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Original Article

Box Behnken's Design of Fast-Dissolving Ondansetron Buccal Films and Assessing the Impact of Independent Variables on their Swelling and Folding Endurance Constraints

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ABSTRACT

Objectives: The project intends to create and evaluate oral fast-dissolving Ondansetron (ODN) films and explore how different plasticizers and polymers affect ondansetron release at varied doses. **Materials and Methods:** The solvent casting method was used to make the films. Complex formation and compatibility were evaluated using spectral and calorimetric methods to confirm. Utilising the core composite design, which included 13 different Ondansetron Fast-Dissolving Oral Films (OFDOFs) formulas, the produced Ondansetron Fast-Dissolving Oral Films (OFDOFs) were optimised. Using the Design Expert-v.11 software, the impacts of three variables, including HPMC K4M (X_1), Carbopol 934 P (X_2), and propylene glycol levels (X_3), on two responses, Folding Endurance (FE) and Swelling Index (SI), were examined. Numerical optimisation increased the FE (Y_1) and maximised the SI (Y_2). **Results:** The statistical analysis findings showed that X_1 greatly enhances Y_1 and Y_2. While X_2 and X_3 significantly prejudiced the responses optimistically. It was found that the best films were created at the midpoint concentration of both X_1 and X_2. Moreover, as X_3 levels increased, the elasticity and FE also improved, in addition to the film's quality. **Conclusion:** The study concludes that the prepared buccal films of ODN exhibited great mechanical and physical qualities in addition to their other physicochemical assets. This dosage form is expected to offer a bioavailability benefit over conventional dosage forms due to its rapid onset of action and anticipated partial avoidance of pre-systemic metabolism.

Keywords: Buccal, Design, Evaluation, Folding endurance, Patch, Swelling.

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INTRODUCTION

Drugs in oral films do not deteriorate due to the activities of stomach acid, bile, digestive enzymes, and other first-pass concerns, making them safer, faster acting, and needing less medicine overall.[1,2] Due to its rational dosage formulation and ease of administration, the oral film may dissolve more rapidly and promote compliance.[3] Oral films offer an option for those with dysphasia and those who experience nausea, such as chemotherapy patients, because they dissolve quickly and don't require water.[4]

Ondansetron, a 5-HT3 antagonist and potent antiemetic, is used to alleviate nausea and vomiting brought on by cancer therapy. Its oral bioavailability is limited to 60-70% due to first-pass metabolism,[5] and its half-life is just 3-5 hr. Studies show that Ondansetron Hydrochloride (ODN) adheres effectively to the buccal and sublingual mucosa.[6] Given the aforementioned considerations, this study will attempt to optimise the positive effects of ODN by developing quickly dissolving sublingual films. Several factors should be optimised to produce a suitable oral patch. In this regard, experimental design may be thought of as a statistical approach that permits the evaluation of several independent factors on a particular response with a restricted number of tests.[7] The effect of each independent variable on a particular response is first explicitly examined. The degree to which one variable affects the others is then calculated using multiple regression. The interaction of independent factors was investigated to identify any potential antagonistic or synergistic connections. In several investigations, this method has been heavily utilised to define and develop patch formulations.[8]

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In the current work, we used box-Behnken design (BBD) to optimise a mouth-dissolving film.

MATERIALS AND METHODS

Materials

Ondansetron was gifted from Walksman Semlan Pharmaceuticals Ltd., Ananthapuramu. Hydroxypropyl methylcellulose K4M, carbopol 934 P and propylene glycol were from SD Fine chemicals. Double distilled water is used in entire procedures whenever required.

Method of preparation

Oral films contain a drug, water-soluble polymer, plasticizer, fillers, surfactants, sweeteners, colours, flavours etc. The solvent casting method was adopted in making the films.

Dose calculation

The dose calculation was done as per the Table 1.[9,10]

HPMC K4M and carbopol 934P were dissolved in 5 mL of distilled water, and the mixture was vigorously agitated for 15 min before being allowed alone for 5 min to let any trapped air bubbles escape. 5 mL of distilled water was used to dissolve the propylene glycol, methylparaben, and ODN in a different container. After 15 min of continuous stirring and agitation, this mixture received another 15 min of mixing. After that, the solution was left to settle for 10 min to get rid of any air froth. Ondansetron Fast Dissolving Oral Films (OFDOFs) were created by pouring the slurry over the required surface and allowing it to dry for a while in an oven.[11,12] After drying, the OFDOFs were carefully removed, ideally by air drying or in an oven, and cut into an appropriate size (Table 2 and Figure 1).

Evaluation

Compatibility studies

The DSC investigation was carried out using PerkinElmer Diamond DSC equipment. On an aluminium pan, 2-5 mg of the sample was placed, and it was heated from 30 to 200°C at a rate of 10°C/min. Pyris software from Connecticut, USA-based Perkin Elmer Life and Analytical Sciences was used to examine the data.

The compatibility of the ODN with excipients was evaluated using FTIR spectrum analysis. This analysis was carried out to check for any changes in the chemical composition of the ODN following its combination with the excipients.[13] The FTIR spectra for pure ODN and ODN with polymers were used to determine the optimal formulation and assess the accuracy of the ODN in the formulation.

Post formulation study

Appearance and film quality

The appearance of the OFDOFs must be considered. It is important to visually inspect the footage to determine how it appears.[14]

The quality of the OFDOFs was evaluated using their elasticity (endurance >30 times), spreadability while sheeting down over the casting cups, tackiness, ease of casting cup removal, and appearance. 20% of the total value was allocated to each criterion.[15]

Film thickness and weight

Screw gauges were used to restrict the thickness of the OFDOFs three times. The average of the three measurements was then determined. This is necessary to determine the consistency of the OFDOF thickness since it directly affects the precision of the dose in the OFDOFs.[16]

On an analytical scale, the OFDOFs were weighed. The average weight of each OFDOF was calculated. OFDOFs should have an essentially constant weight. The right quantity of excipients and ODN should be in the OFDOF.[17]

Folding endurance

For the analysis of the OFDOFs' bounciness via stowage and hold, the Folding Endurance (FE) of the OFDOFs is crucial. It snapped because the OFDOFs kept folding it in the same location. This is meant to demonstrate strong cinematic qualities. The 2x2 cm OFDOFs were cut in half, folded many times, and then snapped. The exact amount of FE was determined by counting how many times the OFDOFs could be twisted into the same position without being in violation. Three times, each decision was repeated.[18]

Table 1: Description of dose calculation.

Parameter	Value
Area of the Petri plate.	28.26 cm^2
Size of each 2x2 cm^2 OFDOF.	4 cm^2
Number of 2x2 cm^2 OFDOFs in the plate.	28.26 cm^2 / 4 cm^2=7.065 OFDOFs
Amount of ODN in each OFDOF.	4 mg
The total amount of ODN to be encumbered in each plate.	7.065 OFDOFs x 4 mg per OFDOF=28.26 mg
Therefore, the amount of ODN to be encumbered in each plate is 28.26 mg.	

pH

One OFDOF was dissolved in 10 mL of distilled water, and the pH of the resulting solution was measured to calculate the pH value. Each conclusion was obtained three times. There must be some consistency in the pH measurement on strip.[19]

Content uniformity

The OFDOF with 10 mg of ODN was dissolved in 100 mL of water to create solutions with 100 µg/mL of medicine. After obtaining a sample aliquot of 1 mL, 10 mL of it was produced by dilution with water. Using a UV-spectrophotometer set to 248 nm, the solution was then filtered using Whatman filter paper, and the results were compared to a blank made of fake OFDOFs that had already experienced the same process. For each batch of the OFDOFs, studies on content homogeneity were authorised in duplicate. It varies between 85 and 115%.[20,21]

Disintegration time

It was resolutely visible in a glass beaker with 25 mL of distilled water whirling inside of it. The point at which the OFDOFs were

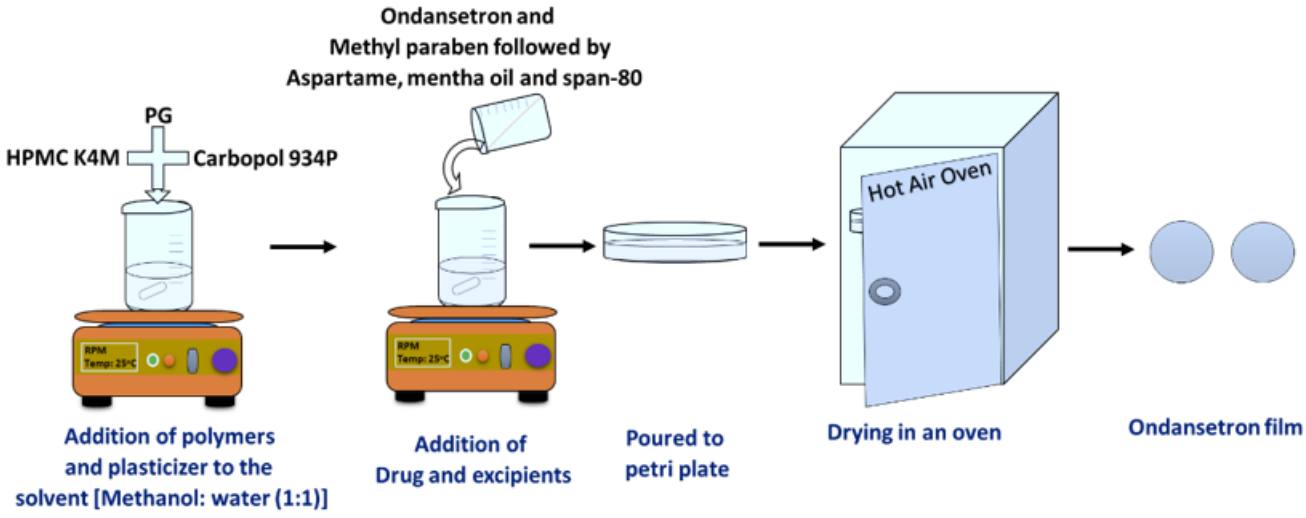

Figure 1: Flow diagram of OFDOFs making.

Table 2: Composition of OFDOFs.

Formulation	Ingredients									
	Ondansetron	HPMC K4M	Carbopol 934P	Propylene Glycol (mL)	Methyl paraben (mg)	Aspartame (mg)	Mentha oil (mL)	Methanol	water	Span-80 (mL)
OFDOF-1	4	500	30	2	2	10	0.06	q.s	q.s	0.06
OFDOF-2	4	600	30	2	2	10	0.06	q.s	q.s	0.06
OFDOF-3	4	500	60	2	2	10	0.06	q.s	q.s	0.06
OFDOF-4	4	600	60	2	2	10	0.06	q.s	q.s	0.06
OFDOF-5	4	500	45	1	2	10	0.06	q.s	q.s	0.06
OFDOF-6	4	600	45	1	2	10	0.06	q.s	q.s	0.06
OFDOF-7	4	500	45	3	2	10	0.06	q.s	q.s	0.06
OFDOF-8	4	600	45	3	2	10	0.06	q.s	q.s	0.06
OFDOF-9	4	550	30	1	2	10	0.06	q.s	q.s	0.06
OFDOF-10	4	550	60	1	2	10	0.06	q.s	q.s	0.06
OFDOF-11	4	550	30	3	2	10	0.06	q.s	q.s	0.06
OFDOF-12	4	550	60	3	2	10	0.06	q.s	q.s	0.06
OFDOF-13	4	550	45	2	2	10	0.06	q.s	q.s	0.06

Table 3: Actual and predicted responses towards the factors.

Formulation	Factors			Response			
	(X_1:HPMCK4M) (mg)	(X_2: 934P) (mg)	(X_3:PG) (mL)	Folding endurance		Swelling index (%)	
				Actual	Predicted	Actual	Predicted
OFDOF-1	550	45	2	37.00	37.00	98.70	98.70
OFDOF-2	600	30	2	30.00	31.38	95.00	94.94
OFDOF-3	550	60	3	29.00	30.00	93.00	93.64
OFDOF-4	550	30	3	25.00	24.75	88.10	88.44
OFDOF-5	600	45	3	33.00	31.88	97.10	96.83
OFDOF-6	600	60	2	35.00	35.13	97.90	97.54
OFDOF-7	500	60	2	26.00	24.63	90.00	90.06
OFDOF-8	550	30	1	30.00	29.00	93.50	92.86
OFDOF-9	500	45	1	23.00	24.13	90.90	91.18
OFDOF-10	500	45	3	20.00	20.38	91.10	90.40
OFDOF-11	500	30	2	24.00	23.88	89.30	89.66
OFDOF-12	600	45	1	31.00	30.63	96.80	97.50
OFDOF-13	550	60	1	28.00	28.25	91.00	90.66

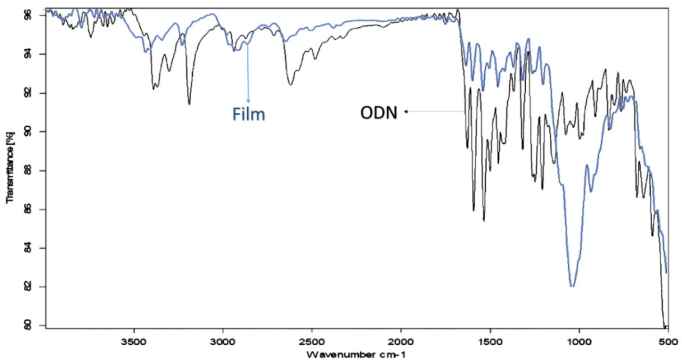

Figure 2: FTIR spectra of ODN and the OFDOFs.

underway to disrupt, break apart, or crack was known as the *in vitro* disintegration period. There were three times it was done.[22-24]

In vitro dissolution

A 500 mL pH 6.8 phosphate buffer was investigated for *in vitro* dissolution at 37±0.5°C and 50 rpm using the USP-II device. Each OFDOFs sample (2x2 cm square) was dipped into the dissolving medium, and at intervals of 1, 2, 3, 4, 5, 6, 7, 8, and 10 min, the pertinent aliquots were taken out and then replaced with the same amount of dissolution liquid. Spectrophotometric analysis of samples from each batch was performed at 248 nm (UV spectrophotometer, Shimadzu) after they had been filtered using Whatman filter paper. The test was conducted under sink circumstances. For each batch, the dissolving test was carried out three times.[25,26]

Box-Behnken Response surface methodology for OFDBFs

To evaluate how particular characteristics affect various reactions, the Design Expert (version 11) programme was used. The effects of HPMC K4M, carbopol, and PG levels on the FE (Y_1) and SI (Y_2) were evaluated for 13 runs.[27]

RESULTS AND DISCUSSION

ODN is a white, odourless, somewhat bitter substance. At 178.5±2.25°C, ODN melted. 248 nm was discovered to be the ODN λ_{max}. In distilled water, ODN showed maximum absorption at 248 nm in wavelength. By measuring the absorbance of diluted stock solutions (2, 4, 6, 8, 10, 12, and 14 µg/mL) at 248 nm, a standard curve was constructed. ODN had an r^2 of 0.9988, a slope of 0.0784, and an intercept of 0.002 for correlation. The FTIR spectrum represents the characteristic peaks and stretches present in the ODN spectrum that were found to be undisturbed even in ODN with excipients (Figure 2).[28]

Design of experiments with results

The actual and predicted independent variables for the dependable variables were as per Table 3.

The film-forming capacity was good in all formulations, whereas OFDOF-6, OFDOF-9, and OFDOF-12 were the best among them. And they were excellent in appearance. OFDOF-1, OFDOF-3, and OFDOF-13 were tacky compared to other films. The pH was closer to neutral. The weight and thickness of the films were also uniform, with less deviation. The disintegration time of the OFDOFs ranged from 16.20±0.47 (OFDOF-4) to

19.85±0.41 (OFDOF-13) min, with FE from 18±1 (OFDOF-2) to 31±1 (OFDOF-13), and the drug content was uniform (Table 4).[29]

Response Surface Methodology for Optimization of OFDOFs

Using the Expert Design11 tool, it was determined how the selected factors affected the various answers. The BBD was used to optimise OFDOFs for minimum disintegration time, maximum initial dissolution rate, highest dissolution efficiency, and optimum quality. Table 2 shows the BBD of the trials together with the actual and expected results.[29]

Statistical Analysis

Different statistical methods, including linear, quadratic, interactive, and polynomial terms, were used to examine the impact of control factors on the replies. Table 4 provides an overview of the model terms' coefficients and corresponding *p*-values for Y_1 and Y_2. If a factor's reaction had a p-value of less than 0.1 ($p>0.1$), it was regarded as having significant responses. The non-significant terms ($p>0.1$) were excluded from the regression model to make it simpler. An increase or reduction in the corresponding reaction to an alteration in the level of the component or variables contributing to that word was represented by a positive or negative coefficient, accordingly. ANOVA, r^2, and modified r^2 were used to assess the validity of the experimental design (Table 5). High r^2 and adjusted r^2 suggested that the examined answers had strong data fit.[30]

Effect of factors on the folding endurance (Y_1) of the OFDOFs

The FE plays a perilous role in the flexibility of the OFDOFs during handling. OFDOFs showed variations in the FE from 20 to 37. It was maximum for OFDOF-1 and least for OFDOF-10 (Figure 3).

Effect of independent variables on the swelling index (Y_2) of the OFDOFs

The availability of the drug for release and the bioavailability of the ODN following dissolution are both critically dependent on the SI of OFDOFs. SI variations in OFDOFs ranged from 88.1 to 98.7%. According to Figure 4, it was highest for OFDOF-1 and lowest for OFDOF-4.

To determine how the control factors influenced the disintegration time, the results were statistically examined. The findings in Table 4 demonstrated that the quadratic model was best able to match the disintegration values based on the highest r^2. The model's validity was further shown by the decent level of agreement between the anticipated and adjusted r^2. Additionally, the response's appropriate accuracy was >3, showing a sufficient

Table 4: Results of evaluated parameters for the OFDOFs.

Batch	pH	Weight (g)	Thickness (mm)	Disintegration (min)	Tensile strength (N/mm²)	Cum. DR @40min (%)	% Drug content
OFDOF-1	6.85±0.02	0.532±0.05	0.72±0.01	16.60±0.57	35.00±0.05	92.35±2.35	98.25±5.32
OFDOF-2	6.96±0.01	0.632±0.03	0.75±0.04	17.20±0.06	36.00±0.85	91.25±3.69	93.62±3.62
OFDOF-3	6.99±0.02	0.562±0.01	0.72±0.06	18.40±0.84	41.95±0.96	95.87±6.48	98.07±4.05
OFDOF-4	6.56±0.01	0.662±0.04	0.73±0.04	16.20±0.47	42.00±1.05	95.60±2.05	92.14±1.98
OFDOF-5	6.36±0.02	0.546±0.03	0.74±0.06	19.62±0.70	35.62±0.74	89.32±6.11	95.97±3.93
OFDOF-6	6.69±0.01	0.646±0.05	0.70±0.05	18.15±0.15	34.26±0.36	89.65±2.00	93.66±4.44
OFDOF-7	6.60±0.03	0.548±0.02	0.72±0.03	19.28±0.56	42.50±0.55	97.82±1.84	91.02±7.15
OFDOF-8	7.02±0.01	0.648±0.03	0.75±0.02	17.84±0.23	43.20±0.27	98.00±4.15	90.28±4.51
OFDOF-9	6.95±0.05	0.581±0.01	0.71±0.04	18.25±0.95	30.20±0.07	87.10±3.62	94.88±6.95
OFDOF-10	6.88±0.04	0.611±0.03	0.74±0.02	17.18±0.95	37.00±0.41	92.00±3.12	94.30±4.50
OFDOF-11	5.79±0.03	0.583±0.01	0.70±0.01	19.27±0.66	38.88±0.65	95.51±2.88	97.15±2.98
OFDOF-12	6.84±0.03	0.613±0.02	0.73±0.01	18.02±0.81	45.00±0.82	99.98±1.65	97.81±4.55
OFDOF-13	6.98±0.02	0.597±0.01	0.71±0.02	19.85±0.41	40.00±0.73	91.00±2.84	95.84±4.14

Table 5: ANOVA of designated models for diverse responses of OMDOFs.

Response	Model	Sequential *p*-value	Adjusted r^2	Adequate precision	Significant terms	F- value
Y_1	Quadratic	0.0387	0.8781	11.09	X_1, X_1^2, X_3^2	10.61
Y_2		0.0516	0.9348	12.96	X_1, X_2X_3, X_2^2, X_3^2	20.11

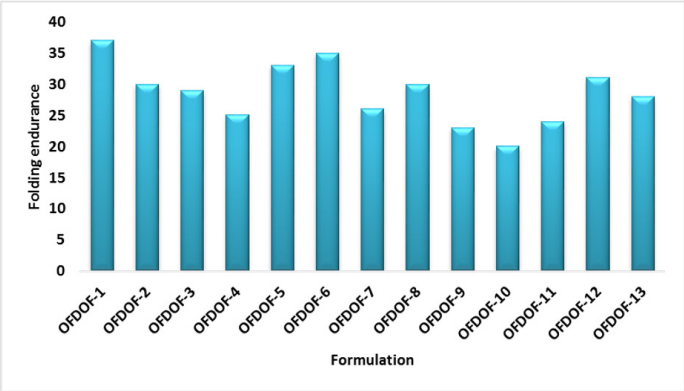

Figure 3: Folding endurance of OFDOFs.

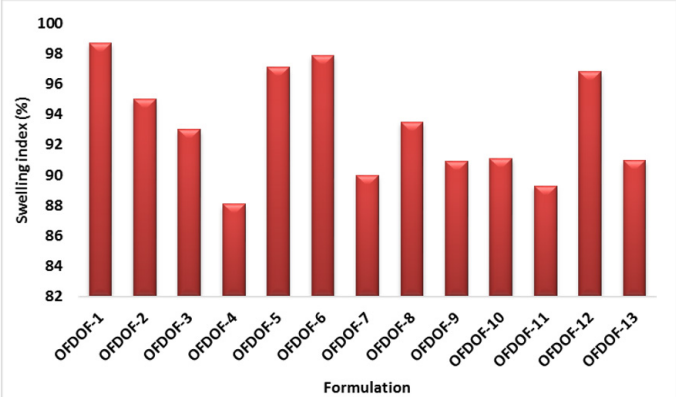

Figure 4: Swelling index of OFDOFs.

signal-to-noise ratio, proving the chosen models potential to explore the design space.

Analysis of Variance (ANOVA) for FE supported the importance of the quadratic model, as shown by its F-value of 10.61. The sequential *p*-value of 0.0387, which showed a log-likelihood of 31.75, confirmed that the data fit the proposed model. The quadratic model was represented by the following equation utilising coded factors:[30]

$$FE=+37.00+4.50\ X_1+1.12\ X_2-0.6250\ X_3+0.7500\ X_1X_2+1.25\ X_1X_3+1.50\ X_2X_3-4.75\ X_1^2-3.50\ X_2^2-5.50\ X_3^2$$

According to the statistical study, the polymer concentration (X_1) significantly affects the FE. The FE increases significantly as X_1 and X_2 are increased. Flexibility and FE are positively impacted by plasticizer concentration (X_3). The response surface plots for the examined factors' impacts on FE ($Y_{1)}$ were displayed in Figures 5A and B. It's interesting to note that when X_1 and X_2 grow, the FE improves dramatically (Figure 5A). The FE of the OFDOFs increased when X_3 was increased from 1 to 3 mL (Figure 5B).[31]

The relevance of the quadratic model was supported by analysis of variance (ANOVA) for the SI, which had an F-value of 20.11 and a sequential *p*-value of 0.0156 with a log-likelihood value of 15.16. The following equation was created using coded factors to describe the quadratic model:[32]

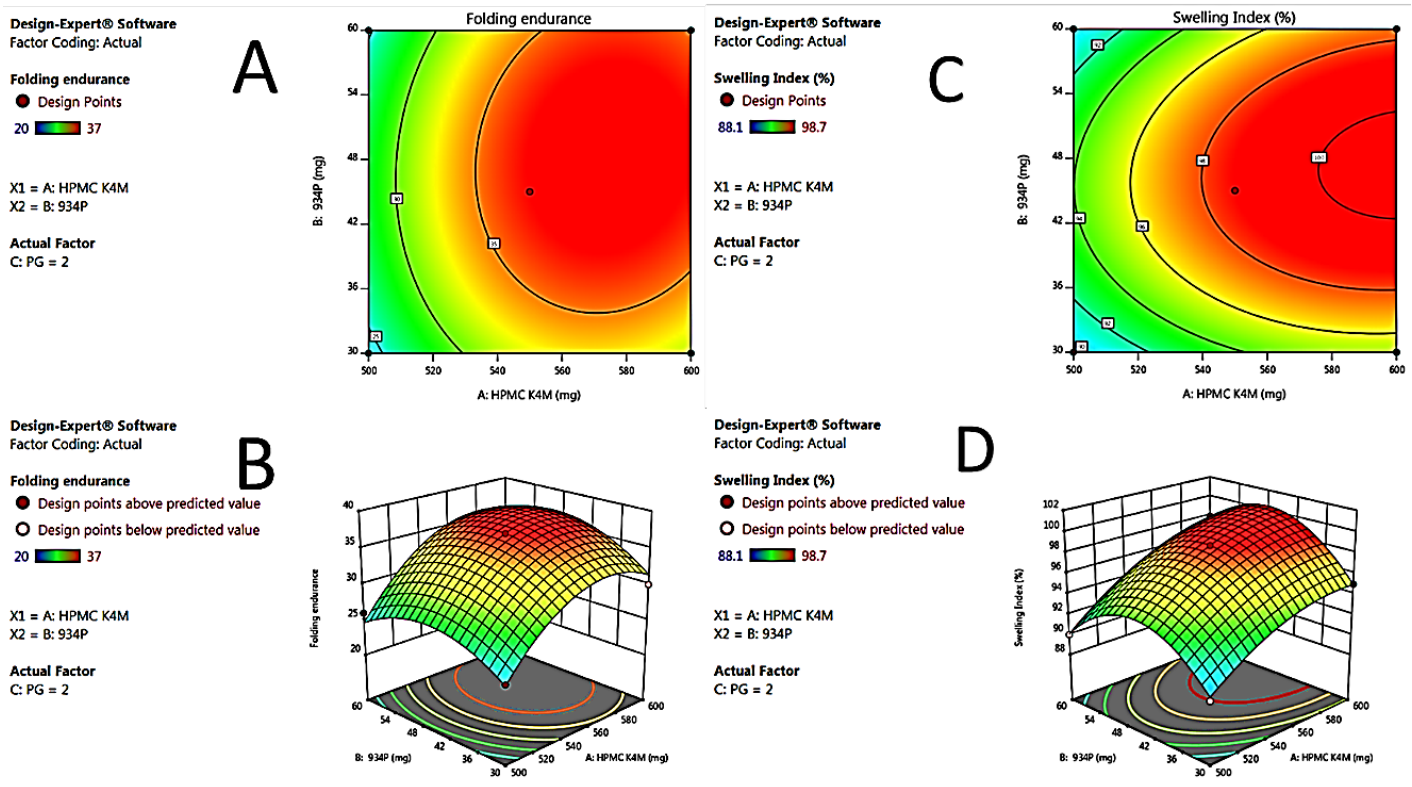

Figure 5: Effect of polymer concentrations (X_1, X_2) and plasticizer levels (X_3) on Y_1. (A): 2D plot B) 3D plot; Effect of X_1, X_2 and X_3 on Y_2 (C): 2D plot D) 3D plot.

$$SI=+98.70+3.19X_1+0.75B-0.3625\ X_3+0.55\ X_1\ X_2+0.025\ X_1X_3+1.85\ X_2X_3-1.54\ X_1^2-4.11\ X_2^2-3.19\ X_3^2$$

According to the statistical study, the polymer concentration (X_1) significantly affects the SI. The SI increases significantly as X_1 and X_2 are increased. The swelling is also positively impacted by plasticizer concentration (X_3). The response surface plots for the examined factors' impacts on SI ($Y_{2)}$ were displayed in Figures 5 C and D. It's interesting to note that when X_1 and X_2 grow, the SI improves dramatically (Figure 5C). The SI of the OFDOFs increased when X_3 was increased from 1 to 3 mL (Figure 5D).

CONCLUSION

Oral dissolving films containing 4 mg ODN were effectively created and verified for our research study. Understanding how two responses, namely folding endurance and swelling index, were impacted by independent variables (polymers and plasticizer concentration), was substantially facilitated by the experiment's design, which was adopted in this study. This dosage form is also projected to start working quickly and mainly avoid pre-systemic metabolism, which will increase its bioavailability and provide it with an advantage over conventional dosage forms.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

5-HT3: 5- Hydroxytryptamine; **ODN:** ondansetron hydrochloride; **BBD:** Box Behnken design; **OFDOF:** Ondansetron fast dissolving oral films; **HPMC:** Hydroxy Propyl methyl cellulose; **DSC:** Differential Scanning Calorimetry; **FTIR:** Fourier Transform Infra-red: **FE:** Folding endurance; **SI:** Swelling index; **UV:** Ultra violet; **USP:** The United States Pharmacopoeia; **PG:** Propylene glycol; **mL:** Millilitre; **h:** Hour.

SUMMARY

Fast-dissolving ondansetron films of ondansetron were developed by solvent casting method Ondansetron Fast-Dissolving Oral Films (OFDOFs) were designed and optimised as per Design Expert Design 11 software. The independent variables were the levels of HPMC K4M (X_1), Carbopol 934 P (X_2), and propylene glycol (X_3), on two responses namely folding Endurance (FE) and Swelling Index (SI). The prepared films were assessed for physicochemical assets including thickness, disintegration, folding endurance, swelling index and drug release. The results revealed that X_1 greatly enhances Y_1 and Y_2. While X_2 and X_3 significantly influenced the responses positively. It was found that the best films were created by the midpoint concentration of both X_1 and X_2. Additionally, as X_3 is increased, the film's quality rises. The study summarizes that the prepared buccal films offer a bioavailability advantage over conventional dosage forms due to their rapid onset of action and anticipated partial avoidance of pre-systemic metabolism.

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