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Original Article

Formulation and Optimization of Fast Dissolving Buccal Films of Hydralazine HCl Using Design Expert Software

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ABSTRACT

Aim and Objectives: This study aimed to design and optimize Fast-Dissolving Buccal Films (FDBF) containing Hydralazine HCl, with the goal of developing an effective treatment for hypertension. **Materials and Methods:** Solvent casting method was employed to prepare the films. Optimization focused on the effects of independent variables such as Pullulan, PVP and PG on the percentage of drug release and the disintegration time of the film, using a 23 factorial design. Polynomial equation analysis was used to derive equations from the results, effectively describing the influence of the independent variables on the selected responses. Three-dimensional surface plots are generated to depict the relationship between both variables and a design layout was developed for the optimized formulation using Design Expert software version 13.0 trial edition. **Results:** The Optimized Formulation (OF) exhibited a rapid disintegration time of 48 sec, cumulative drug permeation at 70.3%, and excellent physicochemical properties and ex vivo drug release through goat buccal mucosa was 69.4%. The short-term stability test of the optimized formulation OF, performed according to ICH, indicated stability test at 30°C±2°C and 65%±5% relative humidity for one month. **Conclusion:** These findings suggest that the developed formulation offers a novel dosage form that can enhance drug delivery, provide a quicker onset of action, and improve patient compliance significantly.

Keywords: Fast-dissolving buccal films, Hydralazine HCl, Pullulan, 23 Factorial design.

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INTRODUCTION

Hypertension is diagnosed when the systolic blood pressure is 140 mmHg or above and the diastolic blood pressure is 90 mmHg or higher. The goal of creating Fast Dissolving Buccal Films (FDBF) is to reduce the dissolution time, this results in a quicker onset of action and bypasses the first-pass metabolism of the drug.[1]

Hydralazine HCl is a direct-acting vasodilator used to treat hypertension. It functions as both a vasodilator and an antihypertensive agent. Hydralazine causes arterial vasodilation by altering intracellular calcium release and interfering with calcium influx in smooth muscle cells. Additionally, it inhibits myosin protein phosphorylation and chelates trace metals essential for smooth muscle contraction, leading to increased heart rate, stroke volume, and cardiac output, Hydralazine HCl is classified as a BCS class *III* drug, characterized by high solubility but low permeability, with a half-life of approximately 2-8 hr and a bioavailability of 26%.[2]

Buccal drug delivery directly connects to the systemic circulation, by passes 1st pass metabolism due to which there is 100% bioavailability of drug and also drug dosing is significantly reduced.[1]

Fast-dissolving buccal films deliver drugs through absorption in the mouth, either through the buccal or sublingual routes, or via the small intestines enterically, these films are composed of hydrophilic polymers that quickly dissolve on the tongue or within the buccal cavity, enabling drug delivery to the systemic circulation upon contact with liquid. This approach has arisen as a sophisticated substitute for conventional tablets, capsules and liquids commonly employed in both prescription and over-the-counter medications. Similar in size, shape, and thickness to a postage stamp, these thin films are designed for oral administration.[3]

Fast dissolving buccal films offer several advantages, including rapid onset of action, ease of administration without the need for water, improved patient compliance, enhanced bioavailability

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by bypassing the gastrointestinal tract, potential for better taste masking of active pharmaceutical ingredients, The capacity of these films to dissolve quickly without water offers an alternative for patients with swallowing difficulties due to conditions like dysphagia or those experiencing nausea, such as chemotherapy patients. Numerous fast-dissolving products are accessible globally, both over-the-counter and prescribed with many new chemical entities under development using this innovative approach.[4]

MATERIALS AND METHODS

Materials

Hydralazine HCl was received as a gift sample from HETERO Pharma Hyderabad, Pullulan, PVP, Tween 80, Citric acid, Mannitol were obtained from the pharmaceutics department.

Methods

- Preformulation studies
- UV spectroscopy

Determination of Absorption Maxima

10 mg of Hydralazine HCl was precisely measured and placed into a volumetric flask having 100 mL capacity. It was dissolved in 50 mL of Phosphate buffer with a pH 6.8. The volume was then adjusted to the mark using phosphate buffer of pH 6.8. This preparation yielded a standard stock solution with a concentration of 100 µg/mL.[5] A subsequent dilution was conducted with 6.8 buffer from this stock solution to attain a concentration of 10 µg/mL. The diluted solution is then subjected to scanning between 400 nm to 200 nm using a UV Spectrophotometer (Shimadzu 1900i).[6]

Calibration curve of Hydralazine HCl

Aliquots of 0.3 mL, 0.6 mL, 0.9 mL, 1.2 mL, 1.5 mL, 1.8 mL, and 2.1 mL were prepared to achieve concentrations of 3 µg/mL, 6 µg/mL, 9 µg/mL, 12 µg/mL, 15 µg/mL, 18 µg/mL and 21 µg/mL, respectively[7] absorbances of the prepared solutions were observed at 207 nm against a blank (PBS 6.8 pH) using a UV-visible spectrophotometer. A standard-calibration graph was then plotted for absorbance versus concentration.[8]

FT-IR study

The FTIR spectra of Pullulan, PVP-K30, Hydralazine HCl, a physical mixture of Hydralazine HCl with Pullulan, and the formulated film were recorded using an FTIR Spectrophotometer (Shimadzu IR Spirit Japan). This analysis aimed to investigate the compatibility of the components across a wavelength range of 4000-400 cm^{-1} by preparing the samples in a KBr dispersion.[9]

Differential Scanning Calorimeter (DSC)

The thermal properties of Hydralazine HCl were analysed with differential scanning calorimetry (Shimadzu DSC 60 plus, Tokyo, Japan). About 5 mg of Hydralazine HCl was weighed, placed in a pan and sealed with an aluminium lid. The sample were then subjected to a temperature ranging from 30 to 350C with a constant 10°C per minute heating rate.

Drug incorporation measurement

$$\text{Area of mould} = l \times b$$

A= 7.8 x 5.2,

A = 40.56 cm,

Area of rectangular mould is 40.56 cm^2.

Area of square film is 1.5 x 1.5 = 2.25 cm^2.

$$\text{Hence, } \frac{\text{area of mould}}{\text{area of film}} = \frac{40.56}{2.25} = 18.22\text{cm}^2$$

Dose of Hydralazine HCl is 3.0 mg per 1.5 cm film.

For entire rectangular mould it is 4×18.22= 72,88.

Hence per rectangular mould there must be 72.88 mg to get 72.88 mg of drug per 1.5 cm square film.

Design of Experiment (DOE)

Experimental Design (DOE) is a methodical approach aimed at understanding the interplay between process variables and the final product's performance. In this study, a 2^3 full factorial design was employed to explore how different independent variables affect dependent variables. The chosen independent variables (factors) for investigation were Pullulan (mg) (X1), PVP (Polyvinylpyrrolidone) (mg) (X2) and PG (Propylene Glycol) (mL) (X3). The dependent variables (responses) under scrutiny were disintegration time (s) (Y1) and cumulative drug permeation (%) (Y2) as shown in Table 1. Analysis of Variance (ANOVA) was conducted to analyse the data.[1]

The selection of factors (X1, X2, and X3) and their respective levels was based entirely on preliminary trials aimed at ensuring the successful formulation of FDBF. Table 2 presents the experimental runs, Detailing the specified dependent variables alongside other essential ingredients crucial for FDBF formulation, all experiments were randomly conducted for each batch of formulation. A total of 8 experimental runs were assigned and correspondingly each formulation was prepared.[1]

Formulation of Fast Dissolving Buccal Film

The FDBF were formulated with the use of solvent casting method, sufficient amount of Pullulan and PVP was added into a beaker containing water which is used as the solvent and these polymeric solution is stirred and sonicated for about 2 hr, after

sonicating for 2 hr other excipients such as citric acid, Propylene glycol, Tween 80, Mannitol were added and stirred on a magnetic stirrer until the solution is thoroughly mixed, then the solution is poured on a rectangular mould which has been lubricated using glycerine and kept in the hot air oven at a temperature of 60C for around 24 hr, after this the film is peeled and cut into 1.5 cm square shape and were wrapped in aluminium foil and stored in the desiccator.[10]

Evaluation

Thickness

The films thickness was gauged using a screw gauge. Measurements were taken at six different locations on each film, Subsequently, the average thickness was calculated along with mean and standard deviation were calculated.[11]

Weight variation

To assess the film weight, a set of three films from each formulation underwent individual weighing, followed by the calculation of the average weight.[12]

Folding endurance

The folding endurance of the formulation film was measured through the repetitive folding of a small strip until it fractured. Then, the mean folding endurance of all formulation was noted.[8]

Surface pH

The films were kept in contact with 1 mL of distilled water for 5 min at room temperature and pH was observed using pH paper in contact with the surface of the film.[13]

Table 1: Design of Experiments 2^3 factorial design variables and responses.

Independent variable	High	Low
Pullulan	1350	650
PVP	450	150
P.G.	0.8	0.2

Drug content

The drug content of three segments of the film was measured. each measuring 1.5×1.5 cm. Each sample was liquefied in 100 mL of pH 6.8 phosphate buffer. After filtration, the solution underwent suitable dilution with pH 6.8 phosphate buffer prior to spectrophotometric drug content determination (Shimadzu UV-1900 Spectrophotometer, Japan). The mean drug content of the three films was computed, and the films were considered satisfactory if the content was in a range of 85-115% of the expected drug quantity.[14]

Disintegration time

The disintegration evaluation of FDBF having a surface area of 2.25 cm was conducted using a disintegration apparatus, The film is placed in the tube and the immersion medium was added which is 6.8 Ph buffer and the temperature is maintained around 37°C the immersion rate is kept around 30 immersions per minute and the result was recorded.[15]

In vitro Diffusion study

The release rate of Hydralazine HCl from the formulation was assessed *in vitro* using an open tube containing PBS at pH 6.8 as the diffusion medium for a duration of up to 2 hr. At one end of the tube, a cellophane membrane was securely attached, this end was then submerged in a receptor compartment filled with 200 mL of PBS at pH 6.8, The setup was stirred at a moderate pace and kept at a temperature of 37°C with a tolerance of ±2°C. At regular intervals, samples were withdrawn, and an equal volume was replenished with fresh diffusion medium. Samples were examined utilizing a UV-visible Spectrophotometer (Shimadzu 1900i) calibrated to 261 nm.[5]

Percentage Moisture content

Three films with an area of 1.5 cm x 1.5 cm were accurately weighed and then placed in desiccators for three consecutive days. After this period, the films were extracted and their weights were recorded again. The moisture loss percentage was determined using the following formula.[16]

$$\text{Moisture Content } (\%) = \times 100$$

Table 2: Formulation of FDBF using DOE software.

Ingredients(mg)	F1	F2	F3	F4	F5	F6	F7	F8
Hydralazine HCl	73	73	73	73	73	73	73	73
Pullulan	650	1350	650	1350	650	1350	1350	650
PVP	150	450	150	450	450	150	150	450
Propylene glycol	0.8	0.2	0.2	0.8	0.8	0.8	0.2	0.2
Tween 80	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4
Mannitol	40	40	40	40	40	40	40	40
Water	13	13	13	13	13	13	13	13

Ex vivo Permeation study

Ex vivo permeation analysis of Hydralazine HCl FDBF was conducted using a Franz diffusion cell with goat buccal mucosa. The mucosa, prepared and rinsed with simulated salivary fluid, was placed between the receptor and donor compartments, with the mucosal surface facing the donor side. The receptor compartment contained 13 mL of simulated saliva as the diffusion medium. A 2.25 cm^2 mucoadhesive film was placed in the donor compartment. The setup was mounted on a magnetic stirrer, agitating the receptor solution at 100 rpm and maintaining 37±1°C. At specific intervals, 0.4 mL samples were taken from the receptor compartment, replaced with fresh medium, and analysed for drug content at 261 nm using a UV Spectrophotometer (Shimadzu UV1900i).[17]

Stability study

Stability assessments of Hydralazine HCl FDBF were conducted to assess parameters such as physical appearance, surface pH, drug content, percentage moisture loss, weight variation, thickness, disintegration time and cumulative drug permeation after being stored for 30 days under conditions of 30°C±3°C and 65%±2% relative humidity.[18]

RESULTS

Preformulation studies

Determination of absorbance maxima

The absorbance maximum of Hydralazine HCl was determined using UV spectrophotometer between the range 200-400 nm. The absorption maximum of Hydralazine HCl was found to be 261 nm as shown in Figure 1.

Calibration curve of Hydralazine HCl

After measuring the absorbance of solutions at 261 nm the beers range of Hydralazine HCl was found to be 3-21 mcg as shown in Table 3 and the regression coefficient was found to R^2 = 0.9964, As shown in Figure 2.

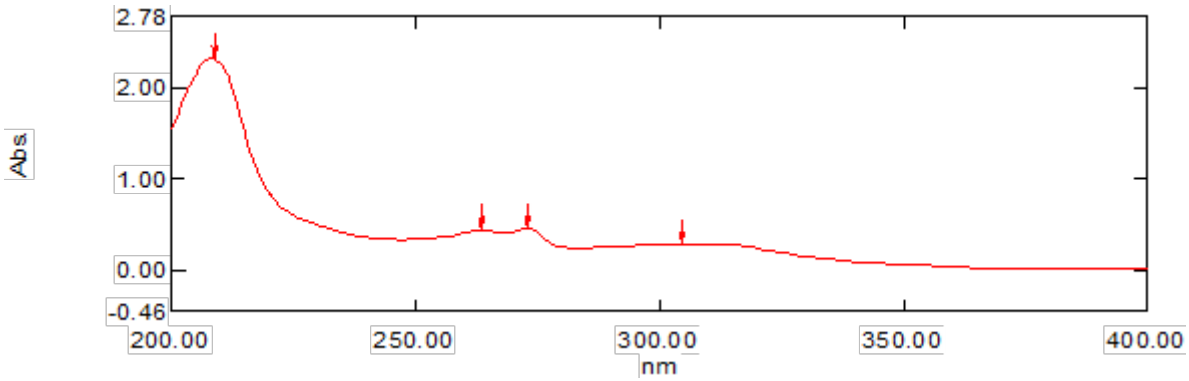

Figure 1: UV spectra of Hydralazine HCl in 6.8 Ph buffer.

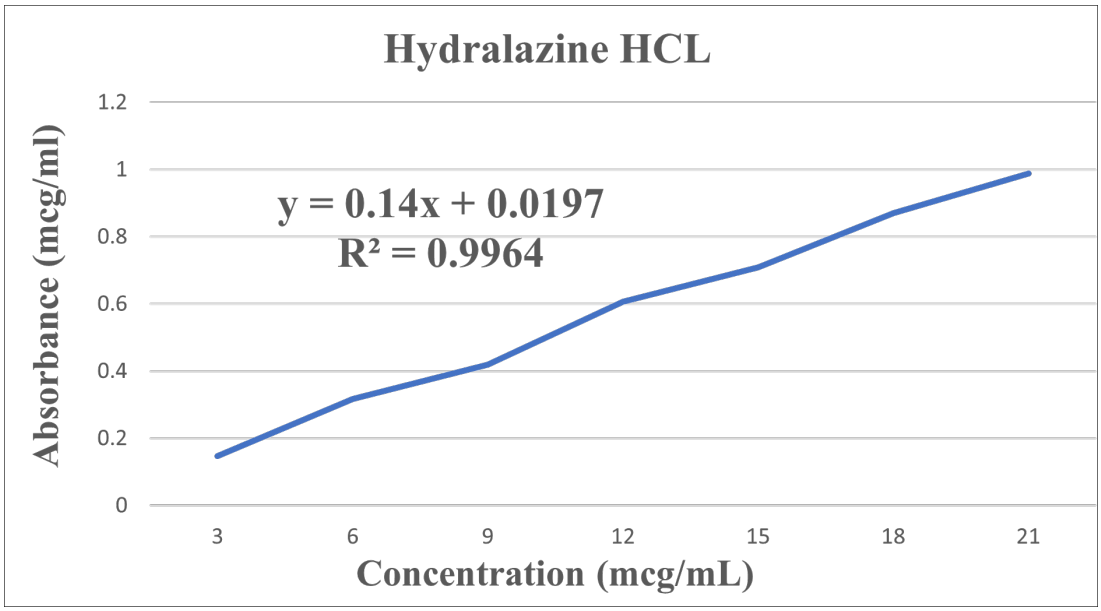

Figure 2: Calibration curve of Hydralazine HCl.

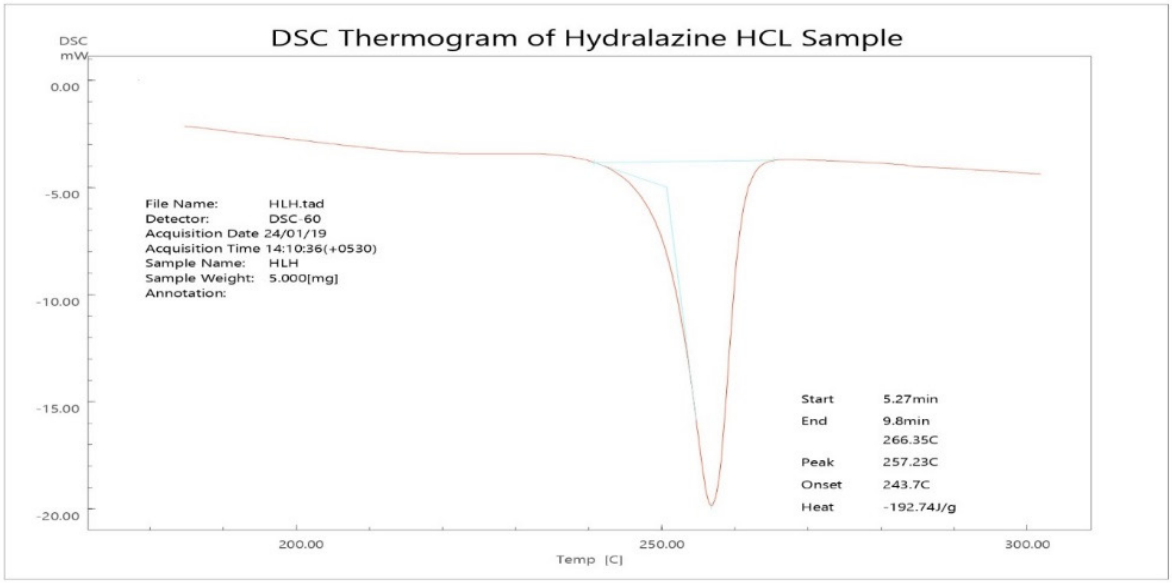

Figure 3: Differential Scanning Calorimetry thermogram.

Table 3: Absorbance of Hydralazine HCl at 261nm.

Concentration (mcg/mL)	Absorbance at 261nm*
3	0.147±0.012
6	0.317±0.013
9	0.419±0.011
12	0.607±0.021
15	0.709±0.022
18	0.87±0.033
21	0.988±0.011

*Mean± SD *n*=3.

Differential Scanning Calorimetry

After performing DSC a sharp endothermic peak at 257°C which is in a standard range of 243°C to 266°C as shown in Figure 3.

Fourier Transform Infrared Spectroscopy (FTIR) Study

After comparing FTIR spectroscopic graph of drug (Figure 4), polymer (Figure 5), mixture of drug and polymer (Figure 6) and the optimised formulation (Figure 7) it was found out that the drug and polymer were compatible as shown in Table 4.

Evaluation

Weight Variation

The weight of the drug-loaded, fast-dissolving strips was determined using a digital balance, Subsequently, the mean weight of all the films was documented. The weight of the strips across all batches (F1-F8) ranged from 57±2 mg to 105±8 mg. Formulation F3 exhibited the lowest weight due to the concentration of both polymers. All the prepared strips were uniform in weight as shown in Table 5.

Thickness

The thickness of the FDBFs ranged from 0.022 ± 0.009 mm to 0.053 ± 0.01 mm, with an increase in thickness corresponding to higher polymer concentrations. The low standard deviation values in all formulations indicate that the prepared films were uniform in thickness as shown in Table 5.

Folding Endurance

Each of the prepared FDBFs containing Hydralazine HCl displayed folding endurance ranging from 143±7 to 212±10 times, indicating good mechanical strength and ensuring flexibility. The combination of polymer and film former (Pullulan, PVP) contributes to adequate strength, while the Plasticizer (PG) enhances film flexibility. Therefore, an optimal concentration of both components would result in FDBF of desirable quality as shown in Table 5.

Surface pH

The surface pH of all FDBF formulations ranged from 6 to 7, which is close to neutral. As a result, no mucosal irritation is expected, thereby enhancing patient comfort and compliance as shown in Table 5.

Percentage Moisture Content

After performing the test, the percentage moisture loss was observed to be in the range of 0.43±0.02 to 1.42±0.05 as shown in Table 5.

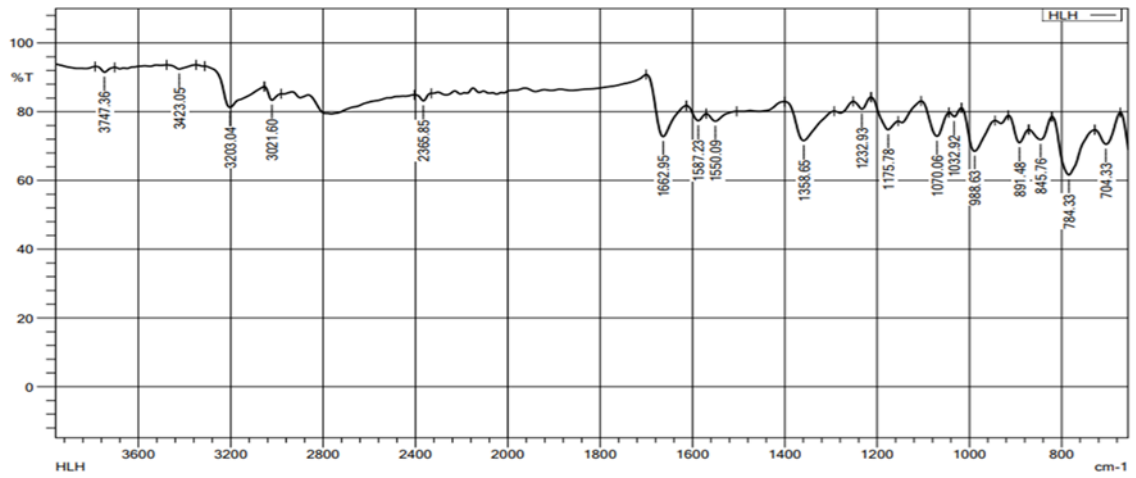

Figure 4: Fourier Transform Infrared Spectroscopy of HLZ HCl.

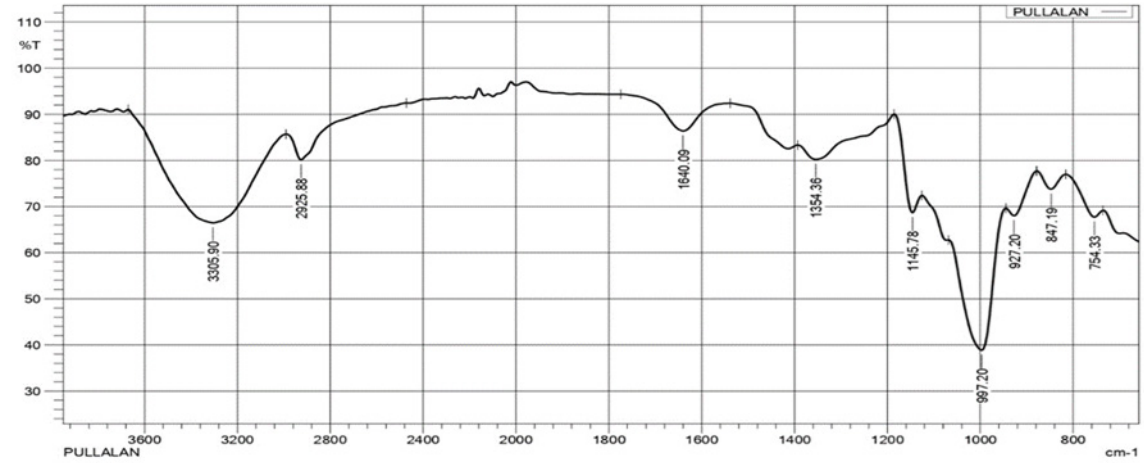

Figure 5: Fourier Transform Infrared Spectroscopy of Pullulan.

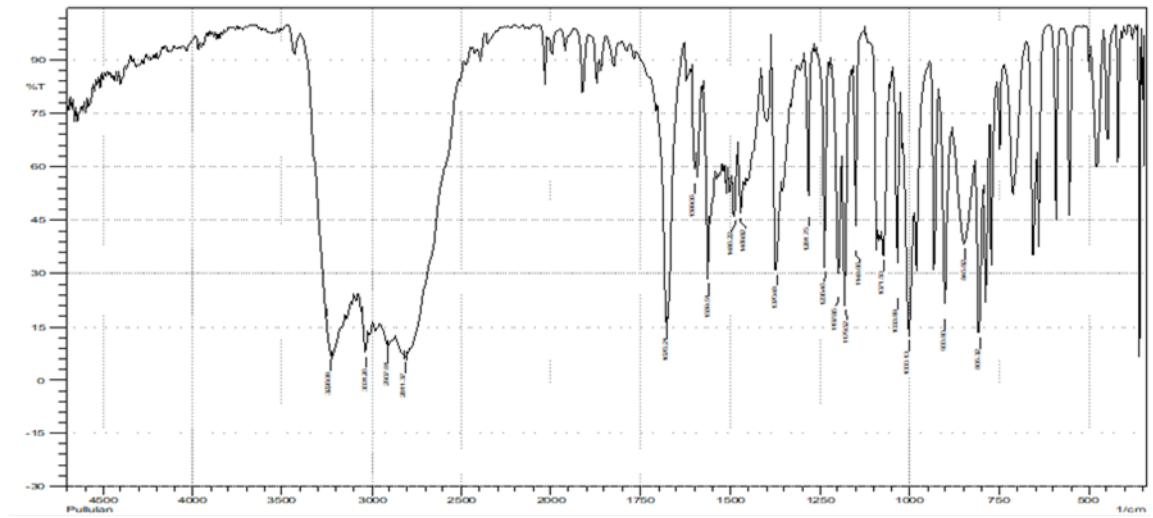

Figure 6: Fourier Transform Infrared Spectroscopy of API and Pullulan.

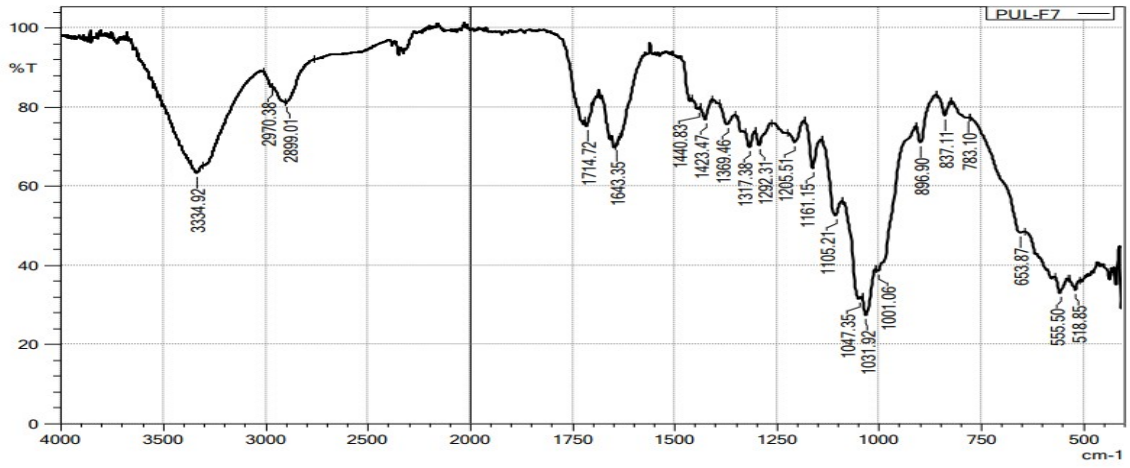

Figure 7: Fourier Transform Infrared Spectroscopy of Optimised formulation

Table 4: FTIR data of pure API, Polymer, API and polymer mixture and optimized formulation.

Functional group	Standard wave no. cm^{-1}	Hydralazine HCl pure drug cm^{-1}	Pullulan polymer cm^{-1}	Mixture of drug and polymer cm^{-1}	Optimized formulation OF for natural polymer cm^{-1}
O-H(bending)	1300-1500	1358.65	-	-	1317.38
C-H(bending)	700-1100	784.33	-	845.82	837.11
C-O-C	1100-1150	-	1145.78	1148.66	1161.15
C-O	990-1096	1070.66	-	1071.50	1047.35
O-H(stretching)	3050-3350	-	3305.90	3226.08	3334.92
C-O-H	1300-1400	-	1354.36	1370.48	1369.46
N-H	1600-1700	-	1640.09	1599.06	1643.35
C=O	1650-1750	1662.95	-	1676.21	1714.72

Table 5: Evaluation results of formulated Hydralazine HCl FDBF.

Formulations codes	Thickness in mm*	Weight variation in mg*	Folding endurance*	Surface pH	%Moisture content in %*	Drug content in %*
F1	0.030±0.004	89±4	200±6	6-7	0.43±0.02	93±2
F2	0.048±0.008	101±7	182±12	6-7	0.62±0.04	97±2
F3	0.022±0.009	57±2	188±12	6-7	1.2±0.03	97±1
F4	0.053±0.01	105±8	190±7	6-7	1.4±0.09	102±1
F5	0.032±0.009	97±5	143±7	6-7	0.83±0.02	96±1
F6	0.042±0.006	98±8	154±8	6-7	0.72±0.06	95±2
F7	0.036±0.004	98±7	212±10	6-7	0.53±0.07	96±2
F8	0.026±0.007	64±5	159±9	6-7	1.42±0.05	98±1

*Mean± SD *n*=3.

Drug Content

The drug content (%) of all FDBFs ranged from 93±2 to 102±1, demonstrating a uniform distribution of HLZ throughout the film. This consistent drug content assures both dose proportionality and uniformity as shown in Table 5.

Disintegration test

The disintegration times are provided in Table 6. F3 exhibited the shortest disintegration time of 18±0.4 sec, while F4 displayed the longest disintegration time of 138±1.0 sec.

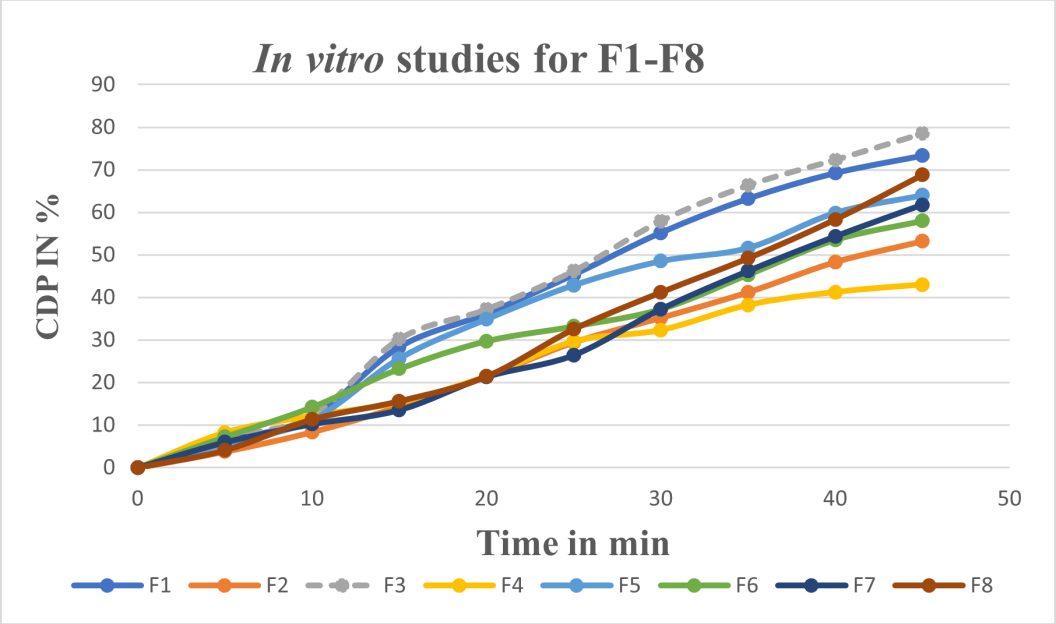

Figure 8: Cumulative drug release of Hydralazine HCl FDBF formulations F1-F8.

Table 6: Results of Disintegration Time and Cumulative Drug Permeation of HLZ FDBF.

	Disintegration Time (s) *	Cumulative Drug Permeation (%)
F1	38±0.2	73.3%
F2	126±0.3	53.2%
F3	18±0.4	78.5%
F4	138±1.0	43%
F5	94±0.5	64%
F6	112±1.0	58%
F7	98±2	61.8%
F8	61±6	68.8%

*Mean± SD *n*=3.

In vitro diffusion study

The cumulative drug permeation for FDF of HLZ (F1-F8) ranged from 43% to 78.5%, with formulation F3 also showing the highest cumulative drug release at 78.5%. The % Cumulative Drug Release (CDR) for all formulations is detailed in Table 6 and Figure 8.

Statistical analysis

Disintegration Time

Disintegration Time (Y1). The Disintegration Time (DT) offers insight into the commencement of action, a crucial aspect for oral thin films. The Disintegration Time (DT) for all the formulated FDBF of HLZ remained under 138 ± 2.8 sec. The influence of the factors (X1, X2, and X3) significantly increased DT (Y1) at higher levels. Figures 9, 10 and 11 displays a counterplot depicting the influence of these variables on disintegration time (seconds). Controlling the disintegration time of FDBF requires consideration of all three factors. Yet, elevated concentrations of Pullulan and PG will yield films that satisfy the criteria for swift dissolution. The findings are consolidated in Table 7. The polynomial equation representing the disintegration time is as follows,[1]

$$\text{Disintegration Time (Y1)} = 85.63+32.88(X1) +19.13(X2) +9.88(X3)$$

The polynomial equation indicated that concentration of Pullulan (X1), PVP (X2) and P.G.(X3) favours the response.

Cumulative Drug Permeation

Cumulative Drug Permeation (CDP) (Y2). The Cumulative Drug Permeation (CDP) provides an indication of the onset of action, this property is desirable for oral thin films. The CDP for all the formulated FDBF of Hydralazine HCl was in the range of 43 to 78%. The influence of the factors (X1, X2, and X3) significantly decreased CDP (Y2) at higher levels. Figures 12, 13 and 14 shows a counter-plot illustrating the impact of these factors on CDP (%). All three factors should be considered when controlling the CDP of FDBF. However, low concentrations of Pullulan, PVP and PG will produce films that meet the condition for higher CDP. The results are summarized in Table 7. The polynomial equation describing the disintegration time is as follows.[1]

$$\text{Cumulative Drug Permeation(Y2)} = 62.58-8.58(X1)-5.33(X2)-3(X3)$$

The polynomial equation indicated that concentration of Pullulan (X1), PVP (X2) and P.G.(X3) favours the response.[1]

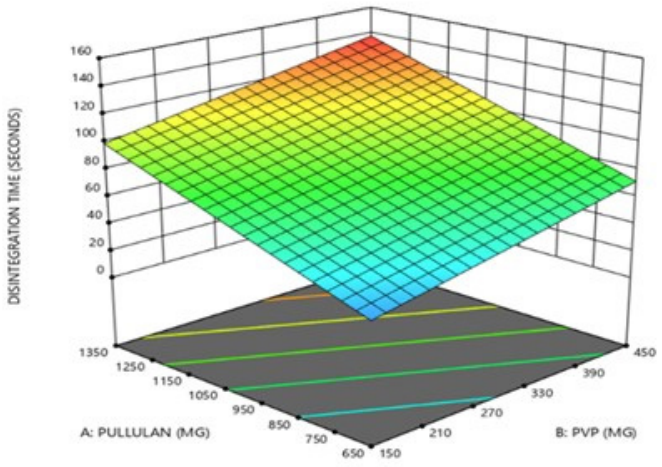

Figure 9: Response surface plot for the influence of polymer on Disintegration time.

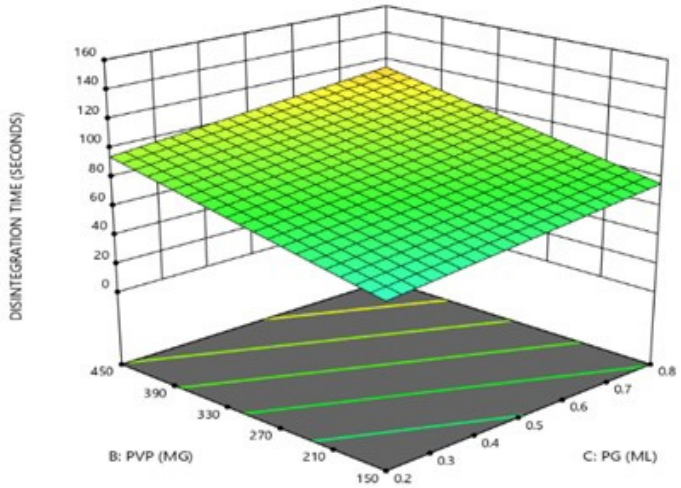

Figure 11: Response surface plot for the influence of PVP and PG on Disintegration time.

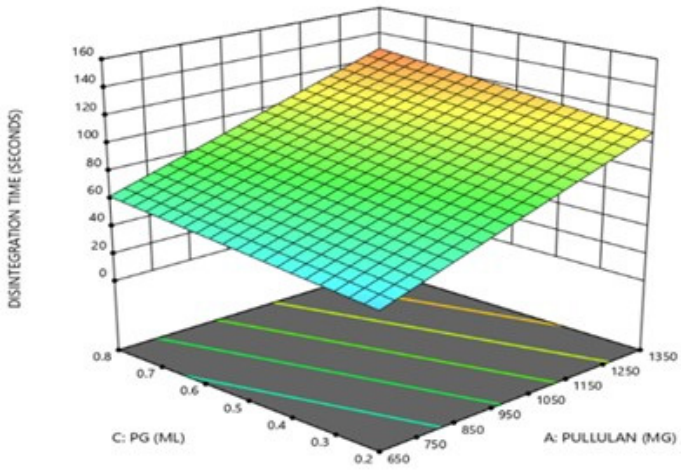

Figure 10: Response surface plot for the influence of Pullulan and PG on Disintegration time.

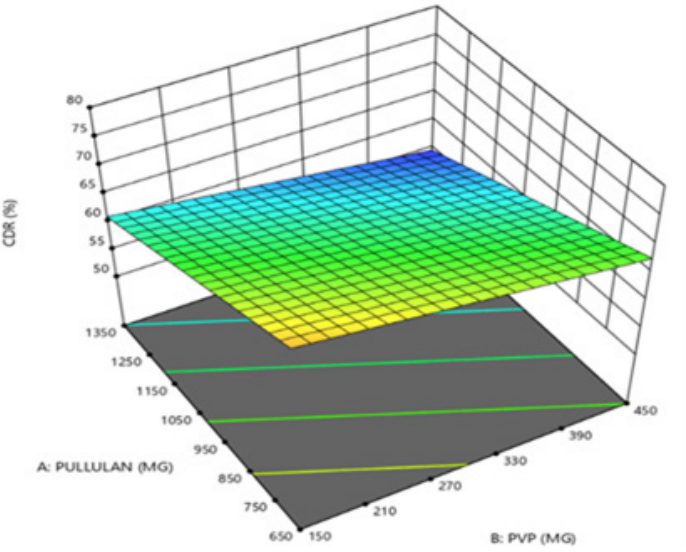

Figure 12: Response surface plot for the influence of polymer on Cumulative drug permeation (%).

Optimisation

Design Expert software provides an optimization feature that allows users to set specific goals for various factors and responses in their formulations. In this study, the objective was to reduce disintegration time while increasing drug release within the defined ranges for the FDBF. Based on these goals, the software generated multiple solutions with desirability score between zero and one. Among these, one formulation, designated as OF, achieved a desirability score of 0.981. This formulation was projected to have a disintegration time of 54.23 sec and a drug release rate of 69.29%, as illustrated in Figure 15, Consequently, DPI was chosen, and its actual performance closely aligned with the software's predictions, meeting all optimization criteria.

Ex vivo studies

The *ex vivo* study was carried out on the optimised formulation which we got from design of experiment and a 69% drug permeation was observed in 60 min as shown in Figure 16.

Stability study

The stability study was conducted using the optimized formulation OF, and the observed results indicate its successful passage of the stability assessment at 30°C ± 2 C and 65% ± 5% Relative Humidity (RH) as shown in Table 8.

DISCUSSION

This study aimed to develop and optimize Fast-Dissolving Buccal Films (FDBFs) containing Hydralazine HCl, providing an efficient and patient-compliant hypertension treatment. The formulation process employed the solvent casting method and utilized a 2^3 factorial design to assess the effects of Pullulan, PVP, and PG on key parameters like drug release and disintegration time. The use of Design Expert software facilitated the creation of polynomial equations and three-dimensional surface plots, revealing the

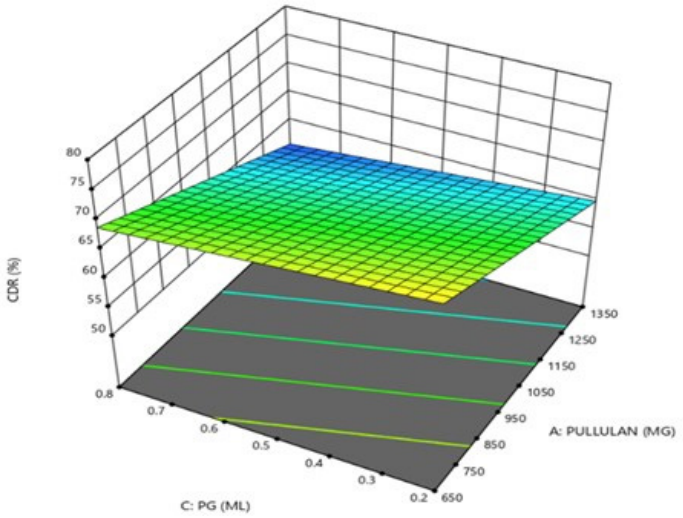

Figure 13: Response surface plot for the influence of Pullulan and PG on Cumulative drug permeation (%).

Table 7: Statistics of ANOVA analysis summary.

Response	Disintegration Time (Y1)	Cumulative Drug Release (Y2)
p value	0.0017	0.0005
R^2	0.9696	0.9835
Adjusted R^2	0.9468	0.9710
Predicted R^2	0.8783	0.9338
Standard Deviation	9.84	1.93
C.V%	11.49	3.09

optimal formulation with a rapid disintegration time of 48 sec and a cumulative drug permeation of 70.3%. These results were achieved due to the synergistic effects of the selected excipients: Pullulan and PVP contributed to the film's quick dissolution and robustness, while PG improved its flexibility and mechanical strength, ensuring rapid breakdown and efficient drug release.

The physicochemical properties of the FDBFs, such as uniform thickness, adequate folding endurance, neutral surface pH, and consistent drug content, were crucial for their performance. The uniform thickness and robustness were attributed to Pullulan, a key film-forming agent, while the neutral surface pH was maintained by carefully selecting excipients compatible with the

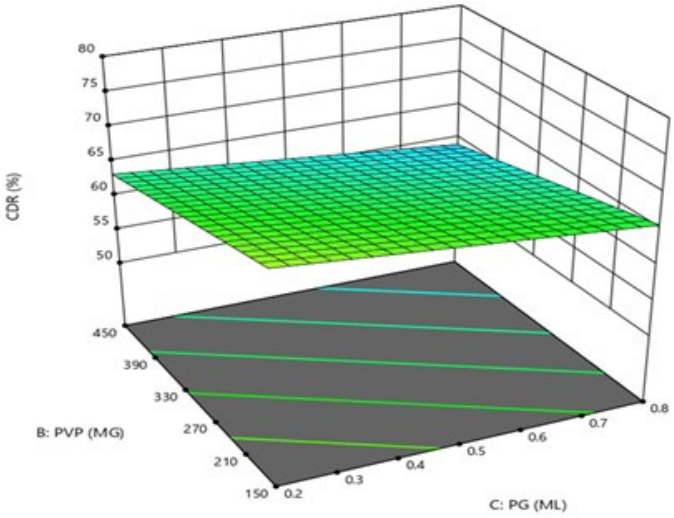

Figure 14: Response surface plot for the influence of PVP and PG on Cumulative drug permeation (%).

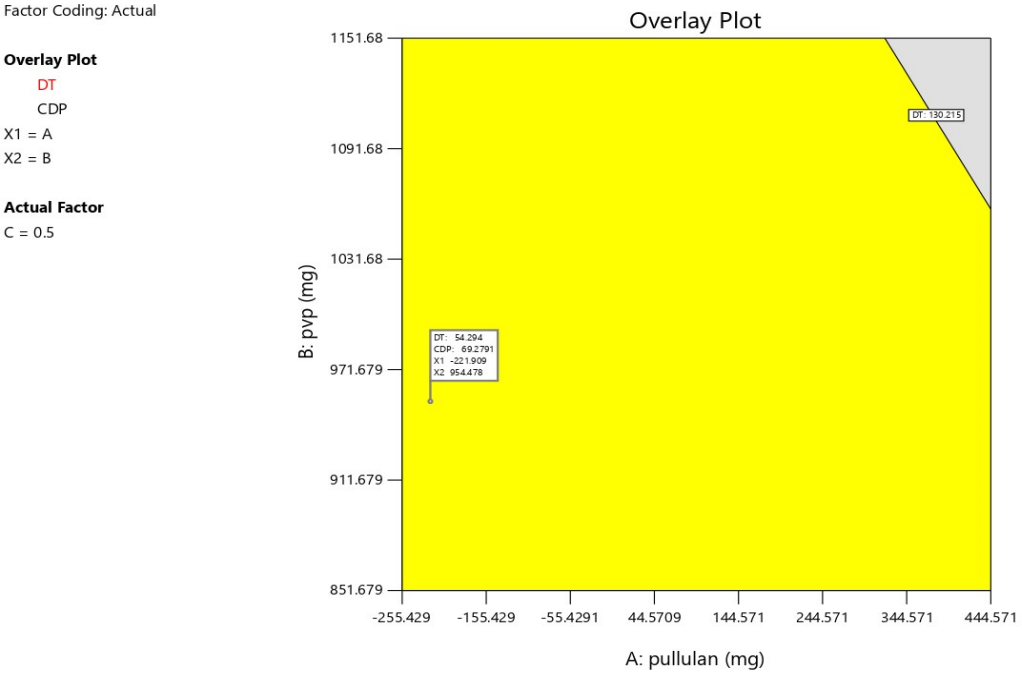

Figure 15: Design space of optimised of formulation.

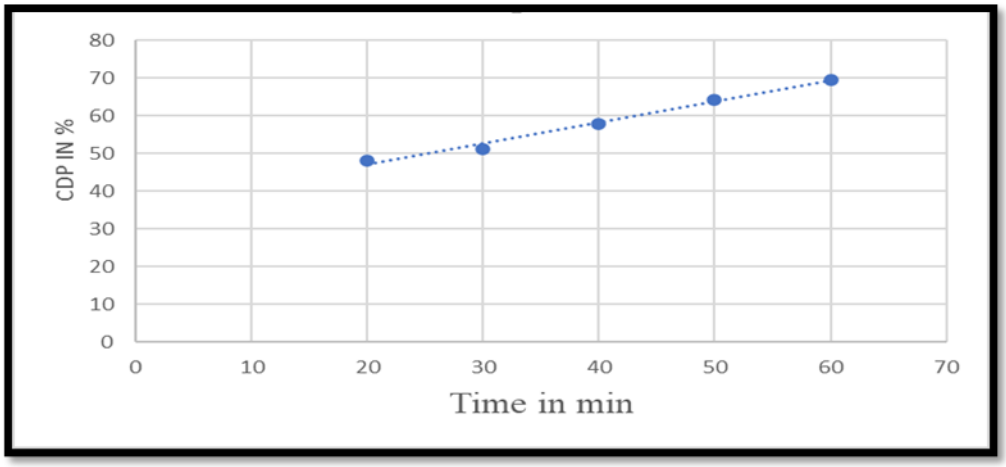

Figure 16: Cumulative drug release of optimised formulation.

Table 8: Results of Stability test results of optimised formulation.

Evaluation parameter at 30°C ± 2 C and 65% ± 5% Relative Humidity (RH).			
	0 Days	15 Days	30 Days
Thickness (mm)	0.049±0.002	0.049±0.001	0.048±0.001
Weight variation(mg)	94.43±0.74	94.21±0.56	93.92±0.66
% Drug content	98.74±0.78	97.88±0.89	97.12±0.86
%Moisture loss	0.63±0.03	0.62±0.03	0.61±0.02
Disintegration time(sec)	48±2	51±1	53±2
CDR%	70.3±0.34	69.8±0.31	68.9±0.36

*Mean± SD *n*=3.

buccal cavity environment. This minimized the risk of mucosal irritation and enhanced patient compliance. The consistent drug content across formulations was a result of the homogeneous distribution of Hydralazine HCl within the polymer matrix, facilitated by the solvent casting method.

Disintegration time is a critical parameter influencing the onset of drug action. The optimized formulation's rapid disintegration time of 48 sec was due to the high solubility and quick dissolution properties of Pullulan and PVP, which facilitated rapid film breakdown upon contact with saliva. The cumulative drug permeation of 70.3% was achieved due to the efficient absorption of the drug through the buccal mucosa, bypassing first-pass metabolism. PG's role as a plasticizer not only improved the film's flexibility but also enhanced the drug release profile by creating a more permeable film matrix.

Stability studies conducted under ICH conditions demonstrated that the optimized formulation maintained its physical and chemical integrity over one month, indicating good stability. This stability can be attributed to the inherent properties of Pullulan and PVP, as well as the absence of moisture-attracting agents in the formulation, which minimized degradation and ensured consistent performance.

The study highlights several advantages of FDBFs, including improved patient compliance, particularly for populations with swallowing difficulties, such as the elderly or those undergoing chemotherapy. The ease of administration without the need for water and the potential for taste masking further enhance patient acceptability. Additionally, the enhanced bioavailability through buccal delivery offers a promising alternative to traditional tablets and capsules, potentially reducing the required dose and associated side effects.

Future research should focus on conducting long-term stability studies to ensure extended shelf life, as well as clinical trials to confirm the efficacy and safety of the optimized FDBF in real-world patient populations. Exploring the scalability of the manufacturing process and conducting cost-effectiveness analyses will also be crucial for commercial viability. Addressing these aspects will pave the way for the potential commercial application of this innovative dosage form.

CONCLUSION

In this research, employing Design of Experiment facilitated the identification of how formulation variables affect FDBF performance. A film of Hydralazine HCl prepared using the

solvent casting method demonstrated the desired drug release percentage and disintegration time. This film exhibited a very smooth surface, attributed to the use of pullulan, and showed no interactions between the drug and polymer. Optimization of the film was achieved through expert design, with statistical analysis yielding equations that effectively described the impact of selected variables on the studied responses. Formulations that released over 78.3% of the drug within 45 min were identified in regions with low pullulan content, facilitating quicker drug release and *ex vivo* studies conducted on buccal mucosa demonstrated a cumulative drug release of 69% at 60 min. Additionally, formulations with an in vitro disintegration time of less than 48 sec were found in areas with higher levels of pullulan. The high drug release percentage in simulated saliva (pH 6.8) suggests that this film could be beneficial for treating acute allergies and situations requiring rapid drug bioavailability.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

HLZ HCl: Hydralazine Hydrochloride; **FDBF:** Fast dissolving buccal films; **PVP:** *Polyvinylpyrrolidone;* **PG:** Propylene glycol; **CDP:** Cumulative drug permeation: **ANOVA:** Analysis of Variance.

REFERENCES

1. Dangre PV, Phad RD, Surana SJ, Chalikwar SS. Quality by design (QbD) assisted fabrication of fast dissolving buccal film for clonidine hydrochloride: exploring the quality attributes. Adv Polym Technol. 2019; 2019:1-13. doi: 10.1155/2019/3682402.
2. Sudhir M, Sruthi V, Reddy TV, Naveena C, Reddy BP, Rahaman SA. Preparation and characterization of oral fast dissolving film of hydralazine HCl. Curr Trends Biotechnol Pharm. 2022; 16(3s):171-8.
3. Parmar S, Amit Gangwal NS. Scholars research library. Sch res Libr. 2011;2(4):373-83.
4. A.M. formulation & evaluation of fast dissolving buccal films of sertraline. Int J Drug Dev Res. 2012;4(1):220-6.
5. Muthukumar S, Sundara Ganapathy R. Formulation and evaluation of hydralazine hydrochloride buccal films by solvent casting method using different polymers for the management of hypertension. Vol. 9(8); 2018. Int J Pharm Sci Res [Internet]. p. 3328. doi: 10.13040/IJPSR.0975-8232.9.
6. Deore AB, Dhumane JR, Wagh R, Sonawane RB. The Stages of Drug Discovery and Development Process. Asian J Pharm Res Dev. 2019;7(6):62-7. doi: 10.22270/ajprd.v7i6.616.
7. Nair MM, Shajan A, Jacob L. Formulation and evaluation of mouth dissolving film of a poorly soluble antihypertensive drug. Int J Pharm Technol. 2016;8(4):21635-61.
8. Roman JJM. Ea. World Journal of Pharmaceutical research formulation. SJIF J. 2021;2(5):1685-703.
9. Sharma PK, Sharma PK, Darwhekar GN, Shrivastava B. Development and evaluation of fast-dissolving oral film of poorly water- soluble drug felodipine. Asian J Pharm. 2018; 12(1):S256-67.
10. Pawar SV, Junagade MS. Formulation and evaluation of mouth dissolving film of risperidone. Int J PharmTech Res. 2015;8(6):218-30.
11. Gorle A, Patil P, Bhaskar R, Ola M. Development and Evaluation of Buccal Film Containing Antihypertensive Agent. ~ 53 ~ Pharma Innov J [Internet]. Vol. 4(1); 2015. p. 53-60. Available from: http://www.thepharmajournal.com.
12. Mohamed MI, Haider M, Ali MA. Buccal mucoadhesive films containing antihypertensive drug: *in vitro/in vivo* evaluation. J Chem Pharm Res. 2011;3(6):665-86.
13. Shelar AC, Patil PS, Rane RA, Gurchal B, Nair SM, *et al.* System. 2020;11(7):6797-811:Article R.
14. Elagamy HI, Essa EA, Nouh A, El Maghraby GM. Development and evaluation of rapidly dissolving buccal films of naftopidil: *in vitro* and *in vivo* evaluation. Drug Dev Ind Pharm. 2019;45(10):1695-706. doi: 10.1080/03639045.2019.1656734.
15. Somani R, Kalyani S, Gavhane Y. Formulation and evaluation of immediate release and controlled release oral film of antihistamine agent: loratadine. World J Pharm Res. 2020;9(7):2145-58.
16. Malviya R, Shukla P, Srivastava P. Preparation, characterization and evaluation of chitosan-gum arabic coacervates as excipient in fast dissolving/disintegrating dosage form. Fabad J Pharm Sci. 2009;34(1):13-23.
17. Jose J, Sisira MV, Prasanth ML, Prasanth CR, Pradeep PS. Design and characterization of buccal films of benzocaine for mouth ulcer. J Pharm Res. 2021;20(3):9-17. doi: 10.18579/jopcr/v20i3.ms21062.
18. Gapat S, Pentewar RS, Sugave BK, Kulkarni KB, Mohalkar AV, Morkhande VK. Preparation & characterization of oral fast dissolving film of Levocetrizine dihydrochloride. World J Pharm Res. 2016;5(8):556-72.

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