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Formulation, Optimization and Evaluation of Mucoadhesive Buccal Patch of Miconazole Nitrate

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Abstract: The Mucoadhesive patches were prepared using a combination of HPMC K4M and Carbopol 940 polymers, containing Miconazole nitrate as API which provided the desired mucoadhesive properties and drug release profile. The patches exhibited good uniformity in drug distribution, with drug content ranging from 94.2% to 98.6%. The surface pH of the patches was within the acceptable range for buccal administration, ensuring minimal irritation or discomfort to the buccal mucosa indicating that they were not excessively acidic or alkaline, thus minimizing the risk of irritation. The patches exhibited good flexibility, as evidenced by their folding endurance values, ranging from 273 to 288, indicating their ability to withstand repeated folding without breaking. In terms of buccal mucosa interaction, the swelling index values indicated that the patches could effectively absorb and retain moisture upon contact with the mucosa. Additionally, the percentage of moisture loss suggested that the patches experienced some degree of evaporation. The mucoadhesion strength of the patches was within the range of 0.544 to 1.055N, signifying their ability to adhere to the buccal mucosa. This property is vital for maintaining prolonged contact and facilitating controlled drug release, thereby enhancing therapeutic efficacy. The steady-state flux values demonstrated variations in the rate of Miconazole nitrate permeation through the buccal mucosa among different formulations. Based on the evaluation data, an optimized batch (F5) was determined using a 3² factorial design, with HPMC K4M and Carbopol 940 identified as critical factors affecting mucoadhesive strength and percentage drug release.

Keywords: Miconazole nitrate, Mucoadhesive, Buccal patch, Sustained release, Oral candidiasis, HPMC K4M, Carbopol 940 polymers

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Introduction

Oral candidiasis, or oral thrush, is a fungal infection caused by *Candida* species, particularly *Candida albicans*, affecting individuals with compromised immune systems, including those with HIV/AIDS, chemotherapy, or immunosuppressive medications (Wani *et al.*, 2009). Traditional oral candidiasis treatment uses topical agents like miconazole nitrate, but conventional dosage forms have limitations in sustained drug release and patient compliance (Ubarhande *et al.*, 2009). Mucoadhesive buccal patches containing miconazole nitrate offer controlled drug release, sustained levels, patient compliance, and convenience, requiring less frequent administration compared to conventional dosage forms (Pingale *et al.*, 2020).

The study developed a mucoadhesive buccal patch of Miconazole nitrate using HPMC K4M and Carbopol 940 polymers, optimized using a 3² factorial design for simultaneous investigation (Rukari *et al.*, 2023). The buccal patches were assessed for weight, thickness, drug content, swelling index, and antimicrobial activity against *Candida* species, determining their quality, performance, and effectiveness in treating oral candidiasis (Sontakke *et al.*, 2012).

Materials and Methods

Miconazole Nitrate was received as a sample as a gift from FDC Ltd. Mumbai, India. Other polymers and excipients include- HPMC K4M, Carbopol-940, Propylene glycol, phosphate buffer (pH 6.8), distilled water, and polyethylene glycol (PEG-400).

Preformulation studies of mucoadhesive buccal patch of miconazole nitrate:

λ_{max} Determination: Using methanol as a blank, it was discovered that the miconazole nitrate's highest absorption occurred at a wavelength of 272 nm. Miconazole nitrate in the amount of 10 mg was weighed and dissolved in 100 ml of methanol (100 g/ml). To represent drug concentrations of 2, 4, 6, 8, and 10 g/ml, 0.2, 0.4, 0.6, and 1 ml of the resultant solution were pipetted out and made up to 10 ml (2, 4, 6, and 10

g/ml). The absorbance of the solutions was detected at 272 nm with a UV-visible spectrophotometer using methanol for the reference standard. After that, the calibration curve was drawn, with concentration (g/ml) along the X axis and absorbance along the Y axis (Sonawane *et al.*, 2023).

Compatibility Study:

Differential Scanning Calorimetry (DSC): DSC (SHIMADZU DSC 60-Plus) was used to analyse the purity and suitability of drugs and polymers. The drugs (miconazole nitrate), and the physical combination of drugs and polymers (Miconazole nitrate, HPMC K4M, Carbopol 940) (stored for 72 h. for proper mixing) as per their concentration in a chosen batch (F5) were measured to get respective DSC thermograms.

Fourier Transform Infrared (FTIR) Spectroscopy: FT-IR spectroscopy was used to analyze solid-state properties of a pharmaceutical solid, including physical combinations and pure drugs, to examine potential interactions between excipients and the drug.

Optimization and Evaluation of Mucoadhesive Buccal Patch:

Preparation of Mucoadhesive Buccal Patches: The mucoadhesive buccal patches were prepared using a solvent casting method. HPMC K4M was dissolved in water, carbopol 940 was added, miconazole nitrate was dissolved in methanol, PEG 400 was added, and propylene glycol was added. After 20 min, the drug solution was cast into a petri plate, dried, and cut into 2x2 cm² pieces for further evaluation as mentioned in Table 1 (Savale, 2017).

Design of experiment (DOE): The experimental setup utilized a 2 factor, 3 level factorial design. The quantity of HPMC K4M (X1) and the quantity of Carbopol 940 (X2) were the Independent variables under investigation. Mucoadhesion force (Y1) and % drug release (Y2) were regarded as dependent variables (Dinte *et*

Table 1: Formulation of miconazole nitrate buccal patch

Ingredient	Formulations Code								
	F1	F2	F3	F4	F5	F6	F7	F8	F9
Miconazole nitrate	159	159	159	159	159	159	159	159	159
HPMC K4M	200	200	200	300	300	300	400	400	400
Carbopol 940	20	30	40	20	30	40	20	30	40
PEG 400	1	1	1	1	1	1	1	1	1
Propylene glycol	7	7	7	7	7	7	7	7	7
methanol	15	15	15	15	15	15	15	15	15
water	10	10	10	10	10	10	10	10	10

al., 2023).

Characterization of Buccal Patch:

Weight variation: Three patch randomly selected 2x2 cm² films were cut, each patch was weighed independently and the mean weight was calculated after being weighed on a digital balance (Narendra *et al.*, 2005).

Film thickness: Randomly cut pieces of 2x2 cm² film were weighed on a digital balance for examination. Weight averages were computed. The film thickness was calculated using a Vernier Caliper micrometer at three separate points for each film, and the mean value was calculated (Kraisit *et al.*, 2018).

Drug content using UV-VIS Method: The uniformity of drugs distribution was evaluated using the spectrophotometric approach by measuring the drug content at several locations across the same film. Individually weighed 1 × 1 cm² pieces of each patch was dissolved in 10 ml of methanol, filtered through paper, and the concentration of miconazole nitrate in the solution was determined by using UV Spectrophotometer at 272 nm. Each preparation was examined three times, and the % of drug content were determined using the equation mentioned below (Adhikari *et al.*, 2010):

$$\% \text{ Drug content} = \frac{\text{Actual amount}}{\text{Theoretical amount}} \times 100$$

Folding endurance: The patch's folding endurance

was employed to calculate how strong it was mechanically to endure folding or how resilient it was to brittleness. It was calculated by folding a patch at one point repeatedly before it broke. The number of folds a film could withstand without breaking was known as its folding endurance. The patch's tensile strength increased as the number of folding endurance value increases (Nikhilitha and Pingale, 2021).

Swelling index: To test the patch's ability to swell, phosphate buffer (pH 6.8) was made. The patch's initial weight was calculated and it was put into the stainless-steel mesh that had already been weighed. The phosphate buffer with a pH of 6.8 was applied to the system. Weighing the system at regular intervals allowed us to detect the rise in patch weight (Swati *et al.*, 2011). The degree of swelling was calculated as:

$$\text{Swelling index} = \frac{W1 - W2}{W1} \times 100$$

Surface pH of films: With the aid of water, patch became slightly moist. By placing the electrode against the patch's surface, the pH was determined. Three patches of each formulation were used in the investigation, and an average was taken (Semalty *et al.*, 2008).

Percentage Moisture Loss: Accurate weights of buccal patches were recorded and stored in desiccators with anhydrous calcium chloride.

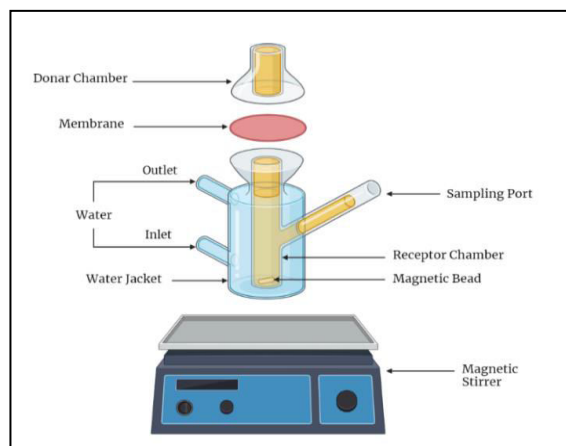


Fig. 1: Diagrammatic Representation of Franz Cell Diffusion Apparatus.

After three days, moisture loss and absorption percentages were determined using a formula (Begum and Aryani, 2023):

$$\text{Moisture loss} = \frac{\text{Loss of weight}}{\text{Sample weight}} \times 100$$

Measurement of Mucoadhesive Strength: The goat cheek pouch was collected and cleaned using a pH 6.8 phosphate buffer solution. The tissue was stored in a phosphate buffer solution. A Teflon cylinder was covered with a membrane and placed in a beaker. One patch was selected from each batch and adhered to the cylinder. A weight was applied to the patch, and mucin binds to it. The procedure was repeated for two more tablets, and the average was calculated and noted (Yamsani *et al.*, 2008; Pingale *et al.*, 2022):

$$\text{Mucoadhesion force} = W1/100 \times 9.81$$

Where, W1 = weight required for detachment of patch from tissue; 9.81= gravitational constant.

Ex Vivo Drug Permeation Study: An ex vivo buccal permeation study was conducted to optimize a formulation of Miconazole nitrate. The study involved a Franz diffusion cell (as shown in Figure 1), fresh goat oral mucosa, and phosphate buffer solutions in donor and receptor compartments. Slow magnetic bead spinning was used to maintain a steady hydrodynamic environment.

Withdrawing samples at regular intervals and

analysing them for drug content with a UV spectrophotometer at 272 nm allowed to assess how much of the drug permeated through the buccal mucosa (Nafee *et al.*, 2003; Khairnar *et al.*, 2009).

Steady State Flux: Once the lag phase has concluded and the quantity continues to increase, steady state flux (J_{ss}) refers to the consistent rate at which the permeant moves across the membrane. This state is recognized as steady when the measured amounts at repeated intervals display minimal differences. The equation $J_{ss} = Q/(A \cdot t)$ is used to calculate J_{ss} , where Q represents the quantity of the compound transported through the membrane within a given time (t), and A signifies the area of the exposed membrane in square centimetres (cm^2). The unit of steady state flux is expressed as quantity per ($\text{cm}^2 \cdot \text{time}$), with time typically measured in hours (Nandi *et al.*, 2022).

$$J_{ss} = Q/(A \cdot t)$$

Drug Release Kinetics: The drug is released through a diffusion mechanism and zero-order rate in matrix systems, analyzed using zero-order, first-order, and release rate kinetics models (Sharan *et al.*, 2010; Fu *et al.*, 2010).

Antimicrobial Activity Study: A nutrient agar plate was inoculated with test organisms, divided into

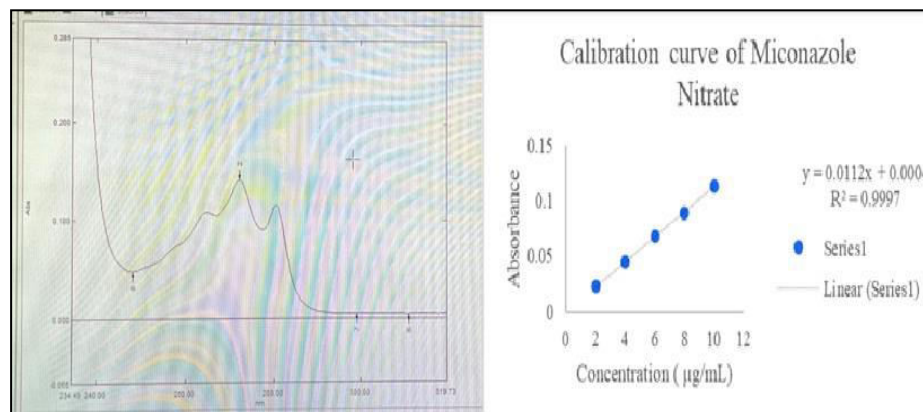


Fig. 2: Calibration curve of Miconazole Nitrate and Spectrophotometric Graph.

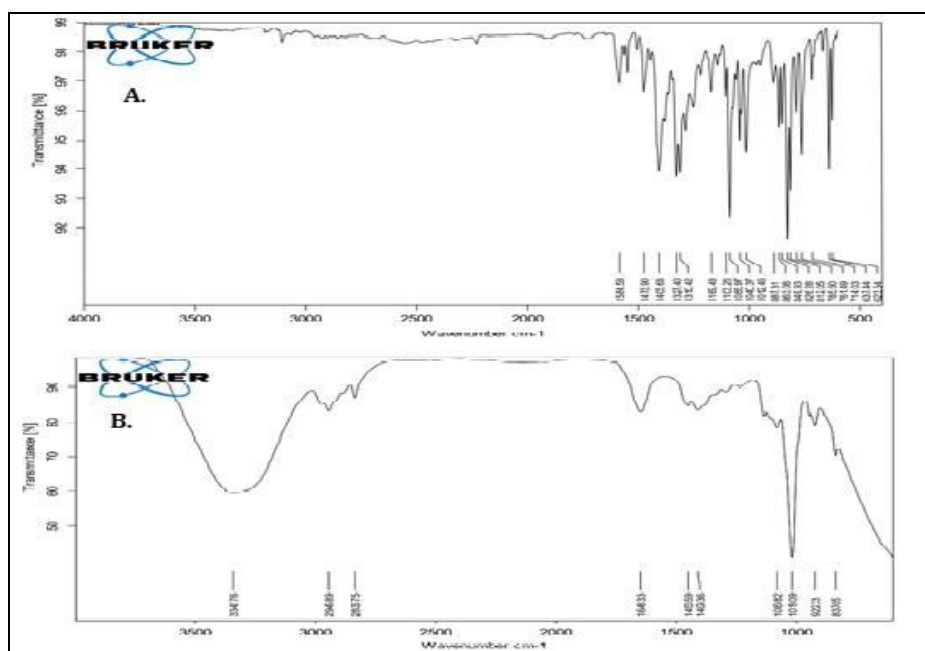


Fig. 3: (A) FT-IR spectra of Miconazole nitrate drug, and (B) FT-IR spectra of Formulation.

four cavities, filled with antibiotic and standard solutions, and incubated at 37°C for 24 h. Zone of inhibition was measured (Balouiri *et al.*, 2016).

Stability Study: A short-term stability study was conducted in a humidity chamber following ICH recommendations Q1C, analyzing responses to improve the formulation at the end of trials (Doijad *et al.*, 2006).

Results and Discussion

Determination of λ_{max} of Miconazole Nitrate: The

λ_{max} value for the miconazole nitrate was found to be 272 nm which was as per the reported value and the drug purity got confirmed (Fig. 2).

Calibration Curve of Miconazole Nitrate: It was discovered that the Miconazole Nitrate solution in Phosphate Buffer pH 6.8 follows Beer Lambert Law and demonstrates linearity ($R^2 = 0.9997$) in absorption at concentrations of 2–10 (µg/ml).

Study of Drug and Excipient Compatibility:

FT-IR Spectroscopy: The pure miconazole nitrate's

infrared spectrum (Fig. 3) depicted the peak at wave number (cm^{-1}) that corresponds to the functional group contained in the drug's structure. The functional group contained in the molecular structure of miconazole nitrate is reflected in the absorption band that it exhibits. The presence of an absorption band that corresponds to a functional group in the structure of Miconazole nitrate confirms the sample's identity and purity. The lack of any shift or removal of the distinctive peaks of miconazole nitrate in the FTIR spectra with any excipients suggests that there are not any interactions between the excipients and the drug itself.

Differential Scanning Calorimetry (DSC): The DSC results of Miconazole nitrate, both as a pure API and in a polymers mixture, suggest the following compatibility assessment:

DSC of API: Endothermic peak at 14.22 min with 188.07 °C: This peak indicates an energy-absorbing process, typically associated with the melting or decomposition of the drug. **Exothermic peak at 15.42 min with 205.31 °C:** This peak represents an energy-releasing process, often associated with crystallization or recrystallization of the drug, depicted in figure 4.

Drug-Polymer Mixture DSC:

Endothermic peak at 14.97 min with 185 °C: This peak still indicates an energy-absorbing process, like the pure drug peak. The shift in the peak time and slightly lower temperature suggests some interaction between the drug and polymers.

Exothermic peak at 15.64 min with 194.31 °C: This peak also represents an energy-releasing process, and again, the shift in peak time and temperature indicates some interactions between polymers and drugs.

Per cent moisture loss: Mucoadhesive buccal patches have moderate moisture loss (11.14%-12.94%), affecting their stability and integrity. Formulations F1 to F9 show acceptable moisture loss levels, indicating better retention and stability.

Swelling Index: The mucoadhesive buccal patches' swelling index ranges from 30.55% to 37.14%, indicating moderate to high swelling, indicating better water absorption and expansion, enhancing drug release properties.

Mucoadhesive Strength: Mucoadhesive strength and force are crucial for separating the buccal patch from the mucosal surface, with higher values indicating stronger adhesion. As polymer concentration increases, so does mucoadhesion force as mentioned in table 2.

Steady state flux: The steady state flux values range from 0.751 $\mu\text{g}/\text{cm}^2\text{h}$ to 0.829 $\mu\text{g}/\text{cm}^2\text{h}$, indicating the variability in drug release and permeation across the different formulations. Among the formulations listed, F5 demonstrates the highest steady state flux value of 0.829 $\mu\text{g}/\text{cm}^2\text{h}$, suggesting a relatively higher release and permeation rate of miconazole nitrate compared to other formulations.

Ex Vivo drug permeation study: Miconazole nitrate drug release percentages vary among formulation batches, with consistent results in batches F1 and F4, and highest percentages in batches F5 and F6 (as shown in figure 5).

Factorial Design: The optimized formulation was developed automatically by Design Expert® Software version 13 based on specified restrictions for each independent variable. The experiments were run, and results were collected. Table 3 presented the data.

Desirability: Desirability is a feature in statistical optimization that maximizes the desirability quotient, affecting target quality. It is a statistical strategy for determining the best option, with the grade determined by the closest values to the real optimal.

Overlay/Graphical Optimization Plots: The figure highlights "perfect zones" for meeting response requirements, demonstrating system failing boundaries. Permissible component parameters are coloured yellow, undesirable component values are grey (Fig. 6).

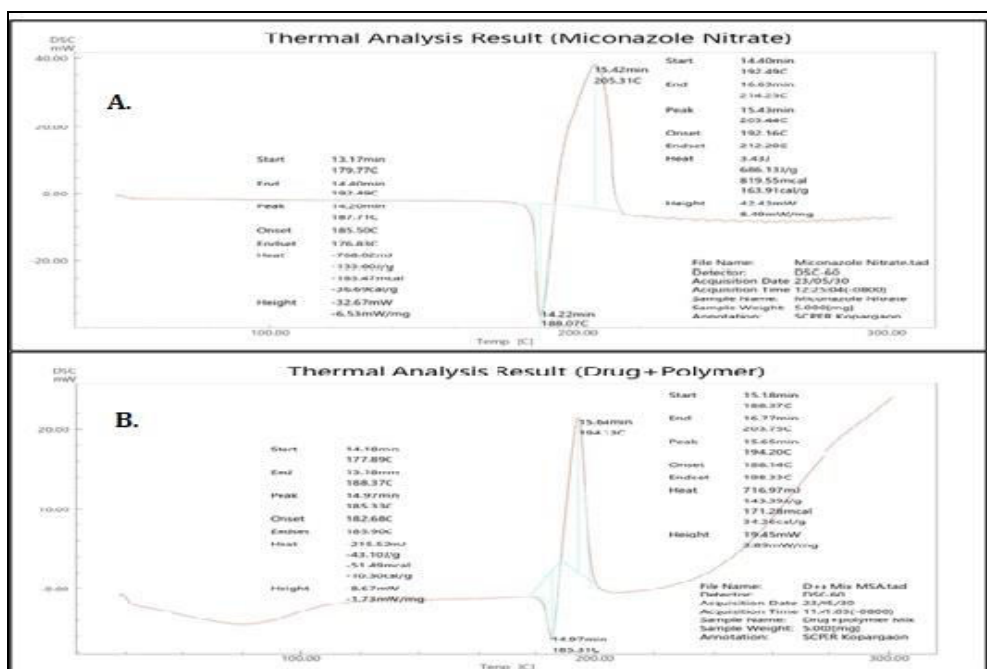


Fig. 4: A. DSC graph of Pure Drug and B. Drug-Polymer Mixture DSC.

Table 2: Evaluation of formulated patch

Formulation Code	Weight (g)	Thickness (mm)	Drug content (%)	Surface pH	Folding endurance	Moisture loss (%)	Swelling index (%)	Mucoadhesion force (N)	Steady State Flux ($\mu\text{g}/\text{cm}^2$ 4 h)
F1	0.273	0.37	94.6 %	6.40	273	12.42	30.55	0.544	0.802
F2	0.230	0.42	95.6 %	6.38	275	12.50	33.33	0.586	0.794
F3	0.354	0.38	94.8 %	6.48	278	11.62	35.13	0.619	0.788
F4	0.325	0.46	96.2 %	6.72	282	11.42	34.28	0.756	0.802
F5	0.382	0.43	98.6 %	6.83	287	12.94	37.14	0.679	0.829
F6	0.407	0.42	94.2 %	6.68	284	11.14	35.31	0.770	0.816
F7	0.388	0.40	98.2 %	6.71	281	12.28	31.42	0.877	0.783
F8	0.401	0.49	94.4 %	6.62	286	11.89	32.35	0.991	0.761
F9	0.431	0.51	94.2 %	6.78	288	12.63	34.21	1.055	0.751

Confirmation of optimized batch: The optimized concentrations of both the polymers are HPMC K4M 300mg and Carbopol-940 30 mg was found to be optimum concentration, i.e., batch F5 (containing these polymeric concentrations) was found to be the optimum batch. **Drug Release Kinetic:** The study used regression coefficient method to analyze drug release data from the F5 patch formulation, revealing zero order kinetics for Miconazole nitrate with $R^2 = 0.9452$, and a first order equation for in vitro drug release characteristics.

Antimicrobial Activity: Miconazole nitrate showed significant antimicrobial activity against *Candida*

spp., with a 25 mm inhibition zone, while nystatin showed a slightly stronger 22 mm zone.

Stability Study: The optimized transdermal patch (F5) underwent stability testing for three months, demonstrating good uniformity, acceptable surface pH, folding endurance, and moisture absorption/retention of Miconazole nitrate, as shown in Figure 7. The 3^2 factorial design optimized the patch, resulting in the highest inhibition zone against *Candida* spp.

Conclusion

The mucoadhesive buccal patches of Miconazole nitrate were prepared and evaluated. The patches

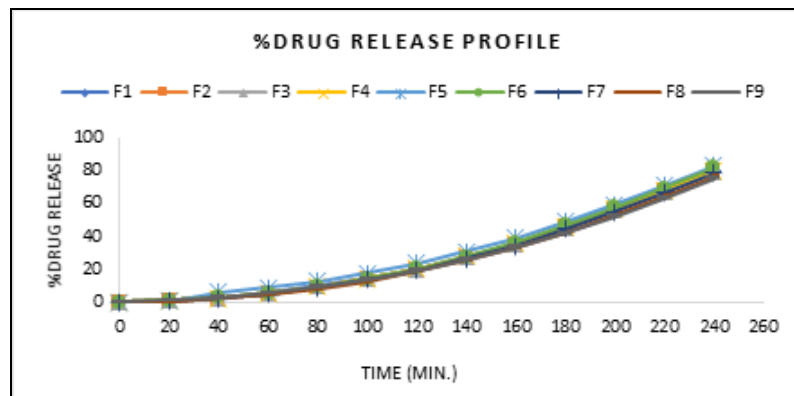


Fig. 5: Percentage Drug Release Profile.

Table 3: 3^2 Factorial design with factors and responses

	Factor 1	Factor 2	Response 1	Response 2
Run	A: HPMC K4M (mg)	B: CARBOPOL 940 (mg)	Mucoadhesive strength (N)	% Drug release (%)
1	200	20	0.544	80.26
2	200	30	0.586	79.47
3	200	40	0.619	78.86
4	300	20	0.756	80.26
5	300	30	0.679	81.65
6	300	40	0.77	78.34
7	400	20	0.877	76.34
8	400	30	0.991	76.15
9	400	40	1.055	75.1

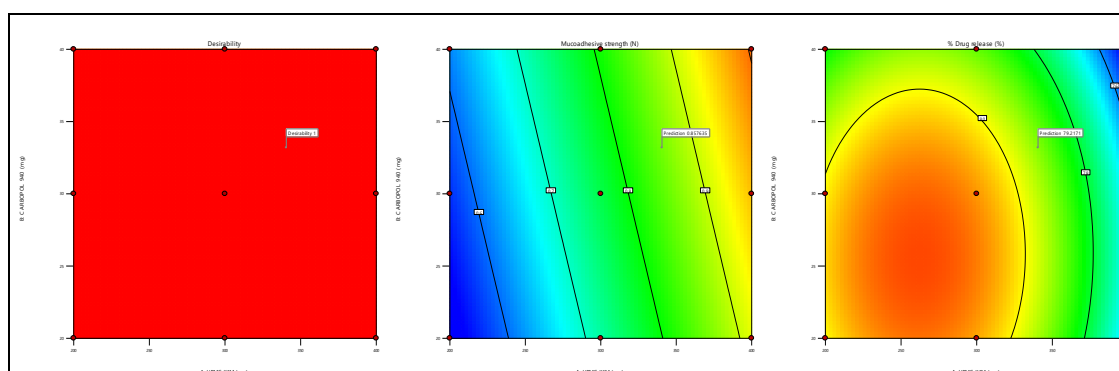


Fig. 6: A. Contour Plot of Desirability B. Counter plot of response 1 (Mucoadhesive strength) C. Counter plot of response 2 (%drug release).

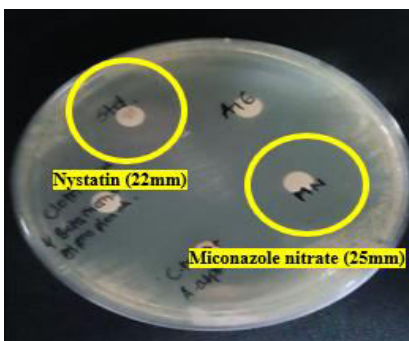


Fig. 7: Antimicrobial activity against nystatin using the cup and plate method.

Table 4: Stability Studies of Optimized Formulation

S. No.	Parameters	Miconazole nitrate			
		Initial	1 month	2 Month	3 Month
1	Drug content (%)	98.62%	98.51%	98.46%	98.12%
2	Cumulative drug release (%)	82.96%	82.67%	82.21%	81.84%
3	Steady state flux ($\mu\text{g}/\text{cm}^2$ 4h)	0.829	0.824	0.820	0.809

showed good uniformity in drug distribution, appropriate pH levels, flexibility, and ability to retain moisture. They also demonstrated strong mucoadhesive properties, ensuring prolonged contact with the buccal mucosa. The permeation rate of Miconazole nitrate varied among the different formulations. Through optimization using factorial design, the most effective batch was identified. The patches exhibited antimicrobial activity against *Candida spp.*, with the optimized batch showing the highest inhibition zone. Additionally, stability studies conducted over three months indicated good stability of the patches composed of HPMC K4M and Carbopol 940 polymers.

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