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Formulation and Evaluation of Chitosan-Based Mucoadhesive Buccal Patch of Prochlorperazine Maleate

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ABSTRACT

The present study aims to develop and evaluate mucoadhesive buccal patch of prochlorperazine maleate. Drugs that have poor solubility, bioavailability, and/or extensive first-pass metabolism can be delivered effectively through the buccal route. Prochlorperazine maleate is an anti-emetic drug that has a high first-pass metabolism rate. Delivery of drug through the mucous lining of the oral cavity avoids hepatic metabolism of the drug and increases its bioavailability. Patches were prepared using chitosan 4% w/v as maximum concentration and 30 %w/v of glycerin as a plasticizer. The patches were evaluated for mucoadhesion, drug release, folding endurance, surface pH, swelling index, drug content was found to be in the range of 17.4±0.016 to 38.45±0.3, 57.56 ±0.01 to 41.15 ± 0.08, 354 ±1.15 to 386 ± 5.4, 6.2 ± 0.04 to 6.77 ± 0.05, 26.77±0.03 to 86.52±0.04, 95.93±0.04 to 99.77±0.07. The optimized batch showed a maximum *in vitro* drug release at 6 h i.e. 52.28 ± 0.06 % and mucoadhesion strength 32.64±0.3 g.

INTRODUCTION:

Most drugs suffer from low bioavailability due to various reasons such as low solubility, low permeability, first pass metabolism and PgP efflux[1,2]. List of drugs having low bioavailability due to extensive first pass after oral administration is extensive hence formulation scientists always look for alternative strategies to increase the bioavailability[3]. Mucoadhesive drug delivery through buccal route has been extensively studied and proven to be safe and effective for local as well as systemic delivery[4].Buccal route offer advantages over oral route as it overcomes deficiencies of oral route & have certain advantages which include easy accessibility, direct entry into systemic circulation, avoidance of first-pass metabolism and increase in bioavailability[4].Out of different dosage forms employed to administer a drug through oral route such as buccal patches have unique characteristics of flexibility, rapid onset, and sustained release, as well as termination of the dosage form, are easy.

Prochlorperazine Maleate is piperazine derivative &an anti-emetic drug that belongs to BCS Class II and shows first pass metabolism. It is also used to treat psychosis and bipolar disorder, emesis related to chemotherapy. In a healthy volunteer half-life of the drug is found to be 4-8 h. The oral bioavailability of prochlorperazine maleate is 5.7 % as it undergoes extensive hepatic first-pass metabolism by CYP2D6 & CYP3A4, therefore, it is a suitable candidate for buccal delivery. Buccal tablets of prochlorperazine are reported (S.Vijay Kumar et al 2016), but buccal films are preferred over tablets in terms of their flexibility and comfort (Peh & Wong 1999). The buccal film of prochlorperazine is also reported using HPMC(Kolli CS et al) but suffered from limited bioadhesion time due to the hydrophilic nature of the polymer.[4]Thus the objective of the work was to develop a mucoadhesive buccal patch of prochlorperazine maleate to enhance its bioavailability by increasing its residence time and avoiding its first pass metabolism.

Chitosan due to its cationic nature exhibits stronger and longer adhesion, it also has an effect on transmucosal permeation [5]. Hence in this research, we have developed mucoadhesive buccal patches of prochlorperazine maleate using chitosan as a mucoadhesive polymer.

MATERIAL & METHODS:

MATERIALS:

Prochlorperazine maleate gifted from Mehta pharmaceuticals Mumbai, Chitosan & tween 80 were procured from local market and was of the extra pure grade.

Calibration curve by UV analytical method:

A series of solutions of Prochlorperazine maleate in Phosphate buffer pH 6.8 over concentration range 2-14 µg/ml was prepared. The absorbance of all the solutions was measured using phosphate buffer pH 6.8 as blank at 255 nm using a double beam spectrophotometer. A standard plot of absorbance v/s concentration of drug in µg/ml was prepared.

Excipient compatibility study:

The drug and excipients were kept in ratios likely to occur in the formulation and stored at 40^{o}C for 2 weeks. After 2 weeks mixtures were analyzed by FTIR spectrometry (IR Affinity-1, Shimadzu, Japan) for any possible chemical interaction. Also, any sign of melting or discoloration were looked for.

Formulation of buccal patches[6,7,8]:

Buccal patches were prepared using solvent casting method.

Table 1: Formulation Table of Buccal Patches of Prochlorperazine maleate

SR. NO	INGREDIENTS	QUANTITY	CATEGORY
1	Prochlorperazine maleate	3 mg/cm^2	Drug
2	Glycerin	30 % w/v of polymer	Plasticizer
3	Tween 80	0.1 ml	surfactant
4	Chitosan	2%	polymer
5	DMSO: Methanol	1:1	solvent

Chitosan (2.5% w/v), Glycerin (30% w/w of polymers) and tween 80 (0.1 ml) were dissolved in casting solvent (20ml) DMSO: Methanol (1:1) the required amount of prochlorperazine was incorporated in this solution with continuous stirring till homogeneous. This solution (25 ml) was poured into Petri plates and air dried for 12 h.

Experimental Design:

The formula (Table 1) optimization was done by 3^2 factorial design using Design expert (Version 11.0; Stat-Ease Inc., Minneapolis, Minnesota, USA) software for mathematical modeling and analysis of responses. The optimal levels of variables viz concentration of polymer and plasticizer were determined (Table 2) to achieve desired responses.

Table 2: Variables and Their Levels Used In 3^2 Factorial Design

INDEPENDENT VARIABLES	**SYMBOL**	**LEVELS**		
		-1	0	+1
Chitosan concentration (%)	Factor 1	2	3	4
The concentration of Plasticizer (ml)	Factor 2	0.12	0.18	0.24
DEPENDENT VARIABLES	**UNITS**	**CONSTRAINT**		
Drug release (Response 1)	%	Maximize		
Folding endurance (Response 2)	-	In range		
Mucoadhesion (Response 3)	g	Maximize		

Factorial batches:

Table 3: Formulation Ingredients of Mucoadhesive Buccal Patches Using 3^2 Factorial Design

FORMULATION CODE	INGREDIENTS	
	Chitosan (mg)	Plasticizer (glycerol)
F1	400	0.12
F2	600	0.12
F3	800	0.12
F4	400	0.18
F5	600	0.18
F6	800	0.18
F7	400	0.24
F8	600	0.24
F9	800	0.24

EVALUATION OF FACTORIAL BATCHES:

Primary Evaluation[9]:

All batches were visually inspected for their color & clarity. The weight of each patch was measured using digital balance.

Film thickness[9,10]:

The thickness of patches was determined using digital Vernier caliper. Thickness was measured at five different positions i.e. at center followed by four corners and the mean thickness was calculated. Maximum variation in the patches should be less than 5% and mean ±SD calculated.

Drug content[10]:

A patch of $1cm^2$ was dissolved in 100 ml phosphate buffer 6.8the resulting solutions were then filtered and analyzed by UV Spectrophotometry at 255 nm.

Folding endurance[10]:

The patch was repeatedly folded at the same place till it broke or folded up to 300 times, which is considered satisfactory to reveal good properties. The number of times the film

could be folded at the same place without breaking gave the value of folding endurance. This test should be performed on six films of each formulation and mean±S.D calculated.

Surface pH[10,11]:

1 X 1 cm patch was properly cut and placed in 1ml distilled water and allowed to swell for at least 30 min. pH was measured by bringing the electrode to the surface of the patch using a digital pH meter. Surface pH measured should be near to neutral because acidic or alkaline pH of the patch can cause irritation to the oral mucosa.

Swelling studies[12,13]:

A patch of size 1 cm ^{2}wasweighed individually (designated as W_1) and placed separately in Petri dishes containing 4 ml of phosphate buffer pH 6.8. After 1-hour patches were withdrawn from the Petri dishes and excess water was removed carefully by using filter paper. The swollen patches were reweighed (W_2). The swelling index was calculated using the equation:

$$\text{Swelling index} = W_2 - W_1 / W_1 \text{---------(1)}$$

Where, W_1 – an initial weight of the patch

W_2- a final weight of the patch

Mucoadhesion test[14]:

Mucoadhesion test was performed using a texture analyzer (CEB Texture Analyzer, Make-Brookfield Engineering Labs, Inc., Model No. Texture Pro CT 3). The buccal mucosa of sheep was used as a model membrane. A patch was carefully attached to a 10 mm cylindrical probe (TA3/100 probe) by a two-way tape. The upper platform was moved to the mucosal surface. The sample was brought towards mucosal at a speed of 1 mm/s at a distance of 15 mm and the hold time was 10 sec. Maximum detachment force (g) was determined for each sample.

***In-vitro* release study[11]:**

The release study from buccal patches was performed by using a USP type II apparatus. The dissolution medium used was 250ml of phosphate buffer pH 6.8. The temperature and speed

were maintained at 37 ± 0.5° C and 100 rpm respectively. Patches (F1-F9)were placed in the apparatus and samples were withdrawn at 1 h time intervals up to 6 h, after every interval same amount of fresh medium was replaced. The samples were then analyzed by using a UV spectrophotometer at 255 nm.

Determination of *in-vitro* Residence Time [15]:

In-vitro Residence time of buccal patch was calculated by using USP disintegration test apparatus. The medium used was 800ml of phosphate buffer pH 6.8. The mucosa was mounted on a glass slide that was then vertically attached to the apparatus. The patch was initially hydrated with the phosphate buffer and then placed on the mucosa. The glass slide was then placed vertically into the apparatus and allowed to move up & down in the dissolution medium so that the patch gets completely immersed in the buffer solution. The time required to detach the patch from the mucosa was recorded.

***Ex-vivo* permeation study[14,16]:**

Diffusion studies were carried out by using Franz diffusion cell out to evaluate the permeability of drug across the sheep buccal mucosa. The mucosal membrane was clamped in between donor and receiver chamber of the diffusion cells for permeation studies. Receptor compartment contained phosphate buffer pH 7.4 at 37˚ C. The patch was placed on the membrane surface in donor compartment and aliquots were removed at time intervals of 1,2,3,4,5 h from the receptor compartment to be replaced by equal volume of fresh dissolution medium. The amount of drug permeated was assayed using a UV-Visible spectrophotometer at 255 nm.

RESULTS & DISCUSSION:

Calibration curve by UV analytical method:

The calibration curve was established at 255 nm and Beers law was obeyed between the concentration range of 2 to 14 µg/ ml. and the equation of line was y = 0.0586x - 0.0206 & the R^2 value was found to be 0.9957.

Excipient compatibility study:

The samples kept for compatibility did not show any physical changes. The IR Spectra of prochlorperazine maleate shows a peak at 2891.32 (C-H STRETCH), 3104.28 (C=C),711 (C-Cl). All these peaks were retained in the spectra with excipients and no new peaks were observed. There was no interaction between the drug & excipients. These peaks were not affected by excipients and are characteristic of the drug. (Figure 1).

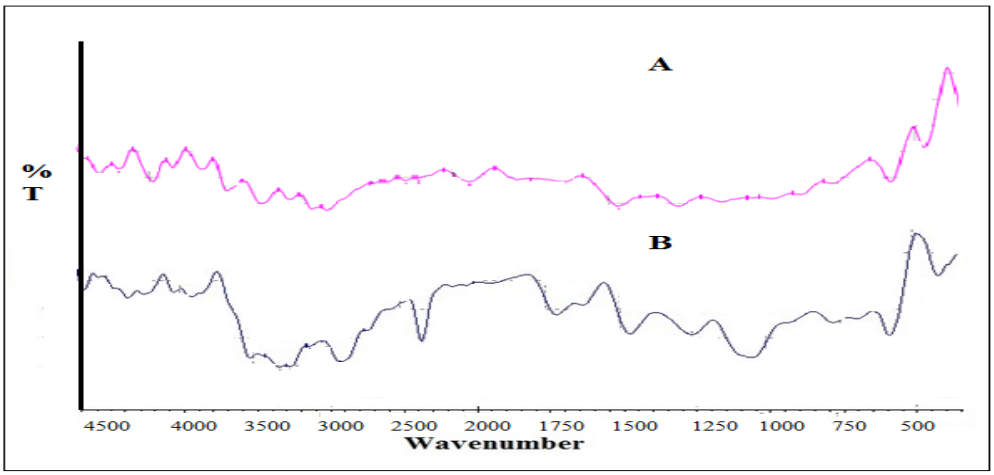

Figure 1: FTIR Spectra of Physical Mixture of Drug & Excipient. A (Prochlorperazine Maleate), B (Physical Mixture)

Chitosan was used as mucoadhesive polymer because of its excellent mucoadhesive properties and also its biocompatible nature. Tween 80 was used as the aid in solubilizing the drug along with DMSO: Methanol (1:1) solvent system. Various solvents such as ethanol & methanol and solvent systems such as DMSO: ethanol, DCM: Methanol and solvents were used and DMSO: Methanol system was found to be satisfactory. Plasticizer plays a vital role in the preparation of patch and is a crucial requirement because it provides flexibility to the patch. In order to attain desired flexibility, it is necessary to optimize the plasticizer & its concentration. Glycerin was used as plasticizer because it provided desired flexibility as compared to PEG 400/800 or propylene glycol in initial trials. The results are given in table 4:

Evaluation of Factorial Batches:

Table 4: Choice of Plasticizer

Polymer concentration	Plasticizers	Plasticizer concentration	Results
2%	Propylene glycol	30% w/w of polymer	Thick & hard patch with no flexibility
2%	PEG 400	30% w/w of polymer	Thick &shrinked patch with no flexibility
2%	PEG 800	30% w/w of polymer	Shrinked& hard patch with no flexibility
2%	Glycerin	30% w/w of polymer	Thin patch with desired flexibility and not easily breakable

The patches prepared were dried at room temperature because drying the patches in hot air oven caused shrinkage of patches. The drying time for procuring completely dried patches was 2 days. Drying time was an important factor because improper drying would cause moisture retention that would, in turn, lead to a decrease in the integrity of the patch and render patch easily breakable.

3^2 factorial design was used to determine the effect of independent variables on dependent variables. The factors chosen were a concentration of polymer & concentration of plasticizer as they had a crucial impact on the responses. Responses i.e drug release, mucoadhesion force, folding endurance were chosen because these were the important characteristic that determined the behavior of the formulation & was dependent upon the factors.

Evaluation of Factorial Batches:

After preparation of patches, they were evaluated for their physical characteristics and the patches were found to be clear & were of pale brown color. Patches were then evaluated for further parameters. (Table 5)

Table 5: Evaluation of Factorial Batches (n=3)

F code	Weight variation (mg)	Thickness mm	Drug content %	Folding endurance	Surface pH	Swelling index %	Mucoadhesion (adhesive force) g	Drug release %
F1	25.4±0.04	0.28±0.02	99.48±0.06	354±1.15	6.26±0.04	26.77±0.03	17.4±0.16	57.65±0.01
F2	30.9±0.01	0.29±0.02	97.21±0.03	367±6.4	6.56±0.13	58.9±0.05	22.54±0.02	46.94±0.06
F3	35.8±0.05	0.22±0.06	95.93±0.04	358±7.7	6.61±0.03	76.69±0.07	25.47±0.04	41.15±0.08
F4	37.7±0.06	0.27±0.08	99.77±0.07	375±12.1	6.77±0.05	33.15±0.01	18.54±0.05	58.11±0.06
F5	38.5±0.02	0.30±0.05	99.63±0.03	386±5.4	6.68±0.03	64.48±0.08	25.43±0.02	57.22±0.09
F6	38.5±0.05	0.31±0.04	98.91±0.01	390±4.6	6.58±0.005	83.42±0.01	27.25±0.05	50.46±0.05
F7	39.2±0.04	0.28±0.04	98.06±0.08	364±14.0	6.58± 0.01	40.30±0.03	21.01±0.04	55.09±0.06
F8	40.5±0.03	0.33±0.04	98.20±0.09	375±5.27	6.46±0.03	69.20±0.06	27.25±0.04	52.17±0.01
F9	66.8±0.04	0.39±0.06	96.92±0.07	371±4.02	6.33± 0.03	86.52±0.04	38.45±0.3	49.01±0.04

The average weight of the batches (f1-f9) ranged from 25.4±0.04 to 66.8±0.04mg. A linear increase in weight of the patches was observed as the concentration of chitosan increased. A thickness of the patches ranged from 0.28±0.02 to 0.39±0.06 mm.

The prepared patches showed drug content ranging from 95.93±0.04 to 99.77±0.07 % respectively. Folding endurance of the patches indicated that the patches show good flexibility and the values are within the range i.e. >300 folds.

Ideally, the pH of buccal patches should be near to neutral to avoid the irritation caused due to acid/alkaline pH thus the above results showed that the surface pH of the patches was close to neutral indicating that the pH lies within the range.

The swelling index of the patch is directly related to the concentration of the chitosan. As chitosan shows good swelling properties the results above indicate an increase in the swelling characteristics with an increase in the chitosan concentration i.e. from 26.77±0.03 % to 86.52±0.04 %.

It was observed that the mucoadhesion increased with the increase in the concentration of chitosan thus indicating a direct correlation between the concentration of polymer &mucoadhesion which can be attributed to cationic nature of an amino group of chitosan and electrostatic interaction with a negatively charged sialic group of mucin. [5]

The drug release studies carried out using USP type II apparatus showed the controlled release of drug based on the polymer concentration used as chitosan when used in higher concentrations retards the release. The drug release ranges from 41.15±0.08 to 58.11±0.06%. (Figure 2).

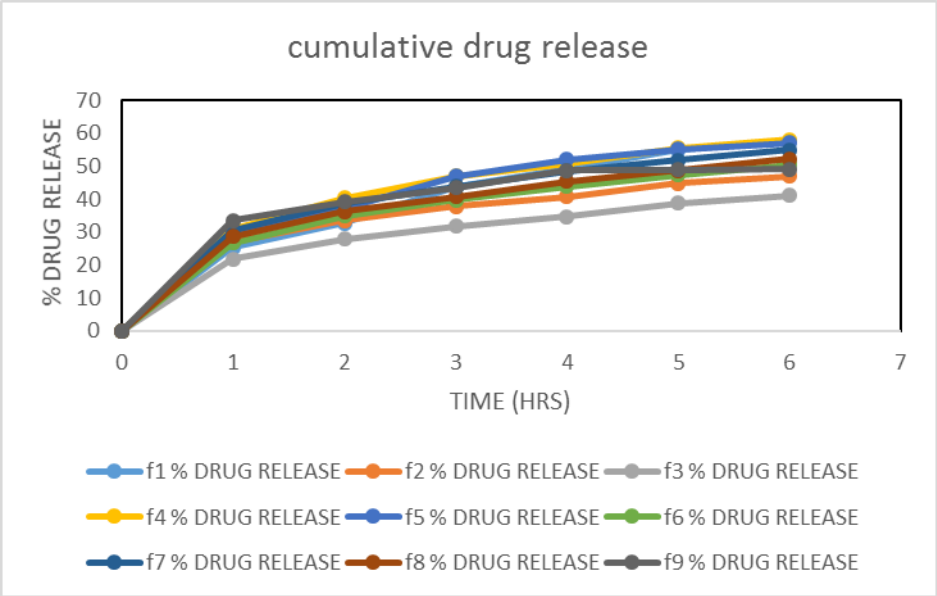

Figure 2: Cumulative Drug Release Profile

Statistical design:

A 3^2 factorial design was applied to determine the influence of the independent variable on dependent variables such as folding endurance, drug release and mucoadhesion using design expert 11.0. The results of the statistical design and the summary of responses are provided further.

Influence of the independent variable on folding endurance:

Equation 2 describes the effect of polymer and plasticizer concentration on folding endurance. Plasticizer imparts flexibility to the film increase in plasticizer concentration increases flexibility & thus decreases the folding endurance. The polymer concentration improved folding endurance due to the increase in strength of the film. The interaction of both the factors showed the positive effect as compared to the effect of individual factors. (Figure 3)

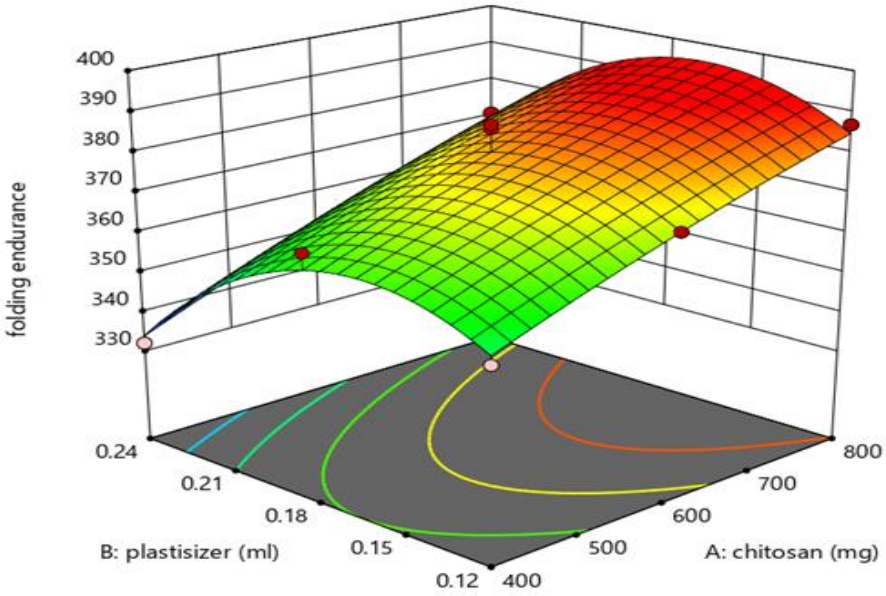

Figure 3: Response Surface of Folding Endurance

Folding endurance=380.33+15.38A-9.67B+1.50AB-1.50A^2-18.00 B^2------(2)

Influence of the independent variable on drug release:

Equation (3) indicates the impact of polymer and plasticizer concentration on the release of drug from the formulation. Increase in the polymer concentration leads to a decrease in the drug release as chitosan acts as release retardant when used in higher concentration thus showing retardation in the release.

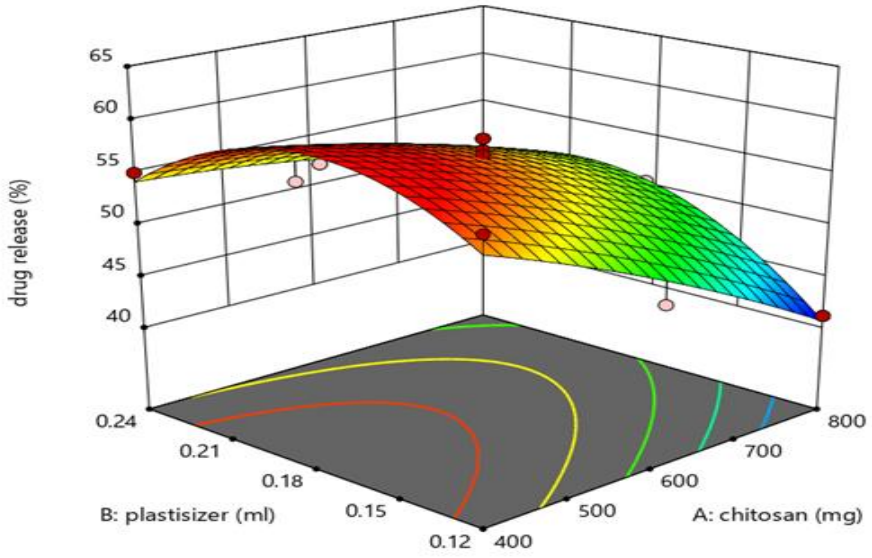

Figure 4: Response Surface of Drug Release.

Drug release=+56.56-5.04A+1.75B+2.61 AB-0.8950 A^2-5.62B^2-------(4)

Influence of the independent variable on mucoadhesion:

There is a linear relationship between the concentration of chitosan and mucoadhesion(equation 5). Chitosan exhibits cationic nature due to the presence of amino group & hence electrostatic interaction occurs between the positively charges chitosan and a sialic group of the mucin leading to strong mucoadhesion. On the other hand, the concentration of plasticizer shows very little increase in the mucoadhesion of patches.

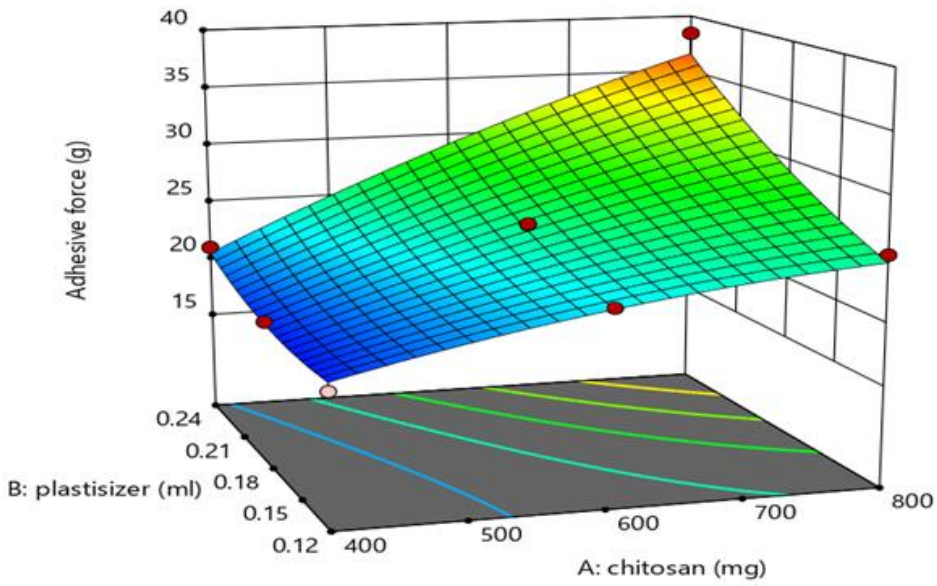

Figure 5: Response Surface of Mucoadhesion Force

Mucoadhesion=+24.92+5.69A+3.51B+2.37 AB-0.9087 A^2-1.04B^2------(5)

Table 6: Summary Table of Responses

Sr. No.	Responses	R^2	P Value	Model Significant/ Not Significant
1	Drug release %	0.9377	0.0014	Significant
2	Folding endurance	0.9393	0.0015	Significant
3	Mucoadhesion (g)	0.9447	0.0010	Significant

P-values less than 0.0500 indicate model terms are significant. In this case, A, B, B^2 are significant model terms. Values greater than 0.1000 indicate the model terms are not

significant. Also, the R^2 values manifest the exceptional accession between the formulation variables and response framework.

Depending upon the data provided of the factorial batches the software suggested an optimized design Table 7.

Table 7: Optimized Batch

INGREDIENTS	QUANTITY
Chitosan	4%
Glycerin	0.20ml
Tween 80	0.1 ml
Solvent	1:1
Desirability	0.828

Evaluation of the optimized batch:

The optimized batch suggested from the software was prepared and evaluated for the same parameters as that of factorial batches. The optimized batch was further evaluated for *Ex-vivo* permeation and *in-vitro* residence time, all determinations were done in triplicate.

The prepared patch had a mean weight of 68.8mg and was of thickness 0.37mm. The drug content of the patch was 97.02%. The patch showed good flexibility as it sustained389folds at the same point without breaking. The results showed that the surface pH of the patches was close to neutral indicating that the pH lies within the range i.e 6.39. Swelling index of the patch was 87.01% which contributed to the adhesiveness of the patch.

The force required to detach the force from the mucosal surface was evaluated thus indicating the mucoadhesive behavior of the patch and was found to be 32.64±0.3 g(adhesive force). The amount of drug released from the patch at 6^{th}h was calculated using USP type 2 apparatus and was found to be 52.28±0.06 %. Analysis of *vitro* release data suggested release kinetics following Korsemeyer- Peppas model (r^2 = 0.9953) the value of n =0.58indicates diffusion release behavior.

The *in-vitro* residence time using USP disintegration apparatus showed a residence time of more than 12 hon the mucosal surface while the flux from *ex vivo* permeation studies was found to be 10.27 µg/h/cm^2.

The results obtained from the optimized batch shows good mucoadhesion strength as well as drug release.

CONCLUSION:

Prochlorperazine undergoes the first-pass metabolism when administered orally and therefore show less oral bioavailability. The mucoadhesive buccal patches of prochlorperazine formulated using chitosan as mucoadhesive polymer offer prolonged *in-vitro* residence time and *in-vitro* drug release. Chitosan has excellent mucoadhesive& swelling properties that allow the formulation to reside for the longest time on the mucosal surface.

The factorial design revealed that the amount of chitosan and plasticizer used has the direct effect on the mucoadhesion strength and drug release characteristics of the patches. Higher concentration of polymer increases the mucoadhesion strength and also increases the time required for drug release as it retards release due to its binding capacity.

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