FORMULATION AND CHARACTERIZATION OF PROCHLORPERAZINE FILMS FOR BUCCAL DELIVERY

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ABSTRACT
Background and Objective: Oral drug delivery is preferred by patients of all age groups, including paediatrics and geriatrics. However, 26-50% population find it difficult to swallow tablets and capsules. One of the best routes for drug administration is through the oral cavity mucosa, it offers advantages like preventing gastrointestinal degradation, bypassing first-pass metabolism, and improving patient acceptance. Hence, aim of the study was to formulate Prochlorperazine maleate into oral thin films to increase its oral bioavailability and improve patient compliance. **Materials and Methods:** 3^2 full factorial design is applied to optimize the formulation by taking Concentration of chitosan and Concentration of Sodium carboxymethylcellulose as independent variables and swelling index and % drug release at 30 minutes as dependent variables. A total of 9 batches were formulated and measured. Statistical analysis was further validated by design expert software (version 13, Stat -Ease Inc., and Minneapolis, MN). **Results and Discussion:** It was observed that chitosan and Sodium CMC have influenced the design and optimization of Prochlorperazine buccal films and had significant effect on swelling index and drug release. Buccal film F7 has shown the ideal characteristics for buccal therapy of Prochlorperazine and exhibited suitable release characteristics.

KEYWORDS: Buccal film, Prochlorperazine maleate, Mucoadhesive, Buccal drug delivery, Factorial design.

INTRODUCTION
Drug delivery through the oral route is the most preferred route by patients and administering drugs by this route helps to accomplish both local and systemic effects. Mostly, tablets and capsules are taken by oral route and patients of almost all age groups including paediatric and geriatric patients. However, it has been reported that around 26-50% of patients find it difficult to swallow tablets and hard gelatine capsules. Also, very little attention is given to patients experiencing dysphagia (difficulty swallowing) because most prescribed drugs are tablets or capsules. The older patient population often experiences tablets sticking in the throat, and this problem in taking prescribed formulations leads to discomfort and undermines treatment efficacy.[1] Patients struggling with dementia and other medical conditions like stroke, Parkinson's disease, cerebral palsy, thyroidectomy, and neck radiation therapy, also face the problem of dysphagia where refusal to swallow is very commonly noticed.[2] Pharmaceutical oral wafers or films are gaining a lot of interest due to their tendency to dissolve or disaggregate spontaneously in the oral cavity. They make for an appealing method of administration. These films hold potential advantages like rapid disintegration, no swallowing or chewing, no co-administration of water, accurate dosing compared to liquid products, great safety, and efficacy along with patient compliance.[3]

Mucoadhesive-based drug delivery systems have been widely used in both local and systemic diseases in recent years, with various methods used including ocular, nasal, oral, rectal, and vaginal mucosal epithelium.[4] One of the best routes for drug administration is through the oral cavity mucosa. When compared to ocular, nasal, rectal, and vaginal routes, this route has many advantages, including preventing drug degradation in the gastrointestinal tract, bypassing first pass hepatic metabolism, having low enzymatic activity, and having higher patient acceptance. It can also quickly permeate low molecular weight drugs through mucosal epithelium due to the larger surface area of the oral mucosal layer compared to the ocular and nasal mucosal layers.[5]

Prochlorperazine maleate is an antipsychotic, antiemetic, and mildly sedative piperazine phenothiazine derivative. It is well absorbed from the gastrointestinal tract and is distributed to the majority of body tissues, with high concentrations found in the liver and spleen. Prochlorperazine enters the enterohepatic circulation and is primarily excreted in faeces. Because of the high first-pass metabolism, oral bioavailability is only 16%.[6]

Hence by formulating it into oral thin films we could increase oral bioavailability thereby bypassing the first-pass metabolism and improving the patient compliance.[7]

1. MATERIALS AND METHODS
1.1 Materials
Prochlorperazine was procured from Yarrow Chem Mumbai, chitosan was procured from Balaji Drugs India, Sodium carboxymethylcellulose and PVA was procured from S-D fine chem ltd., Mumbai. Glycerol was obtained from Qualigens fine chemicals. All the other chemicals and solvents used were of AR grade.

1.2 Experimental design
Factorial design was applied to design and understand the interaction between the formulation variables and their impact on the final formulation. In this current work a 3^2-factorial design with two factors and three levels were selected to study the response of the independent variables i.e., Concentration of chitosan (X1) and Concentration of Sodium carboxymethylcellulose (X2) on the dependent variables swelling index (Y1) and % drug release at 30 minutes (Y2). A total of 9 batches were formulated and measured. Statistical analysis was further validated by design expert software (version 13, Stat -Ease Inc., and Minneapolis, MN).

Table 01: Experimental design: Factors and Responses.

Formulation	Types of variables	Variable	Optimization level used		
Prochlorperazine Buccal Film	Independent	X1- Concentration of chitosan (mg) X2- Concentration of Sodium carboxymethylcellulose (mg)	Low	0	100
			Medium	-1	125
	Dependent	Y1- Swelling index Y2- % drug release at 30 minutes	High	1	150

Table 02: Combination of factors as per 3^2 factorial designs.

Formulation	X1	X2
F1	-1	-1
F2	0	-1
F3	+1	-1
F4	-1	0
F5	0	0
F6	+1	0
F7	-1	+1
F8	0	+1
F9	+1	+1

1.3 Preparation of buccal film of prochlorperazine
The solvent casting method is one of the most popular methods to be used in the preparation of thin films [8]. In this method drug and polymers are dissolved separately in suitable solvent. When both solutions are ready and fully dissolved both the solutions are mixed and stirred thoroughly until the mixture is formed as one. Once the mixture is mixed properly it is ready for casting. Casting is accomplished by pouring the solution onto the petri plates, avoiding any air bubbles, and allowing it to dry. After it is dried a thin film is obtained.
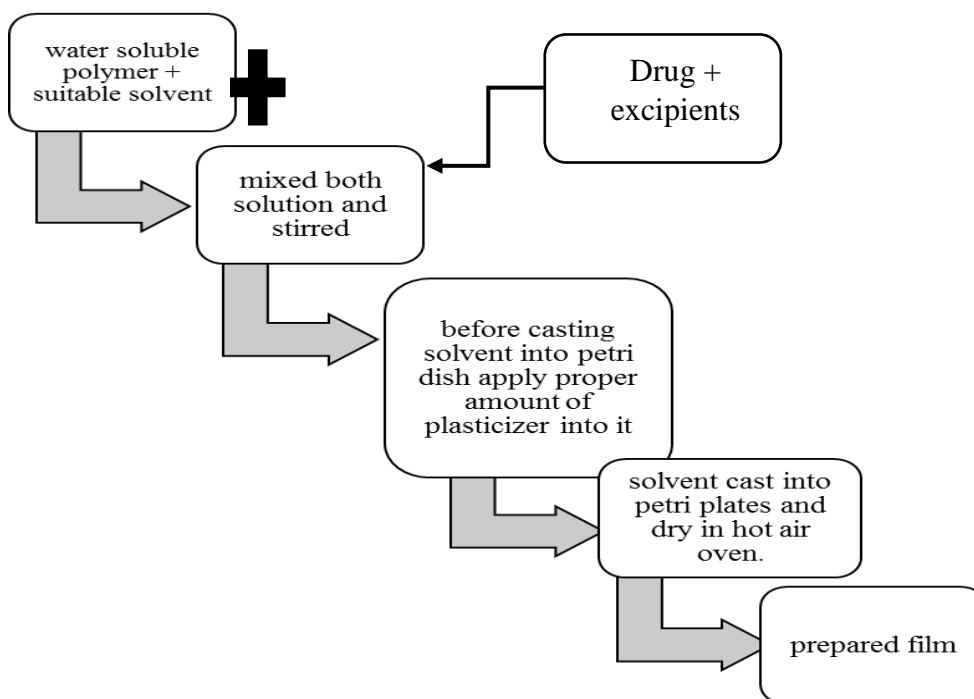

Fig. 1: Flow chart for solvent casting method.

2. EVALUATION OF BUCCAL FILMS

2.1 Thickness uniformity analysis
The thickness of each film was measured with a digital vernier calliper at five different locations (the centre and four corners) and the mean thickness was computed. Samples with air bubbles, nicks, or tears were not analysed [9].

2.2 Drug Content
Three film units 1^2 cm each of every formulation were placed in separate 100 ml volumetric flasks, and 100 ml of phosphate buffer pH 6.6 was added, which was continuously stirred for 1h.[10] Similarly, a blank was performed with a drug free patch. The solutions were filtered and absorbance was measured using UV-spectrophotometer at 290nm.

2.3 Surface pH measurement
An agar plate was prepared and pH was maintained at nearly neutral 6.7.[11] A pH paper was placed on the surface of the swollen wafer to measure the surface pH. The average of the three readings was calculated.

2.4 Folding Endurance
The folding endurance of the film can be determined by manually folding the film repeatedly at the same axis until a crack or tear is observed. The number of folds a film can withstand can be taken as the value of folding endurance.

2.5 Swelling Index study
A film was cut into 1x1 cm and accurately weighed and conduct the swelling measurement by immersing it into 10ml of simulated saliva maintaining pH 6.2 and temperature maintained at 37^oC. After 20 minutes the film was removed carefully from the saliva and excess moisture was cleaned. Then the films are weighed and % swelling index was calculated using the following formula:
SD%=(Dt-Do)/Do x 100
where SD (%) is the percent swelling obtained by the diameter method,
Dt is the diameter of the swollen wafer after time t,
Do is the original wafer diameter at time zero.[12]

2.6 *In-vitro* dissolution study
The in vitro drug release is conducted on paddle type dissolution apparatus that is equipped with six paddles. In order to mimic the in vivo adhesion and to prevent the films from floating, each film was fixed to a rectangular glass slab and placed at the bottom of the dissolution vessel prior to starting the dissolution test. The dissolution medium contains 250 ml of simulated salivary fluids pH maintained at 6.75. The rotation speed was kept at 50 rpm and temperature was maintained at 37 ± 0.5 ^{o}C. At regular time intervals i.e., after every 30 minutes 5ml sample was withdrawn and filtered through a 0.45 μm membrane filter and analysed by UV spectrophotometer at a fixed λ max value of 290nm. The withdrawn amount of dissolution medium was calculated. Cumulative percentage of drug released in the respective dissolution medium was plotted as a function of time.[9]

3. RESULTS AND DISCUSSION
Full factorial experimental design, Design Expert (version 13, Stat -Ease Inc., and Minneapolis, MN) was used to investigate the impact of independent variables on response. Table 02 lists the nine distinct combinations of prochlorperazine buccal films. A 3^2-factorial design with two factors and three levels were selected to study the response of the independent variables i.e., Concentration of chitosan (X1) and Concentration of Sodium carboxymethylcellulose (X2) on the dependent variables swelling index (Y1) and % drug release at 30 minutes (Y2).

3.1 Physical characteristics of patches
The patches had a flat and smooth surface, they were soft with good strength, and were colourless and translucent. The distribution of the medication and polymer was uniform.

3.2 Thickness, drug content, surface pH, and folding endurance of the films
The prepared buccal films (F1-F9) were measured to have a thickness of less than 0.30 mm, indicating that they are suitable for application into the buccal cavity with the least amount of discomfort (table 03).

The availability of drugs in films and its consistency must be confirmed through the drug content of the films. In order to calculate the prochlorperazine content, portions of film measuring 1 cm2 were punched from various locations. The percentage of drugs in the films was determined to be higher than 80%. This data indicates that the manufactured films contained an adequate amount of drug content, and the content variation was within acceptable bounds. In order to test whether the patch will irritate the mucosa membrane, the pH of the buccal film's surface was measured. The pH of the produced films was found to be close to neutral i.e., ~6 and it is unlikely to irritate or harm the mucosa in any way (Table 03).

The number of folds a membrane may withstand before cracking or breaking is known as folding endurance. It is observable that the folding endurance values rise with an increase in the amount of chitosan and Sodium carboxymethylcellulose in prepared films (F1–F9) under the current experimental conditions. The folding endurance for a decent film should be greater than 250 [9]. Indeed, all the prepared films displayed good folding endurance and the values varied from 282 to 345 (Table 03). The folding endurance of most of the formulation (F3, F5, F6, F7, F8, F9) was more than 300. This shows that the prepared films were having sufficient elasticity. Maximum folding endurance (~ 345) was observed in film F9. These findings show that prepared films may be able to resist breaking while being handled and used.

Table 03: Evaluation of Physical parameters of different mucoadhesive buccal patches of Prochlorperazine.

Formulation	Thickness (mm)	pH	Swelling index	Drug content (mg)	Folding endurance
F1	0.29	6.9	153.29	2.47	282
F2	0.31	6.9	128.29	2.50	297
F3	0.29	6.9	105.07	2.51	305
F4	0.29	6.83	168.27	2.39	295
F5	0.28	6.88	147.6	2.42	314
F6	0.26	6.8	115.42	2.46	324
F7	0.33	6.9	181.94	2.42	318
F8	0.31	6.9	167.82	2.54	331
F9	0.28	6.88	126.81	2.44	345

3.3 In vitro dissolution studies

The cumulative drug release profiles of Prochlorperazine films containing various ratios of polymer sodium CMC, chitosan and PVA is conducted on paddle type dissolution apparatus that is equipped with six paddles. After time intervals each of 30, 60, 90, 120, 150, 180, 210, 240, 270 and 300 minutes, 5 ml sample was withdrawn, filtered through a Millipore filter of 0.45 μm pore size and assayed spectrophotometrically at λ max 290 nm. Immediately after each sample withdrawal, a similar volume of simulated saliva pH 6.6 was added to the dissolution medium to maintain the volume in the vessel constant. It is apparent from the graph (figure 02) that the drug release is affected by the concentration of chitosan. As the concentration of chitosan increases drug release decreases.
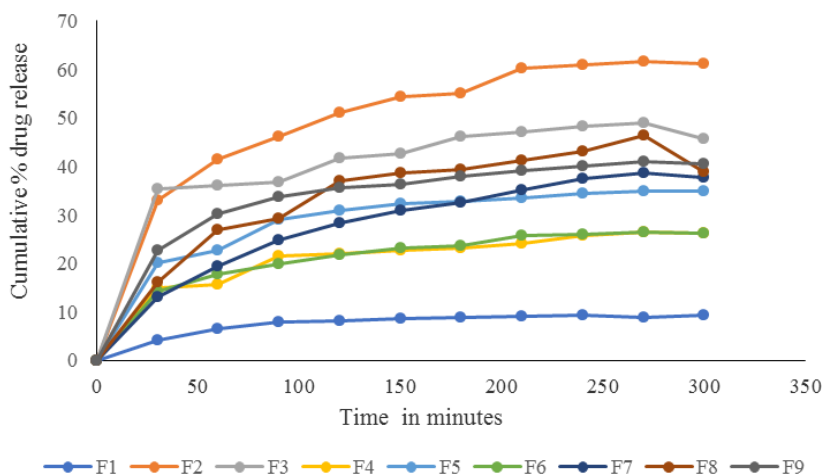
Fig. 2: Dissolution Curve.

3.4 FTIR

FTIR is used for drug-excipient compatibility research. The additives in the formulation may interact with active pharmaceutical substances, causing molecular transformation that impacts the product's stability. Figure 03 represents the FTIR spectrum of Prochlorperazine, and Figure 04 represents the FTIR spectrum of Prochlorperazine, Chitosan, PVA, and Sodium CMC.

The FTIR spectra of pure Prochlorperazine sample shows sharp peaks at $1620.35 cm^{-1}$, $1280.12 cm^{-1}$, $1566.15 cm^{-1}$, $1086.69 cm^{-1}$, $1248.87 cm^{-1}$, $3425.29 cm^{-1}$ (table 04). The same peaks were observed in the FTIR spectra of mixture of all the ingredients. This shows that there are no chemical interactions between the ingredients.

Table 04: FTIR interpretation of pure drug and polymer.

Reference	Drug	Mixture*	Functional group
$1620 cm^{-1}$	$1620.35 cm^{-1}$	$1620.95 cm^{-1}$	C=O
$1280 cm^{-1}$	$1280.12 cm^{-1}$	$1279.47 cm^{-1}$	C-O
$1569 cm^{-1}$	$1566.15 cm^{-1}$	$1565.74 cm^{-1}$	C=C
$1089 cm^{-1}$	$1086.69 cm^{-1}$	$1085.15 cm^{-1}$	C-Cl
$1242 cm^{-1}$	$1248.87 cm^{-1}$	$1248.43 cm^{-1}$	C-O
$3435 cm^{-1}$	$3425.29 cm^{-1}$	$3424.97 cm^{-1}$	-OH

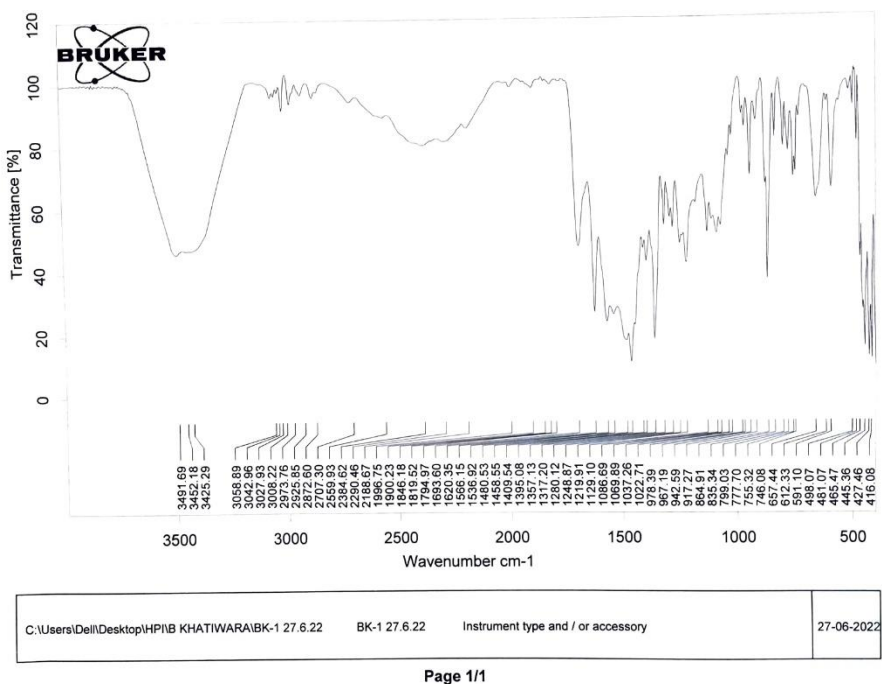*Physical mixture of ingredients of the formulation.*
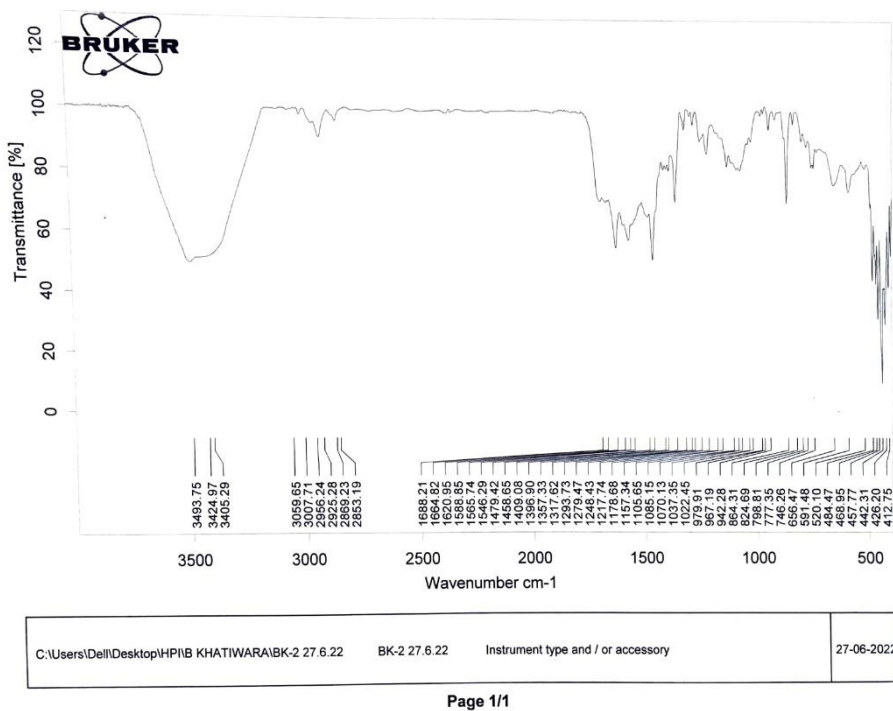
Fig. 3: FTIR spectrum of Prochlorperazine.

Fig. 4: FTIR spectrum of Prochlorperazine, chitosan, PVA and Sodium CMC.

3.5 Result interpretation using Factorial Design
Table 04: Factorial design and their observed response values in the prepared films.

Formulation	Factor X1- Chitosan	Factor X2- Sodium CMC	Response Y1- Swelling index	Response Y2- % Drug release in 30 minutes
F1	-1	-1	153.29	4.14
F2	-1	0	128.29	33.04
F3	-1	1	105.07	35.30
F4	0	-1	168.27	14.95
F5	0	0	147.6	20.20
F6	0	1	115.42	14.19
F7	1	-1	181.94	13.05
F8	1	0	167.82	16.08
F9	1	1	126.81	22.81

3.6 Effect of Formulation Variables on Swelling Index

Understanding the mucoadhesive property and drug release features of the films requires study of the swelling index.[12] This is dependent on the polymer matrix and the film structure. As soon as the film is applied to the buccal mucosa, it begins to hydrate. The hydration process begins as water molecules begin to permeate into the polymer matrix. The matrix of the film swells as the water molecules goes deeper into the film. This swelling of matrix initiates drug diffusion from the film. All of the prepared films exhibited swelling that started as soon as they came into contact with the aqueous medium. Table 04 presents the outcomes of the swelling index values. Formulation F7 showed the highest swelling index amounting to 181.94, followed by F4 and F8 formulations. Formulation F7 had the highest amount of chitosan and least quantity of Sodium carboxymethyl cellulose. Upon applying the factorial, quadratic model was suggested by the Design-Expert® software.

The model F value was found to be 104.42, $P < 0.0500$, and R^2 value of 0.9721, and the model was found to be significant. The final equation in terms of actual factors was found to be as follows.

$$Y1 = +199.06778 + 0.599467\ X1 - 1.04133\ X2.$$

According to the equation above, the swelling index is positively influenced by the amount of chitosan in the film (X1). This means that when the concentration of chitosan in the film rises, so does the swelling index of the film. Additionally, it is clear from the aforementioned equation that the X2 variable has a detrimental impact on the swelling index. The contour plot and surface response plot clearly show the impact of X1 and X2 on the swelling index (figure 05). When the amount of sodium CMC in the film was increased while keeping the chitosan concentration constant, a decrease in the swelling index was seen. The graph (figure 02) makes it clear that as the chitosan concentration is raised, the rate of medication release decreases.

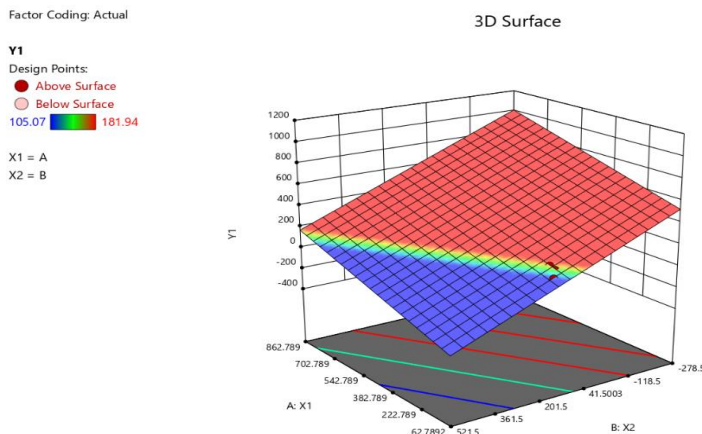### a) Response 1- Y1 (swelling index)
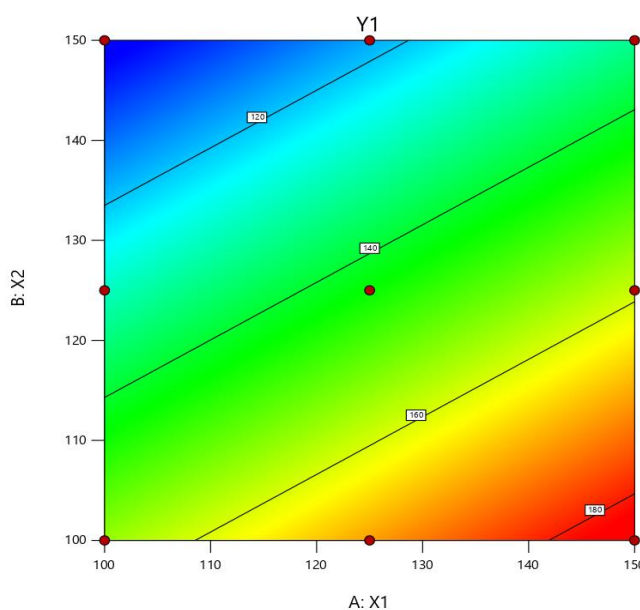
b)

Fig. 5: a) Corresponding contour plot illustrating the link between the two components at different levels. (b) response surface plot showing the influence of two independent variables chitosan and sodium CMC on the swelling index.

3.7 Effect of formulation variables on drug release

Evaluation of the buccal formulation's in vitro dissolution properties is crucial and was chosen as a significant response variable for the optimization study. In fact, a good formulation should offer a fast initial release followed by a prolonged drug release to alleviate nausea and vomiting brought on by chemotherapy. This would make it easier for the drug to be accessible to the patient, bringing about both the instant relief they need and the long-term anti-emetic effects. Therefore, one of the response variables was chosen to reflect the percent drug release in 30 minutes, which is regarded as an important attribute. Within the first 30 minutes of drug release, all of the produced formulations displayed an initial, fast drug release. Application of factorial design suggested a quadratic model for response variable Y2 (percent drug release in 30 min) with model F value of 35.66, P < 0.0500, and R^2 value of 0.9835. This implies that the model was significant. The final equation in terms of actual factors for Y2 was as follows.

$$Y2 = +136.69694 - 2.05290\ X1 + 0.450767\ X2 - 0.001948\ X1X2 + 0.008181 X1^2 - 0.000419 X2^2$$

The above equation indicates that X1, i.e., the concentration of chitosan, has a negative effect on the dependent variable Y2 and the factor X2, i.e., the concentration of Sodium CMC in the film, has a positive effect on the response variable Y2 (percent drug release in 30 min) (Fig.2).

This implies that as the concentration of polymer chitosan increases in the film, percent drug release (30 min) decreases. However, the positive response by Sodium CMC suggests that the drug release increases with the concentration of Sodium CMC in the film. With the use of contour plots and 3D response surface plots, the combined influence of independent variables X1 and X2 may be understood (fig. 06). It should be noted that, in comparison to sodium CMC, the amount of chitosan in the film had a more notable impact on the response. According to the literature, the drug release from buccal films made with a higher chitosan concentration has decreased.

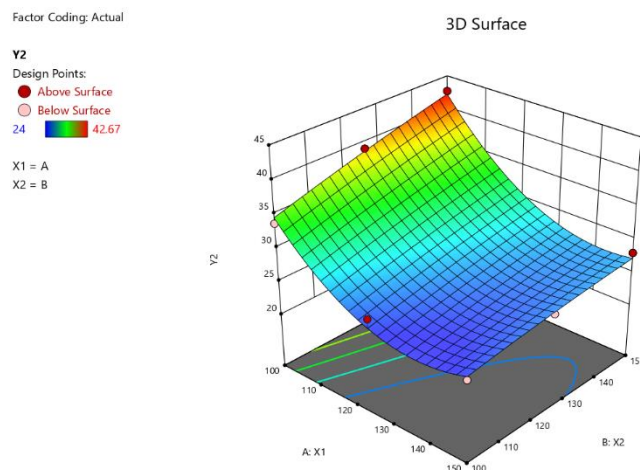**a) Response 2- Y2 (% drug release in 30 mins)**
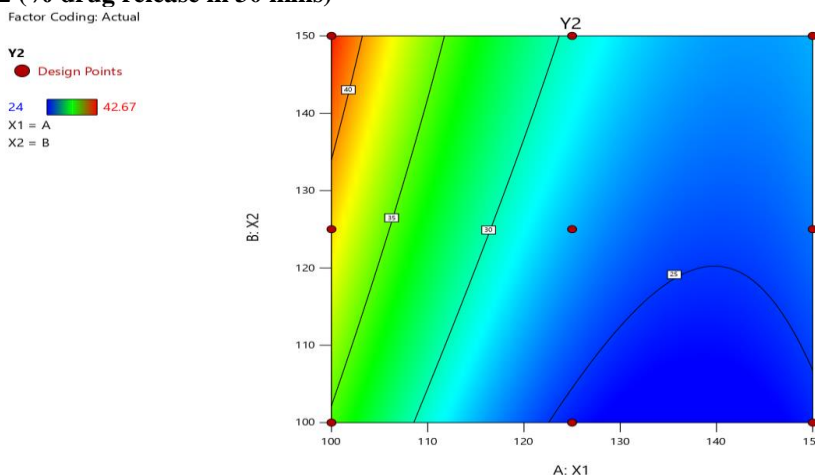
b)

Fig. 6: a) and b) Corresponding contour plot showing the influence of two independent variables (polymers; chitosan and Sodium CMC) on the drug release in 30 min.

4. CONCLUSION

Buccal delivery has been extensively investigated for both local and systemic therapy of various drug molecules by different delivery approaches. Currently, there are only few commercial formulations available or under clinical trials. This low commercial success is probably due to the high production cost. Nevertheless, the recent technological advances in mucoadhesive presents new opportunities and is likely to pave way for several other molecules into clinical use.

In this study, a full factorial (3^2) design was constructed to optimize the mucoadhesive buccal films of Prochlorperazine. The film comprising of specific composition of Sodium CMC, PVA, and chitosan, along with other additives, could be ideal for delivering Prochlorperazine across the buccal mucosa. It was observed that chitosan and Sodium CMC have influenced the design and optimization of Prochlorperazine buccal films and had significant effect on swelling index and drug release. Buccal film F7 has shown the ideal characteristics for buccal therapy of Prochlorperazine. Further in vivo studies are necessary to confirm the potential of the optimized mucoadhesive film (F7).

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