lack of Fit F-value" of 0.51, 0.49, 0.77 and 0.80, respectively indicate the Lack of Fit is not significant relative to the pure error. For response Y1, the "predicted R^2" of 0.1746 is not as close to the

"adjusted R^2" of 0.4704 as one might normally expect. This may indicate a large block effect or a possible problem with the model and/or data. Here, things to consider are model reduction, response tranformation, outliers, etc. For other three responses (Y2, Y3 and Y4), the "predicted R^2" of 0.4147, 0.1341 and 0.5447 respectively are in reasonable agreement with the "adjusted R^2" of 0.5161, 0.3071 and 0.6284 respectively. Another parameter, "adequate precision" measures the signal to noise ratio. A ratio greater than 4 is desirable. This ratio of 7.604, 9.556, 6.475 and 10.895 respectively dor Y1, Y2, Y3 and Y4 indicate an adequate signal.

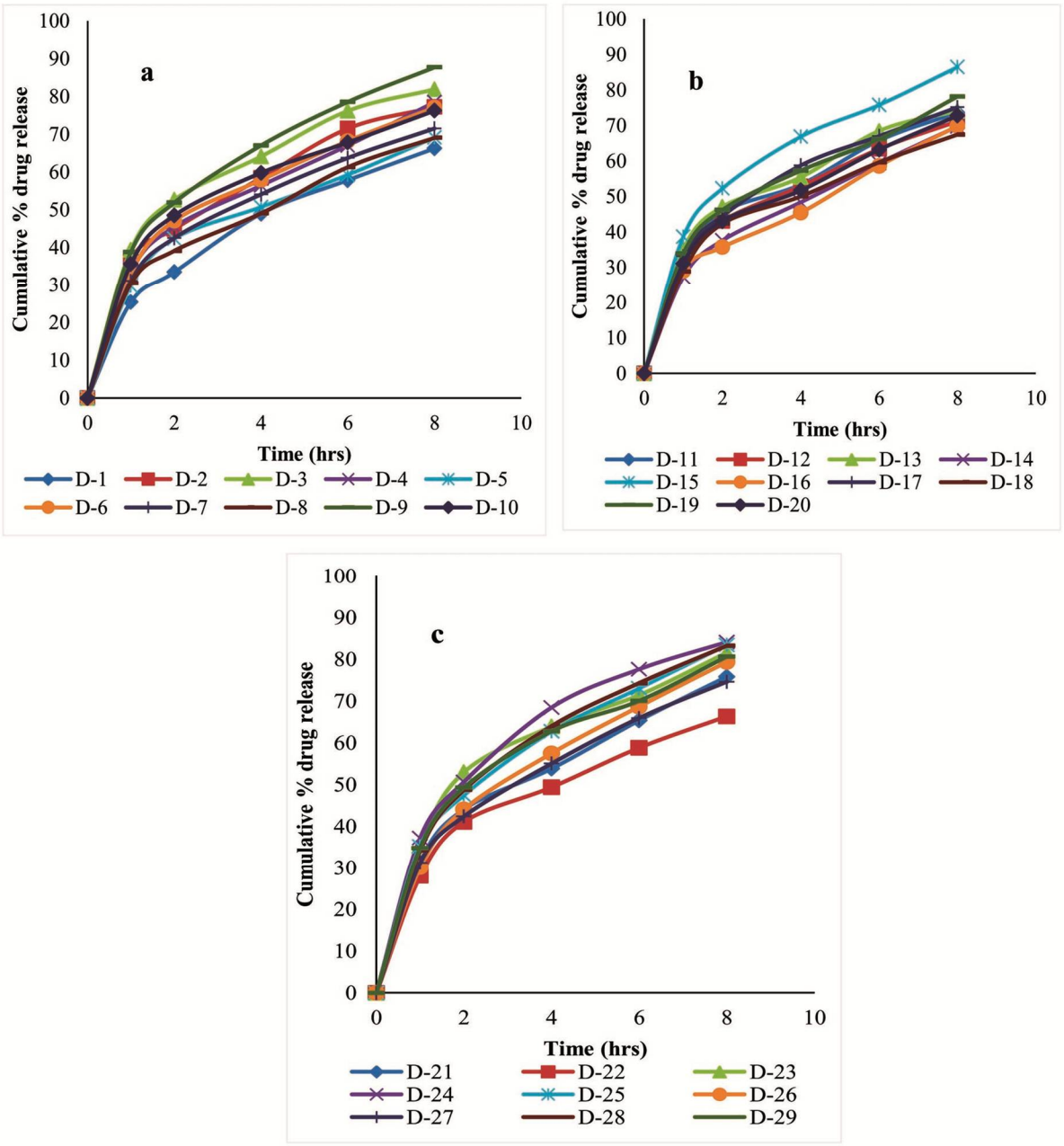

Figure 3. *In-vitro* release profile of domperidone from mucoadhesive formulations; a. D-1 to D-10, b. D-11 to D-20, c. D-21 to D-29.

Table 3. *Ex-vivo* mucoadhesion characteristics of different formulations.

Formulation	Mucoadhesive Strength (gm)	Standard Deviation (n=3)	Force of Adhesion (N)	Mucoadhesion Time (hr)
D-1	28.30	0.215	0.278	8.96
D-2	24.37	0.352	0.239	7.61
D-3	24.20	0.256	0.237	7.25
D-4	25.10	0.245	0.246	7.36
D-5	27.80	0.123	0.272	7.85
D-6	24.60	0.254	0.241	6.36
D-7	26.20	0.541	0.257	7.51
D-8	25.65	0.322	0.251	7.21
D-9	22.08	0.126	0.216	7.20
D-10	24.10	0.326	0.236	6.30
D-11	25.35	0.329	0.248	7.03
D-12	25.45	0.451	0.249	7.11
D-13	26.08	0.158	0.255	7.45
D-14	24.75	0.352	0.242	6.33
D-15	23.10	0.112	0.226	6.13
D-16	27.90	0.185	0.273	8.78
D-17	25.30	0.354	0.248	7.85
D-18	27.50	0.128	0.250	8.20
D-19	26.60	0.210	0.260	7.53
D-20	24.75	0.323	0.242	6.28
D-21	25.80	0.141	0.253	7.51
D-22	27.85	0.410	0.273	8.33
D-23	21.90	0.432	0.214	6.61
D-24	25.10	0.211	0.246	7.26
D-25	21.50	0.325	0.210	6.13
D-26	23.60	0.485	0.231	6.95
D-27	26.30	0.221	0.258	7.41
D-28	22.70	0.326	0.222	6.23
D-29	22.30	0.192	0.218	6.20

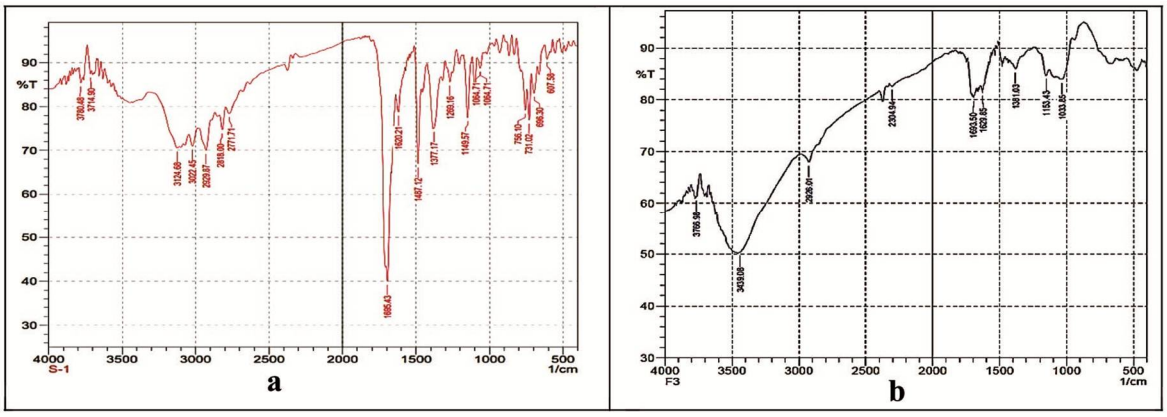

Figure 4. FTIR spectra of pure drug (a) and physical mixtures of pure drug and polymers (b).

Table 4. ANOVA and lack of fit tests of the model for the responses.

Response	F value	Probability > F
Y1		
Model	3.487	0.0103
Lack of Fit	0.507	0.8455
Y2		
Model	8.466	0.0002
Lack of Fit	0.486	0.8756
Y3		
Model	4.103	0.0113
Lack of fit	0.769	0.6962
Y4		
Model	12.836	< 0.0001
Lack of fit	0.801	0.6773

Table 5. Regrssion analysis of the responses.

Quadratic model	Adjusted R^2	Predicted R^2	Adequate precision
Y1	0.4704	0.1746	7.604
Y2	0.5161	0.4147	9.556
Y3	0.3071	0.1341	6.475
Y4	0.6284	0.5447	10.895

Final equation in terms of coded factors. From the follwing equations 1, 2, 3 and 4, it can be observed that, a positive value represents an effect that favors the optimization, while a negative value represents an opposite relationship between the independent and the dependent variables.[21,22] The amount of gellan gum (A) had negative effect on friability (Y1), mucoadhesion time (Y2) and drug release after 1 hour (Y3). The amount of sodium alginate and Methocel K100 M also had negative effect on Y1, Y3 and Y4, while these had positive effect on Y2. The amount of starch had positive effect on Y1 and Y2. It had negative effect on Y3 and Y4.That means, mucoadhesion time increases with an increase in the concentration of sodium alginate, Methocel K100 M, as well as with the starch. On the other hand, drug release rate decreases with the increase in polymer concentration.

$$Y1 = 0.67 - 0.10 \times A - 0.072 \times B - 0.068 \times C + 0.078 \times D + 0.22 \times AB - 0.052 \times AC + 0.22 \times AD - 0.033 \times BC + 0.35 \times BD + 0.13 \times CD \quad (1)$$

$$Y2 = 7.22 - 0.075 \times A + 0.87 \times B + 0.19 \times C + 0.084 \times D \quad (2)$$

$$Y3 = 32.82 - 0.003 \times A - 3.36 \times B - 0.62 \times C - 0.55 \times D \quad (3)$$

$$Y4 = 75.93 + 0.38 \times A - 7.60 \times B - 0.21 \times C - 0.77 \times D \quad (4)$$

Response surface and contour plot analaysis. Two dimensional contour plots and three-dimensional response surface plots are very effective representations of studying the interaction between two factors. These plots help to understand the relationship between the independent and dependent variables. A response surface plot is a 3-D graphical representation of a response plotted between two independent variables and one response variable. The use of 3-D response surface plots allows understanding the behavior of the system by demonstrating the contribution of the independent variables. The geometric illustration of a response obtained by plotting one independent variable against another, while holding the magnitude of response and other variables as constant, is known as a contour plot. Such contour plots represent the 2-D slices of the corresponding 3-D response surfaces. The resulting curves are called contour lines.[11] These types of plots can only express two independent variables at a time against the response. Thus, in this study, independent variables C and D was set at a fixed level and the effect of changing the level of A and B on four dependent variables was considered, as shown in Figures 5-8.

Final Optimized Formulation and evaluation of the responses. In the present study, all four responses were simultaneously optimized by a desirability function that uses the numerical optimization method in the Design-Expert software (Stat-Ease Inc.). Responses Y1, Y2, Y3 and Y4 were transformed into individual desirability scales d1, d2, d3 and d4, respectively. Constraints were fitted against all of the responses, which was presented in the Table 6. For all four responses, the goal was set as, % friability (Y1) to be less than 1%, mucoadhesion time (Y2) to be targeted for 8 hours, Y3 and Y4 (Drug release) to be maximized.

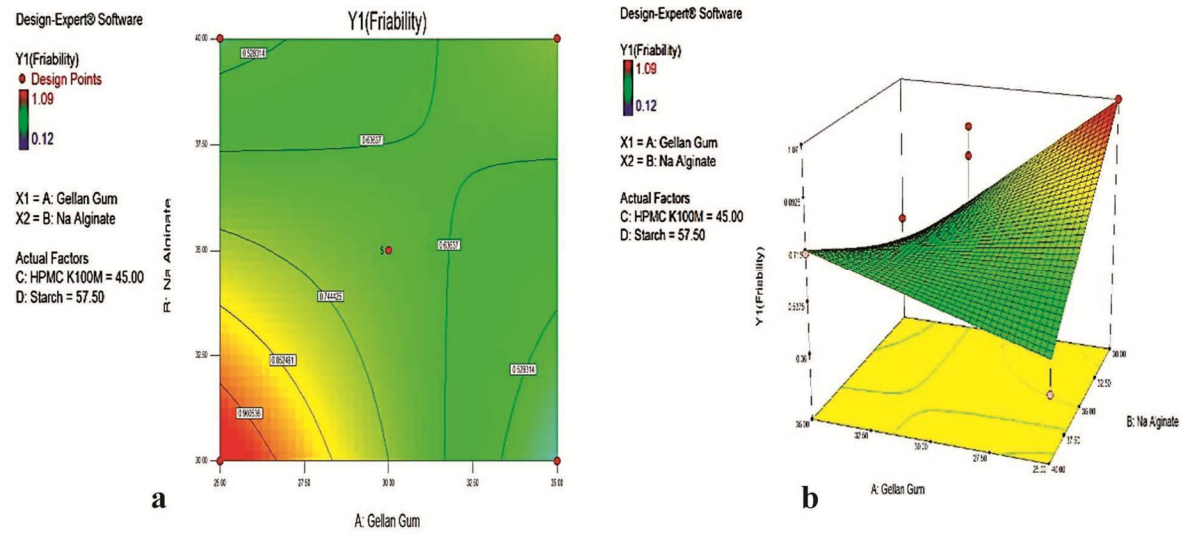

Figure 5. Effects of X1 (Gellan Gum) and X2 (Sodium Alginate) on Y1. a. Contour plot b. Response surface plot.

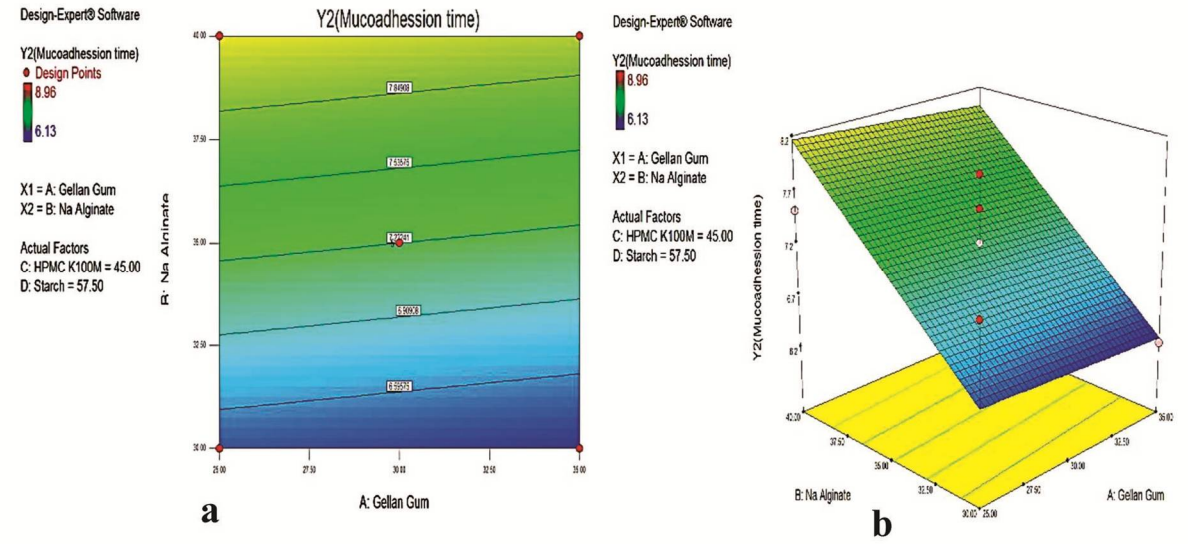

Figure 6. Effects of X1 (Gellan Gum) and X2 (Sodium Alginate) on Y2. a. Contour plot b. Response surface plot.

Table 6. Table of constraints.

Constraints					
Factor	Name	Unit	Goal	Lower limit	Upper limit
A	Gellan Gum	mg	is in range	25	35
B	Sodium Alginate	mg	is in range	30	40
C	Methocel K100M	mg	is in range	40	50
D	Starch	mg	is in range	50	65
Y1	Friability	%	Below 1%	0.12	1.09
Y2	Mucoadhession time	Hours	For 8 hours	6.13	8.96
Y3	Drug release after 1 hour	Hours	Maximize	35	40
Y4	Drug release after 8 hours	Hours	Maximize	66.23	87.7

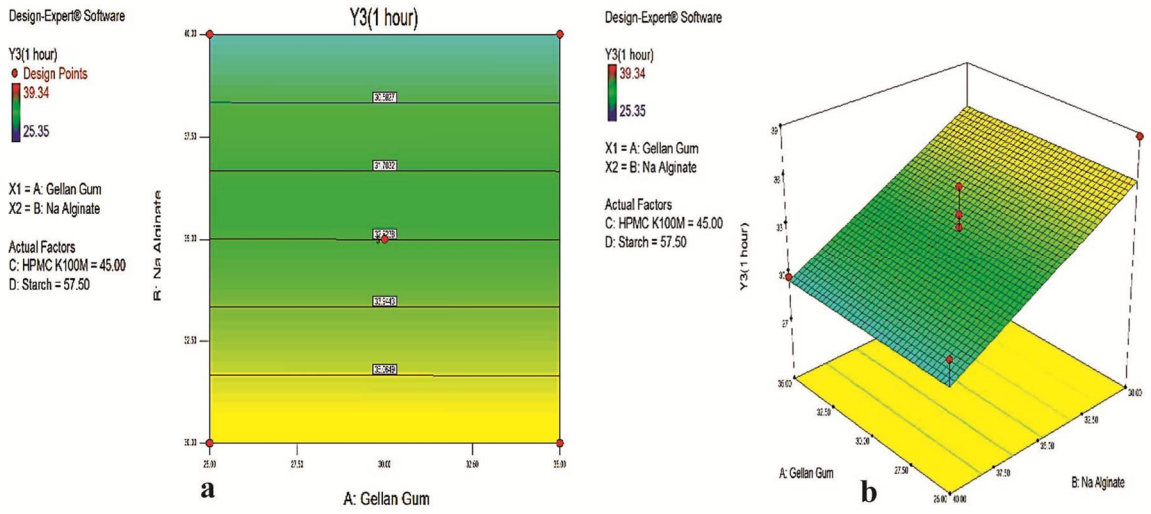

Figure 7. Effects of X1 (Gellan Gum) and X2 (Sodium Alginate) on Y3. a. Contour plot b. Response surface plot.

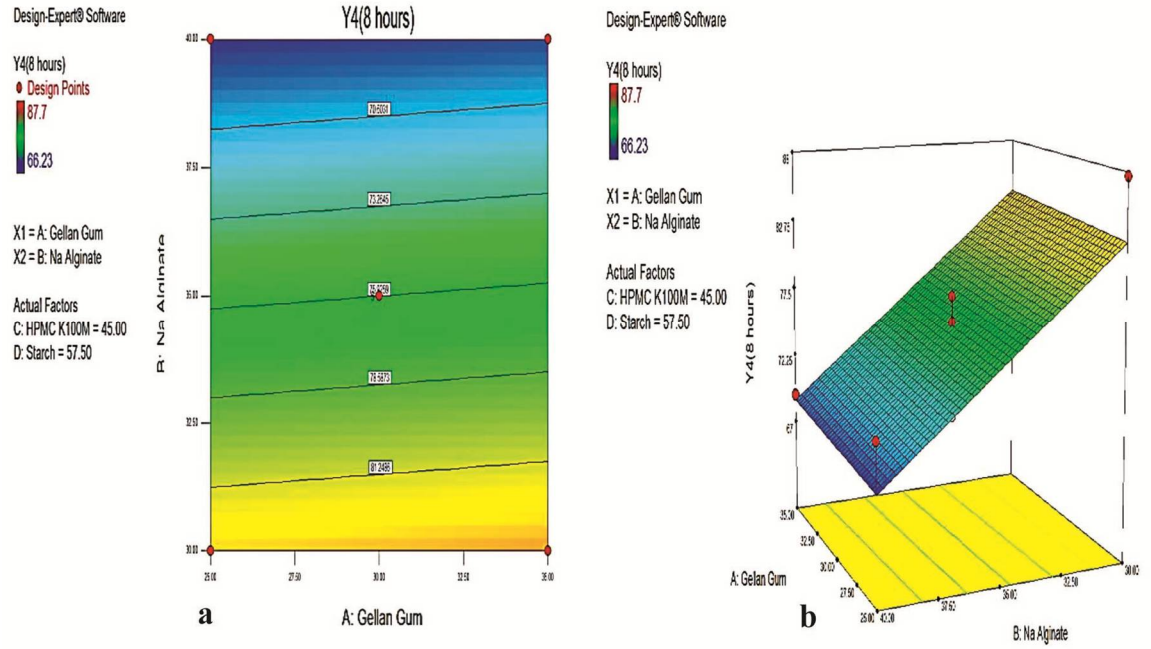

Figure 8. Effects of X1 (Gellan Gum) and X2 (Sodium Alginate) on Y4. a. Contour plot b. Response surface plot.

Consequently, by an extensive grid search over the domain, using the Design-Expert software (Stat-Ease Inc.), the maximum desirability value was calculated. After analyzing all the parameters, the final optimized formula was obtained and prepared accordingly for validation, which was shown in Table 7. On the basis of these factor levels, the predicted values for all responses were generated.

Finally, the predicted values for responses were compared with the experimental values. From the table, it can be seen that the observed values for responses, Y2, Y3 and Y4 were in close agreement with the predicted values. In case of Y1 (% friability), although the observed response was deviated from the predicted value, it can be accepted, as it was within the target range of below 1%.

Table 7. Final optimzed formula and predicted values of responses generated by ANOVA.

Gellan Gum (mg)	Sodium Alginate (mg)	Methocel K100M (mg)	Starch (mg)	Y1 (%)	Y2 (Hr)	Y3 (Hr)	Y4 (Hr)	Desirability
27.18	31.68	49.94	50	0.99	6.79	35.00	81.32	0.6303

The physical parameters and other characteristics of optimized Domperidone mucoadhesive tablets (D*) are given in below tables.

Table 8. Physical properties of optimized domperidone mucoadhesive tablets.

Formulation	Average weight (mg)	Diameter (mm)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)
D*	169 ± 1.02	7.07 ± 0.01	4.69 ± 0.01	6.27 ± 0.14	0.28

Table 9. *Ex vivo* mucoadhesion characteristics of optimized formulations.

Formulation	Mucoadhesive strength (gm)	Standard deviation (n=3)	Force of adhesion (N)	Mucoadhesion time (hr)
D*	23.40	0.211	0.229	6.75

Table 10. Zero order release profile of optimized formulation D*.

Formulation	0 hour	1 hour	2 hours	4 hours	6 hours	8 hours
D*	0	34.02	47.18	57.29	69.01	79.17

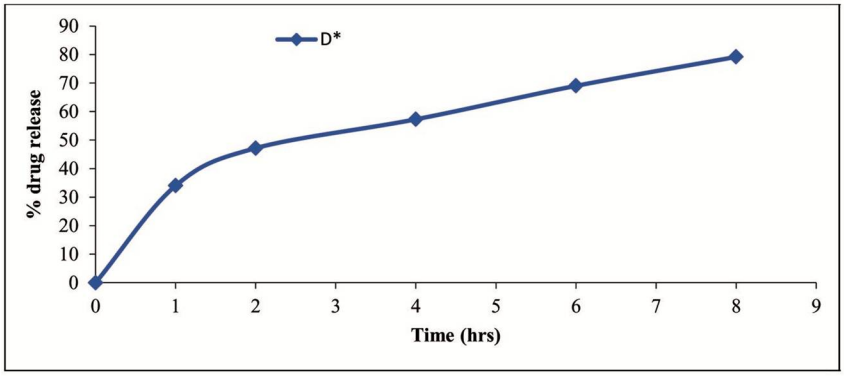

Figure 9. Zero order release profile of optimized formulation.

Table 11. Comparison of predicted and observed values for responses.

Responses	Predicted value	Observed value	Residuals	Bias[a](%)
Y1 (%)	0.99	0.28	-0.71	254
Y2 (Hour)	6.79	6.75	-0.04	0.6
Y3 (%)	35	34.02	-0.98	2.9
Y4 (%)	81.32	79.17	-2.15	2.7

Bias[a] (%) = (predicted value − observed value)/observed value ×100

CONCLUSION

From the result, it was obvious that, the solubility and drug release of domperidone increased because of the prolong retention of tablet in stomach. Optimized tablet met all the criteria set by Box-Behnken design. Physical parameters like average weight, hardness, friability etc. was within official limit. In future, the study may help to develop site specific sustained release formulation for similar drug in optimized way. Again, it is also helpful for patient compliance as sustained release formulation reduces the side effects and the cost of the

formulation will be minimal as lesser amount of effort is needed as it was prepared by using statistical model instead of conventional trial and error based method.

Abbreviation

BBD: Box-Behnken design; RSM: Response surface methodology; ANOVA: Analysis of variance; FTIR: Fourier transform infrared spectroscopy

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