Research Article

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DESIGN AND DEVELOPMENT OF NOVEL MUCOADHESIVE GASTRORETENTIVE FORMULATION OF GLIPIZIDE

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ABSTRACT
The aim of the present study was to develop and characterize a gastroretentive formulation for controlled drug release and to develop innovative gastro retentive formulation based on mucoadhesive patch systems using the solvent casting technique. Glipizide, an antidiabetic agent was used as model drug for formulating films. Mucoadhesive film was formulated using chitosan and HPMC K_4M. PEG 400 was added as plasticizer in film preparation. 3^2 full factorial design was used to formulate the novel gastroretentive formulation. Amount of HPMC $K_4M(X_1)$ and amount of chitosan (X_2) was selected as independent variable while swelling index, folding endurance, mucoadhesion force and Q_8 (% drug release after 8 h) was selected as dependent variables. The film with zigzag folding in the capsule was shown to unfold and swell under acidic conditions and provide controlled release of drug upto12 h in acidic medium. According to 3^2 full factorial design films, 9 batches were prepared and evaluated for surface pH, folding endurance, mucoadhesion force, drug content, *in-vitro* drug release etc. Surface pH of F1- F9 was in between 6.32 to 6.98. Thickness and % drug content for batch F1-F9 was found to be in between 0.236 mm to 0.289 mm and 95.42 % to 99.32 %, respectively. *In-vitro* drug release study of F1-F9 showed utmost 95 % drug release after 11 h. The results indicate that the dosage form is gastroretentive and can provide controlled release of drugs with narrow therapeutic window. Glipizide/ HPMCK_4M / Chitosan (40:150:150) F8 was found to be optimized composition of mucoadhesive films that showed good swelling index, folding endurance, surface pH, mucoadhesion force, Q8 and % drug content.
Keywords: Glipizide, Mucoadhesive film, Gastroretentive, Chitosan, HPMC K_4M

INTRODUCTION

Oral drug administration has been the predominant route for drug delivery. During the past two decades, numerous oral delivery systems have been developed to act as drug reservoirs from which the active substance can be released over a defined period of time at a predetermined and controlled rate. From a pharmacokinetic point of view, the ideal sustained and controlled release dosage form should be comparable with an intravenous infusion, which supplies continuously the amount of drug needed to maintain constant plasma levels once the steady state is reached[1-4]. Over the past three decades, the pursuit and exploration of devices designed to be retained in the upper part of the gastrointestinal (GI) tract has advanced consistently in terms of technology and diversity, encompassing a variety of systems and devices such as floating systems, raft systems, expanding systems, swelling systems, bioadhesive systems and low- density systems. Gastric retention will provide advantages such as the delivery of drugs with narrow absorption windows in the small intestinal region. Also, longer residence time in the stomach could be advantageous for local action in the upper part of the small intestine, for example treatment of peptic ulcer disease[5-9]. Gastroretentive mucoadhesive drug delivery is of particular interest for drugs that (1) act locally in the stomach, (2) are primarily absorbed in the stomach, (3) are poorly soluble at an alkaline pH, (4) have a narrow window of absorption, and (5) are unstable in the intestinal or colonic environment. To provide good retention behavior in the stomach, the density of the device should be less than that of the gastric contents ($\approx$1.004 g/cm^3)[6,7]. Drugs that have narrow absorption window in upper part of GI tract i.e. stomach and small intestine, due to short transit time of dosage form, formulation of these drug leave upper part of GI tract and reaches to non-absorbing distal regiment, resulting lesser bioavailability. Mucoadhesive gastroretentive drug delivery systems prolong the drug release rate from formulation in stomach and upper part of small intestine until all the drug is released for the desired period of time. The drug of choice, Glipizide, is an effective anti - diabetic drug particularly in Type II diabetes (Non-insulin dependent diabetes mellitus). It is a second generation sulfonylurea that actually lowers the blood glucose level in human by stimulating the pancreatic cell and thereby releasing the insulin. It has a short biological half-life of 2-5 hours which make it more suitable to be designed as a controlled release formulation. The main purpose of the present research was to develop a controlled drug delivery system of Glipizide for per-oral administration. The aim of the present work was to develop innovative gastro retentive formulation based on drug loaded polymeric film folded in hard gelatin capsule. After ingestion the capsule dissolves and releases the film which then unfolds in the stomach and swells to a larger dimension resulting in its increased retention. Based on this hypothesis, the mucoadhesive films were designed in such a way that they should be retained in the stomach for a prolonged period of time, thus maximizing the exposure of the drug to its absorption site.

MATERIALS AND METHODS

Glipizide was obtained as gift sample from Astron Research Centre, Ahmedabad, Gujarat, India. HPMC K_4M Was received as gift sample from colorcon India. Chitosan was purchased from Merck, India. Other excipients and solvents were used in the present study was of analytical grade.

Experimental Methods

Preparation of Mucoadhesive Films

The mucoadhesive films were prepared by a solvent casting evaporation technique. The Polymer solution was prepared by dissolving the required quantity of Chitosan, HPMC K_4M as release retarding agent and PEG 400 as plasticizer in distilled water. Add accurately weighed amount of Glipizide (40 mg) to the polymeric solution. The prepared viscous solution stirred for 5-6 h to get clear transparent solution. The resultant drug containing polymeric solution was poured on glass mold evenly and allowed for drying in room temperature for 2-3 h and followed to evaporate the solvent in hot air oven for 6 h at 50^0C. After drying, film was cut in the pieces of 2 cm × 2 cm and stored in desiccators for evaluation studies[10-13].

3^2 Factorial Design for Optimization of Glipizide mucoadhesive film

Factorial design is suitable for exploring quadratic response surface and constructing second order polynomial models. The design consists of replicated center points and the set of points lying at the midpoint of the multidimensional cube that defines the region of interest. The nonlinear quadratic model generated by the design in the form;

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

Where, Y is response, b_0 is intercept, X_1 and X_2 are independent factors, $b_1$and b_2 are coefficient of independent factors.

The coefficients with second order terms (b_{11} and b_{22}) indicate the quadratic nature and b_{12} is the interaction term (combining effect of Independent factors). This study investigated utility of a 2-factor, 3-level factorial design and optimization process for mucoadhesive film prepared by solvent casting technique. Amounts of HPMC K_4M (X_1) and Chitosan (X_2) were selected as the independent variables whereas total Y8 % (amount of drug dissolve after 8 h) folding endurance and % swelling, mucoadhesion force were selected as dependent variables. Table 1 showed the composition and experimental runs as per factorial designs.

Calculation of Theoretical drug release profile (TRP) of Glipizide

Elimination half-life ($t_{1/2}$) = 3.4 hours

Time to reach peak plasma concentration (Tp) = 2.1 hours

Volume of distribution of Glipizide (V_d) = 170 ml/kg

By taking average body weight of 60 Kg

Calculation of total dose and maintenance dose:

$$D_t = D_L (1 + 0.693 \text{ X } t/t_{1/2})$$
$$40 = D_L (1+ 0.693 \text{ X } 12/ 3.4)$$
$$D_L = 11.59$$

Where, D_t = total dose, D_L =loading dose,
$T_{1/2}$ = Half-life of drug,
t = time during which sustained release is desired

$$\text{Maintenance dose } (D_m) = \text{Total dose } (D_t) - \text{Loading dose } (D_L)$$

From the above calculation, loading dose (D_L) is 11.59 mg, total dose (D_t) is 40 mg therefore, maintenance dose (D_m) is 28.41 mg.

Characterization of Mucoadhesive Oral Films

Film thickness

The film thickness was measured using Micrometer Screw Gauge (Mitutoyo-25DS) at three different places and the mean value was calculated[14-16].

Surface pH of Films

The films of each formulation were allowed to swell for 2 h. On the surface of agar plate, the surface pH was measured by using a pH paper placed on the surface of the swollen patch[15,16]. A mean of three readings was recorded (n = 3).

% Swelling

After determination of the original film weight and diameter, the samples were allowed to swell on the surface of agar plate kept in an incubator maintained at 37 ± 0.2ºC. Increase in the weight of the films (n = 3) was determined at preset time intervals (1-5 h)[17-20]. The per cent swelling (% S) was calculated using the following equation:

$$\text{Percent Swelling (\% S)} = (X_t - X_0/X_0) \times 100$$

Where X_t is the weight of the swollen film after time t, Xo is the initial film weight at zero time.

Folding Endurance

The films of each formulation of size (2 cm × 2 cm) were cut by using sharp blade. Folding Endurance was determined by repeatedly folding a small strip of film at the same place till it broke. The number of times, the film could be folded at the same place without breaking gave the value of folding endurance[21-25].

Mucoadhesion force

Mucoadhesion of the CR layer of the film to stomach mucosa was evaluated in triplicate using a double beam physical balance. The moist film was then brought into contact with a film (CR layer downwards) attached to the lower surface of another Teflon cylinder suspended from the left arm of the balance by removing a 5 g weight from the right pan of the balance. The balance was kept in this position for 3 minutes after which weights were added slowly to the right pan until the film separated from the mucosal surface. The excess weight on the pan (total weight minus 5 g) is the bio adhesive strength required to separate the film from the mucosa[26-28]. The force of adhesion was calculated using the formula:

$$\text{Force of adhesion (N)} = (\text{Bio adhesive strength}/1000) \times 9.81$$

Determination of drug content

Accurately cited 2 cm × 2 cm diameter of the films was taken and dissolved in methanol and constant volume of solvent. The prepared solutions were analyzed by using UV –Visible spectrophotometer at 276 nm[29].

***In vitro* dissolution studies**

In vitro dissolution studies were carried out employing USP dissolution apparatus (Basket apparatus). 2 cm × 2 cm size films containing 40 mg of equivalent weight of Glipizide was filled into hard Gelatin capsule in zigzag

manner. Basket was rotated at 100 rpm. 900 ml of 0.1N HCl pH 1.2 was taken the dissolution medium. 10 ml aliquot were withdrawn at regular time interval until complete drug release and the sample was periodically withdrawn at suitable time interval and the volumes were replaced with fresh dissolution medium in order to maintain the sink condition. The aliquots were analyzed using UV-Spectrophotometer at 276 nm[30].

RESULTS AND DISCUSSION

Preparation of Gastroretentive Mucoadhesive Films of Glipizide

Novel gastroretentive mucoadhesive films of glipizide for controlled release were prepared using solvent casting method. Films were cut into 2 mm × 2 mm containing 40 mg of glipizide. Composition of films was shown in Table 2.

Evaluation of Mucoadhesive Films

Thickness of film was measured using micrometer screw gauge. Thickness of prepared films found to be in between 0.236 mm to 0.289 mm. Results of measurement of surface pH of batch F1 to F9 found to be in between 6.98 to 3.32. Drug content of films was measured to check content uniformity in films. Drug content of all prepared films found to be in between 95.32 % to 99.32 %. Folding endurance of the films was measured to check the ability of films to fold. Folding endurance of film was in between 211 to 234, which indicated that films had good ability for folding. Swelling index was measured to determine water uptake capacity of films. Figure 1 showed % swelling of films at 2 h, 4 h, 6 h, 8 h, 10 h and 12 h. It showed swelling of films in-between 60.23 % to 65.98 %. Among all 9 batches F8 showed lower swelling index (60.22 %) indicated that there was lower amount of water uptake hence due to this there would be decreased drug dissolution in dissolution medium. Mucoadhesion force was measured to check mucoadhesion of films to mucus membrane of stomach. Figure 2 showed mucoadhesive strength of batch F1-F9.

In-Vitro Dissolution study

In vitro dissolution study of films was carried out using USP dissolution apparatus type I (Basket Apparatus). Film was filled in hard gelatin capsule in zigzag manner and capsule was subjected for *in-vitro* dissolution study for drug release. Figure 3 showed *in-vitro* dissolution curves of batch F1 to F9. *In-vitro* dissolution of batches F1 to F9 showed sustained drug release up to 12 h. Batch F1, F4 and F7 showed 96.98 %, 93.95 % and 98.44 % drug release after 9 h and 10 h, respectively. These indicated as the amount of HPMC K_4M increased drug release decreased. Batch F1, F2 and F3 showed 95.86 %, 97.58 %, 99.89 % drug release after 11 h, 10 h and 9 h, respectively. This indicated influence of increased amount of chitosan in films decreased drug release and also sustained the release of drug. Amount of HPMC K_4M and amount of chitosan both influenced drug release from mucoadhesive films. Increased amount of HPMC K_4M retard the drug release up to some extent but presence of chitosan might be extend drug release up to 12 h.

Kinetic Analysis

Kinetic analysis of the *in-vitro* dissolution profile of batch F1 to F9 was carried out in order to estimate the order of drug release. The dissolution profile of batch F1 to F9 was fitted in the equations of the various kinetic model like zero order release, first order release, higuchi, korsemeyer-peppas, etc using Kinet DS software for dissolution modeling. The results of model fitting were summarized in Table 5. Results indicted among all fitted model best fitted model was zero order model based on r^2 value (0.9829), which suggest that linearity of curve was good and best fitted to zero order model for all 9 batches (F1 to F9) formulated.

Formulation Optimization

Mucoadhesion Strength

Mucoadhesion strength was analyzed using Microsoft Excel for prepared mucoadhesive films. A coefficient with positive sign shows a synergistic effect whereas a coefficient with negative sign shows an antagonistic effect. A coefficient of independent factor X_1 with a positive sign (0.0183) indicated that mucoadhesion was increased as the amount of HPMC K_4M was increased (batch F1, F4 and F7) similarly a coefficient of Independent factor X_2 with a positive sign (0.5166) indicated that mucoadhesion force was increased as the amount of chitosan was increased (batch F1, F2, F3, batch F4, F5, F6 and batch F7, F8, F9). The coefficients with second order terms (b11 and b22) indicated the quadratic nature in which a negative sign indicated (-0.0183 and -0.4133) that as the amount of HPMC K_4M and chitosan added in increased amounts, mucoadhesion was increased (compare batch F1, F5 and F9). The positive sign of the interaction term indicated favorable effect of both HPMC K_4M and chitosan on mucoadhesion strength. Figure 4 showed response surface plot showing effect of X_1 and X_2 on mucoadhesion force.

% Swelling Index

% Swelling index was analyzed using Microsoft Excel for prepared mucoadhesive films. A coefficient with positive sign shows a synergistic effect whereas a coefficient with negative sign shows an antagonistic effect. A coefficient of independent factor X_1 with a positive sign (1.3733) indicated that % swelling was increased as the amount of HPMC K_4M was increased (batch F1, F4 and F7) similarly a coefficient of Independent factor X_2 with a negative sign (-1.8933) indicated that % swelling was decreased as the amount of chitosan was increased (batch F1, F2, F3, batch F4, F5, F6 and batch F7, F8, F9). The coefficients with second order terms (b11 and b22) indicated the quadratic nature in which a negative sign indicated (-0.5066 and -1.4566) that as the amount of HPMC K4M and chitosan added in increased amounts, % swelling was decreased (compared with batch F1, F5 and F9). Figure 5 showed response surface plot showing effect of X_1 and X_2 on % swelling index.

Table 1: Composition of Mucoadhesive Films as per 3^2 Full Factorial Designs

Batch	Coded factors		Actual Factors	
	X_1	X_2	X_1	X_2
F1	-1	-1	50	100
F2	-1	0	50	150
F3	-1	1	50	200
F4	0	-1	100	100
F5	0	0	100	150
F6	0	1	100	200
F7	1	-1	150	100
F8	1	0	150	150
F9	1	1	150	200
levels of 3^2 Full Factorial Designs				
Independent Factors	**Levels**			
	Low(-1)		**Centre (0)**	**High (1)**
X_1= Amount of HPMC K4M (mg)	50		100	150
X_2= Amount of Chitosan (mg)	100		150	200

Table 2: Composition of Mucoadhesive Films of Glipizide

Ingredients	Batch								
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**
Glipizide	40	40	40	40	40	40	40	40	40
HPMC K_4M (mg)	50	50	50	100	100	100	150	150	150
Chitosan (mg)	100	150	200	100	150	200	100	150	200
PEG400 (ml)	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1

Table 3: Results of Film Thickness, Surface pH and % Drug Content

Batch	Thickness (mm) ± S.D	Surface pH ± S.D	% Drug Content ± S. D
F1	0.251 ± 0.021	6.45 ± 0.0143	95.32 ± 0.0156
F2	0.236 ± 0.0101	6.65 ± 0.0198	98.54 ± 0.0135
F3	0.289 ± 0.0151	6.98 ± 0.0126	99.32 ± 0.0126
F4	0.254 ± 0.0126	6.52 ± 0.0320	96.68 ± 0.0189
F5	0.251 ± 0.0120	6.69 ± 0.0256	97.35 ± 0.0124
F6	0.259 ± 0.0212	6.98 ± 0.0165	96.36 ± 0.0198
F7	0.261 ± 0.0156	6.35 ± 0.0123	95.42 ± 0.0175
F8	0.250 ± 0.0135	6.32 ± 0.0156	95.69 ± 0.0165
F9	0.254 ± 0.0185	6.58 ± 0.0101	96.98 ± 0.0154

Table 4: Experimental Runs and Measured Responses as per 3^2 Factorial design

Batch	Independent Variables		Responses			
	X_1	X_2	Mucoadhesion Strength (N/mm^2) Y_1	% Swelling Index Y_2	Folding Endurance Y_3	Q8 (%) Y_4
F1	-1	-1	3.21	61.87	208	75.84
F2	-1	0	3.26	64.75	214	77.62
F3	-1	1	3.25	65.98	220	82.89
F4	0	-1	4.15	61.65	225	73.36
F5	0	0	4.18	64.32	229	75.81
F6	0	1	4.18	65.32	231	78.65
F7	1	-1	4.25	60.23	228	74.65
F8	1	0	4.30	60.22	232	76.14
F9	1	1	4.29	60.69	229	73.94

Table 5: Dissolution Kinetic Modeling of *In-Vitro* Drug Release Profile

S. No	Name of Kinetic Model	R^2	RMSE
1	Zero order model	0.9829	4.1463
2	First Order Model	0.7821	2.5517
3	Korsmeyer-Peppas Model	0.9784	6.9849
4	Weibull Model	0.9549	6.2158
5	Hixson Crowel Model	0.8820	1.3724
6	Higuchi Model	0.5438	2.1452

Table 6: Summary of Results of Regression analysis for Batch F1 to F9

Response		b_o	b_1	b_2	b_{11}	b_{22}	b_1b_2	R^2
Mucoadhesion Strength (N/mm^2)	FM	4.18220	0.0183	0.5166	-0.0183	-0.4133	0.0000	0.9999
	RM	4.18221	0.0183	0.5166	-0.0183	-0.4133	-	
% Swelling Index (%)	FM	64.1011	1.3733	-1.8933	-0.5066	-1.4566	0.9125	0.9748
	RM	64.1011	1.3733	-1.8933	-	-	-	0.9848
Folding Endurance	FM	229.331	3.1666	7.8333	-1.5012	-6.5105	-2.7501	0.9919
	RM	229.331	3.1666	7.8333	-	-	-	0.9929
Q8 (%)	FM	75.9188	1.9383	-1.9366	0.0316	0.9066	-1.9401	0.9138
	RM	75.9188	1.9383	-1.9366	-	-	-	0.9338

FM = Full Model, RM = Reduced Model

Table 7: Check Point Analysis of Mucoadhesive Films

Batch	X_1	X_2	Mucoadhesion Strength (N/mm^2) Y_1		% Swelling Index (%) Y_2		Folding Endurance Y_3		Q8 (%) Y_4	
			O	P	O	P	O	P	O	P
FC1	0.25	0.5	4.33	4.34	63.21	63.21	231.98	231.97	75.43	75.42
FC2	0.5	0.25	4.29	4.29	64.20	64.21	231.76	231.74	76.23	76.22

O = Observed Value, P = Predicted Value

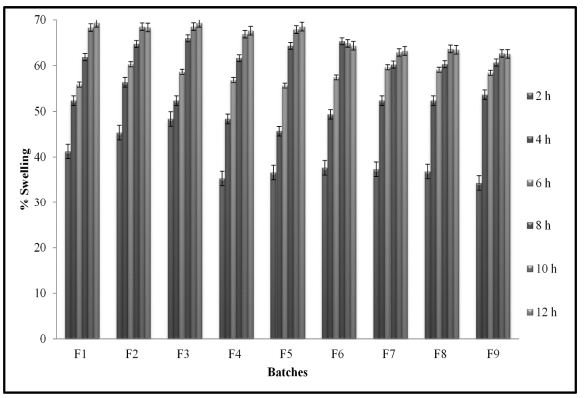


Figure 1: Result of % Swelling of Films after 2 h, 4 h, 6 h, 8 h, 10 h and 12 h

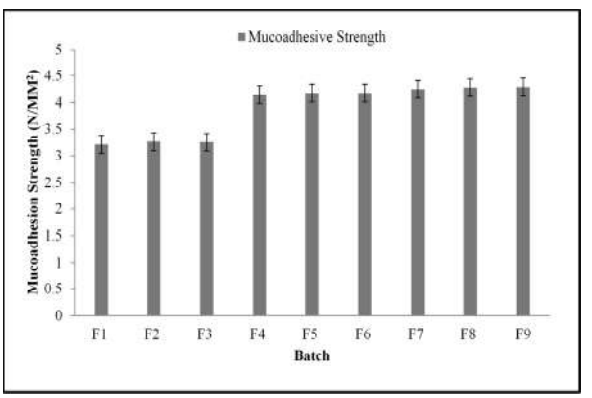
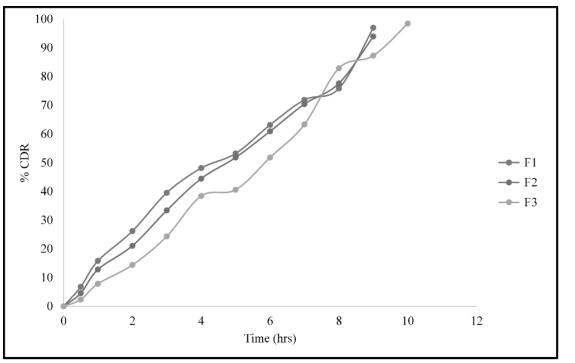
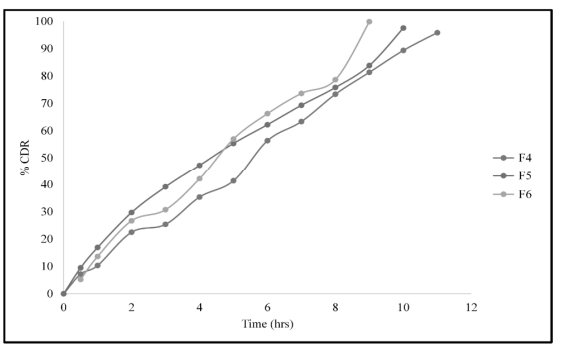


Figure 2: Mucoadhesive Strength of Batch F1-F9





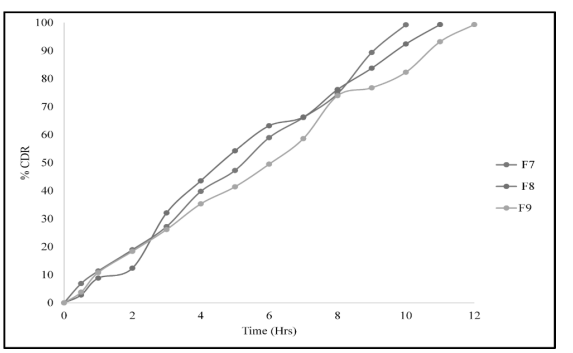


Figure 3: *In-vitro* Dissolution Curve of Batch F1 to F9

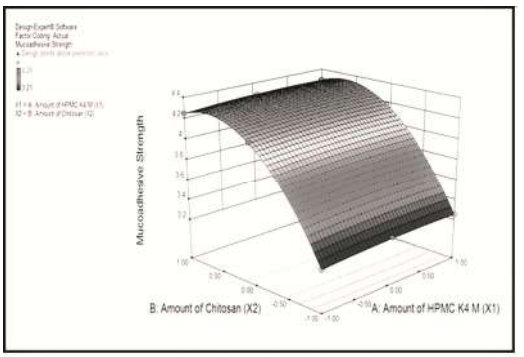


Figure 4: Response Surface Plot Showing Effect of X_1 and X_2 on Mucoadhesive Strength

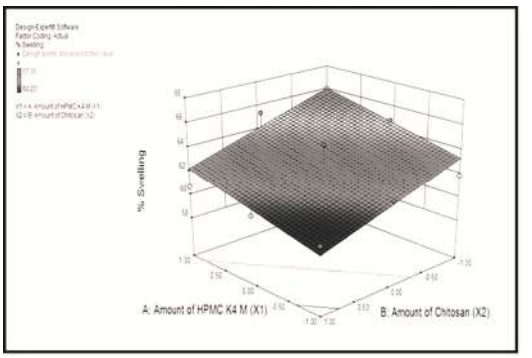


Figure 5: Response Surface Plot Showing Effect of X_1 and X_2 on % Swelling Index

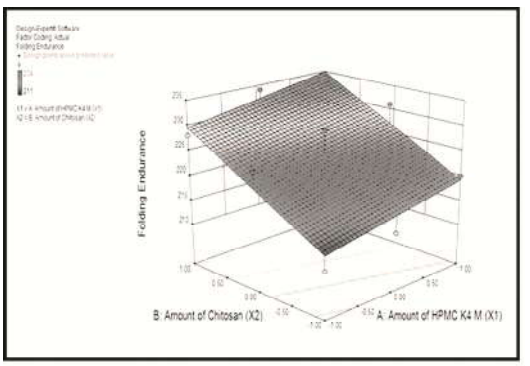


Figure 6: Response Surface Plot Showing Effect of X_1 and X_2 on Folding Endurance

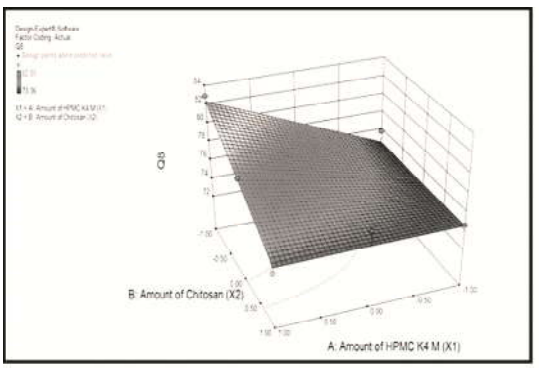


Figure 7: Response Surface Plot showing Effect of X_1 and X_2 on Q8

Folding Endurance

Folding endurance was analyzed using Microsoft Excel for prepared mucoadhesive films. A coefficient with positive sign shows a synergistic effect whereas a coefficient with negative sign shows an antagonistic effect. A coefficient of independent factor X_1 with a positive sign (3.1666) indicated that folding endurance was increased as the amount of HPMC K_4M was increased (batch F1, F4 and F7) similarly a coefficient of Independent factor X_2 with a positive sign (7.8333) indicated that folding endurance was increased as the amount of chitosan was increased (batch F1, F2, F3, batch F4, F5, F6 and batch F7, F8, F9). The coefficients with second order terms (b11 and b22) indicated the quadratic nature in which a negative sign indicated (-1.5012 and -6.5105) that as the amount of HPMC K_4M and chitosan added in increased amounts, folding endurance was increased (compare batch F1, F5 and F9). Figure 6 showed response surface plot showing effect of X_1 and X_2 on folding endurance.

Q8

Q8 was analyzed using Microsoft Excel for prepared mucoadhesive films. A coefficient with positive sign shows a synergistic effect whereas a coefficient with negative sign shows an antagonistic effect. A coefficient of independent factor X_1 with a positive sign (1.9383) indicated that Q8 was increased as the amount of HPMC K_4M was increased (batch F1, F4 and F7) similarly a coefficient of independent factor X_2 with a negative sign (-1.9366) indicated that Q8 was decreased as the amount of chitosan was increased (batch F1, F2, F3, batch F4, F5, F6 and batch F7, F8, F9). The coefficients with second order terms (b11 and b22) indicated the quadratic nature in which a positive sign indicated (0.0316 and 0.9066) that as the amount of HPMC K_4M and chitosan added in increased amounts, Q8 was increased (compare batch F1, F5 and F9). Figure 7 showed response surface plot showing effect of X_1 and X_2 on Q8. It was arbitrarily decided for the selection of optimized batch, optimized batch had higher mucoadhesion strength, lower % swelling index, higher folding endurance and 76 % to 77 % Q8. On the basis of constraints for optimization batch F8 was selected as optimized batch for gastroretentive mucoadhesive film by solvent casting method. To validate the evolved mathematical models, two check points were selected. Two batches were prepared and evaluated for mucoadhesive film. The observed and predicted values were shown in Table 7. Good correlation was found between observed and predicted values. Hence, it might be concluded that the evolved model might be used for theoretical prediction of responses within the factor space.

CONCLUSION

In present investigation, novel gastroretentive mucoadhesive films were prepared by solvent casting method. Films were prepared using HPMC K_4M, Chitosan and PEG 400 as release retarding agent,

mucoadhesive/rate controlling agent and plasticizer, respectively. Methanol was used as solvent for preparation of films. Mucoadhesive films had more gastroretention than other oral gastroretentive dosage form. Prepared films were evaluated for thickness, drug content and surface pH also. Result of evaluation parameters showed thickness of film in between 0.221 mm to 0.251 mm, folding endurance in between 211 to 234, % swelling in between 60.23 % to 65.69 %, surface pH in between 6.25 to 6.98, drug content of all the batches was almost above 97 %, mucoadhesion strength in between 3.21 to 4.29 N/mm^2 and *in- vitro* drug release was controlled up to 11 h. The polymer concentration is a major factor affecting the drug release and mucoadhesion strength of the mucoadhesive films. The observed response is close agreement with the predicted release rates there by demonstrating the feasibility of the procedure. Among all batches F1 to F9, batch F8 was selected as optimized batch because it satisfactorily complied constrains for optimization. In conclusion, novel gastroretentive mucoadhesive films was proved to a good formulation for drug having absorption form stomach and had higher bioavailability in stomach.

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