Formulation And Evaluation Of Buccal Patches Using Citrus Peel Exctract For The Treatment Of Oral Candidiasis

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ABSTRACT

Background: Oral candidiasis is a fungal infection that may benefit from localized antifungal delivery. Citrus peel extract contains phytochemicals with potential antimicrobial properties, making it a candidate for buccal patch development. **Aims:** To formulate and evaluate citrus peel extract-loaded buccal patches for the potential treatment of oral candidiasis. **Materials and Methods:** An experimental laboratory-based study was conducted using four formulations (F1–F4) containing 100 mg of citrus peel extract and varying proportions of HPMC E15 (450, 400, 350, and 300 mg) and chitosan (150, 200, 250, and 300 mg). Extract characterization, phytochemical screening, physicochemical evaluation, in vitro release testing, and antifungal assessment against Candida albicans were performed. **Results:** Extraction yield was 20.3% w/w. Phytochemical screening identified alkaloids, glycosides, flavonoids, saponins, tannins, phenols, proteins/amino acids, and carbohydrates. Patch thickness ranged from 0.21 ± 0.01 to 0.36 ± 0.02 mm, surface pH from 6.45 ± 0.04 to 6.68 ± 0.04, and drug content from 96.12 ± 0.91% to 98.91 ± 0.65%. Formulation F3 demonstrated 98.53 ± 0.73% drug content, 95.1% release at eight hours, and an inhibition zone of 20.9 ± 0.7 mm, compared with 25.4 ± 0.6 mm for clotrimazole and 0 mm for the blank patch. **Conclusion:** Citrus peel extract-loaded buccal patches demonstrated promising preliminary physicochemical and antifungal properties. Further safety, stability, and clinical studies are required.
Keywords: Citrus peel extract; Buccal patches; Oral candidiasis; Candida albicans; Chitosan; Antifungal activity. **How to cite this article**: Govarthanam.S, Prasath Sivakumar, Benazir.M, Priya.M, Akalyha.A.T, Sangeetha.M Formulation And Evaluation Of Buccal Patches Using Citrus Peel Exctract For The Treatment Of Oral Candidiasis. International Journal of Drug Delivery Technology. 2026;16(90s): 635-642; DOI: 10.25258/ijddt.16.90s.62

INTRODUCTION

Oral candidiasis is a common opportunistic fungal infection of the oral cavity, primarily caused by Candida albicans. Although this organism may normally exist as part of the oral microbial community, certain conditions can promote its excessive growth and lead to infection. Diabetes mellitus, immunosuppression, prolonged antibiotic use, denture wearing, and reduced salivary flow are recognized predisposing factors. The condition may present as white plaques, mucosal redness, burning sensations, and discomfort during eating or swallowing, affecting the patient's quality of life [1,2]. Conventional treatment involves antifungal agents such as nystatin, clotrimazole, miconazole, and fluconazole. However, conventional oral formulations may have limited contact time with the affected mucosa because of continuous salivary secretion and swallowing. Repeated administration may also affect patient compliance. Consequently,

mucoadhesive drug delivery systems have attracted interest as an alternative approach for maintaining medication at the affected site and supporting localized treatment [3,4].

Buccal patches are designed to adhere to the oral mucosa and release their incorporated active constituents over a specified period. Polymers such as hydroxypropyl methylcellulose (HPMC) and chitosan are useful in formulation development because of their film-forming and mucoadhesive properties. Their performance depends on characteristics such as thickness, flexibility, surface pH, drug content, adhesion, and release behaviour [4,5].

Citrus peel is a potentially valuable source of natural bioactive compounds, including flavonoids, phenolic acids, and essential oil constituents. These compounds have demonstrated various biological activities, including antimicrobial and antifungal effects in experimental settings [6–8]. Research has also investigated lemon peel essential oil against Candida albicans biofilm formation, providing a rationale for further investigation of citrus-derived materials in oral healthcare [9], [10].

The aim of the present study is to formulate and evaluate buccal patches containing citrus peel extract for the potential treatment of oral candidiasis. The study objectives include preparing the extract using a suitable extraction method, developing patches with appropriate polymers, and evaluating their physicochemical properties, including thickness, flexibility, surface pH, and drug content. Additionally, the study aims to investigate the in vitro release profile and assess the antifungal activity of the prepared patches against Candida albicans.

MATERIALS AND METHODS

Study Design: Experimental laboratory-based formulation and evaluation study.

Study Population: Citrus peel extract-loaded buccal patches prepared using suitable pharmaceutical polymers.

Sample Size: Four formulations (F1, F2, F3, and F4) with varying concentrations of HPMC E15 and chitosan.

Study Duration: Not specified in the provided study document.

Study Setting/Location: Pharmaceutical formulation and evaluation laboratory, Excel College of Pharmacy.

Inclusion Criteria:

- Authenticated citrus peel material suitable for extraction.
- Formulations prepared using the selected pharmaceutical-grade excipients.
- Buccal patches suitable for physicochemical and in vitro evaluation.
- Candida albicans culture suitable for antifungal testing.

Exclusion Criteria:

- Citrus peel material showing contamination or deterioration.
- Patches with visible defects or irregular formation.
- Formulations unsuitable for evaluation due to physical instability.
- Contaminated or unsuitable fungal cultures.

Statistical Analysis: Data were initially entered into Microsoft Excel and subsequently analyzed using SPSS software (version 27.0; SPSS Inc., Chicago, IL, USA) and GraphPad Prism (version 5). Numerical variables were expressed as mean ± standard deviation (SD), while categorical variables were presented as frequencies and percentages. Comparisons between independent groups were performed using the independent samples t-test, whereas paired t-tests were applied for correlated (paired) data. Categorical variables were analyzed using the Chi-square test, and Fisher's exact test was employed when expected frequencies were small. A p-value ≤ 0.05 was considered statistically significant.

RESULT

Table 1. Composition of Citrus Peel Extract-Loaded Buccal Patch Formulations

Ingredients	Function	F1	F2	F3	F4
Citrus peel extract (mg)	Active ingredient	100	100	100	100
HPMC E15 (mg)	Film-forming polymer	450	400	350	300
Chitosan (mg)	Mucoadhesive polymer	150	200	250	300
Glycerin (% w/w of polymer)	Plasticizer	30	30	30	30
1% Acetic acid (mL)	Chitosan solvent	10	10	10	10
Distilled water	Solvent	q.s. to 20 mL	q.s. to 20 mL	q.s. to 20 mL	q.s. to 20 mL

Table 2. Extraction Yield and Physicochemical Characterization of Citrus Peel Extract

Parameter	Observed value
Weight of powdered citrus peel	40 g
Weight of dried extract	8.12 g
Percentage extraction yield	20.3% w/w
Colour	Dark brown
Odour	Characteristic citrus odour
Physical appearance	Semisolid
Solubility in distilled water	Slightly soluble
Solubility in ethanol	Freely soluble
Solubility in methanol	Freely soluble
Reported melting point	120°C
Maximum absorption wavelength (λmax)	517 nm
Calibration curve equation	y = 0.0024x + 0.0542
Coefficient of determination (R^2)	0.9983

Table 3. Preliminary Phytochemical Screening of Citrus Peel Extract

Phytochemical constituent	Test performed	Observation	Result
Alkaloids	Wagner's test	Reddish-brown precipitate	Present (+)
Glycosides	Legal's test	Pink-red colour	Present (+)
Flavonoids	Shinoda test	Pink/reddish-pink colour	Present (+)
Saponins	Foam test	Stable foam layer	Present (+)
Tannins	Qualitative test	Dark blue/greenish-black precipitate	Present (+)
Phenols	Qualitative test	White precipitate	Present (+)
Proteins and amino acids	Biuret test	Positive colour reaction	Present (+)
Carbohydrates	Benedict's test	Red precipitate	Present (+)

Table 4. Physicochemical Evaluation and Drug Content of Buccal Patches

Parameter	F1	F2	F3	F4
Weight (mg)	176.5 ± 2.8	171.2 ± 3.1	178.1 ± 2.5	179.3 ± 2.7
Thickness (mm)	0.21 ± 0.01	0.30 ± 0.02	0.33 ± 0.01	0.36 ± 0.02
Moisture content (%)	5.21 ± 0.19	4.82 ± 0.17	4.26 ± 0.15	4.13 ± 0.13
Surface pH	6.45 ± 0.04	6.52 ± 0.05	6.60 ± 0.03	6.68 ± 0.04
Folding endurance (folds)	228 ± 5	254 ± 7	281 ± 6	290 ± 8
Tensile strength (MPa)	1.48 ± 0.05	1.72 ± 0.04	2.01 ± 0.06	2.34 ± 0.05
Percentage elongation (%)	24.2 ± 1.1	27.8 ± 0.9	30.6 ± 1.2	35.4 ± 1.3
Drug content (%)	96.12 ± 0.91	97.46 ± 0.84	98.53 ± 0.73	98.91 ± 0.65

Table 5. In Vitro Cumulative Drug Release and Antifungal Activity

A. Cumulative drug release (%)

Time (hours)	F1 (%)	F2 (%)	F3 (%)	F4 (%)
0.5	15.8	13.2	11.4	9.8
1	28.6	25.1	21.9	18.4
2	44.3	39.6	35.8	31.2
3	59.8	54.2	49.6	44.8
4	73.1	67.8	63.4	58.5
5	84.5	80.3	75.8	70.4
6	91.6	88.1	84.2	79.6
7	96.8	94.2	91.3	87.5
8	99.2	97.4	95.1	92.8

B. Antifungal activity against Candida albicans

Test formulation	Zone of inhibition (mm)	Interpretation
Optimized F3 patch	20.9 ± 0.7	Antifungal activity observed
Clotrimazole standard	25.4 ± 0.6	Greater inhibition than F3
Blank buccal patch	0 mm	No inhibition observed

Figure:1. Calibration curve of citrus peel extract

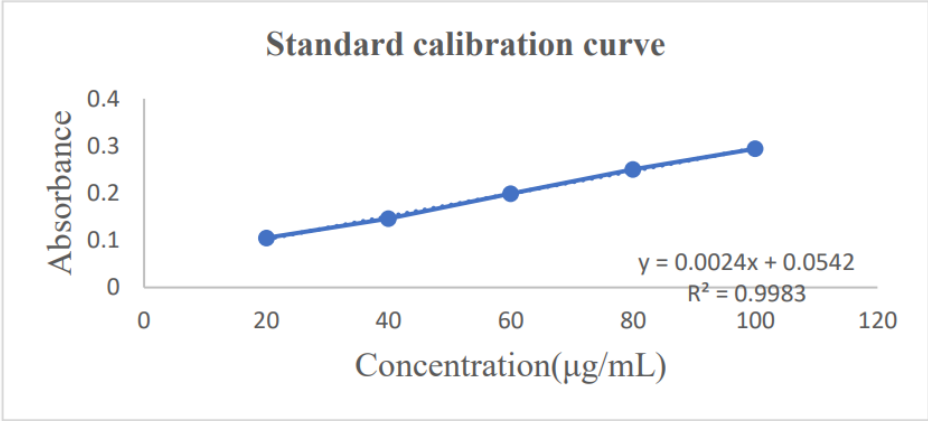


Figure: 2. FTIR spectrum of Citrus peel extract

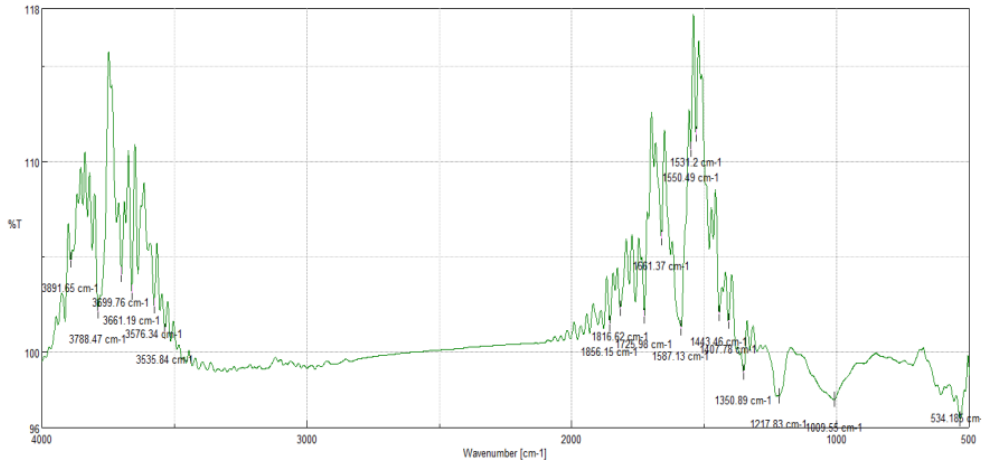
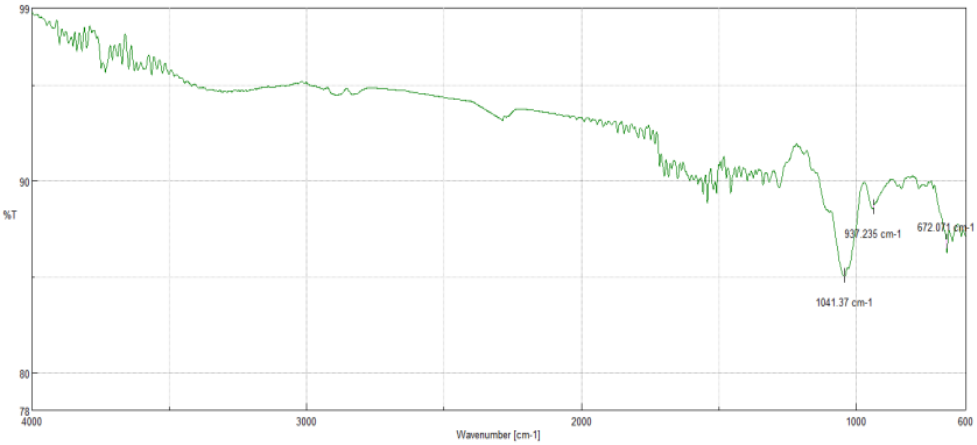


Figure: 3. FTIR spectrum of HPMC E15



Four buccal patch formulations (F1, F2, F3, and F4) were prepared using the solvent casting method by varying the proportions of HPMC E15 and chitosan while maintaining a constant quantity of citrus peel extract (100 mg). HPMC E15 served as the film-forming polymer, whereas chitosan was incorporated to provide mucoadhesive properties. Glycerin was used as a plasticizer to improve the flexibility of the prepared patches. The concentration of HPMC E15 decreased from 450 mg in F1 to 300 mg in F4, while the chitosan concentration increased from 150 mg to 300 mg. The total polymer concentration remained constant at 600 mg across all formulations. This systematic variation allowed the influence of polymer composition on the physical characteristics, mechanical strength, flexibility, and release behaviour of the patches to be evaluated.

The hydroethanolic extraction of citrus peel powder using 70% ethanol yielded 8.12 g of dried extract from an initial quantity of 40 g of powdered material, corresponding to an extraction yield of 20.3% w/w. The obtained extract was dark brown in colour, possessed a characteristic citrus odour, and had a semisolid appearance. Solubility testing demonstrated that the extract was slightly soluble in distilled water but freely soluble in ethanol and methanol. The reported melting point was 120°C. UV–Visible spectrophotometric analysis identified the maximum absorption wavelength (λmax) at 517 nm, which was used for subsequent quantitative estimation. The calibration curve was constructed using concentrations ranging from 20 to 100 µg/mL, and the reported regression equation was $y = 0.0024x + 0.0542$, with a coefficient of determination (R^2) of 0.9983.

Preliminary phytochemical screening demonstrated the presence of several classes of phytoconstituents in the hydroethanolic citrus peel extract. Alkaloids were detected by Wagner's test, which produced a reddish-brown precipitate, while the glycoside test showed a pink-red colour reaction. Flavonoids were identified by the Shinoda test through the development of a pink or reddish-pink colour. Saponins were detected by the formation of a stable foam layer, and tannins produced a dark blue or greenish-black precipitate during qualitative testing. Phenolic compounds were reported as present based on the formation of a white precipitate. The Biuret test indicated the presence of proteins and/or amino acids, while Benedict's test produced a red precipitate, suggesting the presence of carbohydrates. Overall, the screening results indicated that the extract contained multiple classes of phytoconstituents that could contribute to its biological properties.

The prepared buccal patches demonstrated acceptable physical and mechanical characteristics, although differences were observed among the four formulations. The mean patch weight ranged from 171.2 ± 3.1 mg in F2 to 179.3 ± 2.7 mg in F4. Thickness increased progressively from 0.21 ± 0.01 mm in F1 to 0.36 ± 0.02 mm in F4. Moisture content decreased from 5.21 ± 0.19% in F1 to 4.13 ± 0.13% in F4, indicating lower residual moisture in formulations containing higher concentrations of chitosan. Surface pH values ranged from 6.45 ± 0.04 to 6.68 ± 0.04, remaining within a relatively narrow range. Folding endurance increased from 228 ± 5 folds in F1 to 290 ± 8 folds in F4, while tensile strength increased from 1.48 ± 0.05 MPa to 2.34 ± 0.05 MPa. Percentage elongation also increased from 24.2 ± 1.1% to 35.4 ± 1.3%. These findings suggest that increasing the proportion of chitosan was associated with improved mechanical strength, folding endurance, and elasticity. Drug content ranged from 96.12 ± 0.91% in F1 to 98.91 ± 0.65% in F4, with F3 showing a drug content of 98.53 ± 0.73%.

The in vitro drug release study demonstrated a gradual increase in cumulative extract release from all four formulations over the eight-hour observation period. At 30 minutes, cumulative release was 15.8% for F1, 13.2% for F2, 11.4% for F3, and 9.8% for F4. Release increased progressively with time, reaching 99.2%, 97.4%, 95.1%, and 92.8% for F1, F2, F3, and F4, respectively, at eight hours. F1 exhibited the highest cumulative release, whereas F4 showed the lowest release throughout the observation period. F3 demonstrated an intermediate release profile, with 95.1% cumulative release at eight hours. The antifungal evaluation showed that the optimized F3 formulation produced a zone of inhibition of 20.9 ± 0.7 mm against Candida albicans. In comparison, the clotrimazole standard produced a zone of inhibition of 25.4 ± 0.6 mm, while the blank buccal patch showed no inhibition. These findings indicate that the extract-loaded patch exhibited measurable antifungal activity under the experimental conditions, and the absence of inhibition with the blank patch suggests that the activity was associated with the extract rather than the polymeric base alone.

The study demonstrated the feasibility of preparing citrus peel extract-loaded buccal patches using HPMC E15 and chitosan through the solvent casting method. The extract yield was 20.3% w/w, and qualitative phytochemical screening indicated the presence of several classes of phytoconstituents. All four formulations showed relatively consistent drug content and measurable mechanical properties. F3, containing 350 mg of HPMC E15 and 250 mg of chitosan, was selected as the optimized formulation because of its overall balance of physicochemical properties, drug content of 98.53 ± 0.73%, cumulative release of 95.1% at eight hours, and antifungal zone of inhibition of 20.9 ± 0.7 mm.

DISCUSSION

The present study was undertaken to formulate and evaluate buccal patches containing citrus peel extract for the potential management of oral candidiasis. Four formulations (F1–F4) were prepared using different proportions of HPMC E15 and chitosan while maintaining the citrus peel extract content at 100 mg and the total polymer quantity at 600 mg. HPMC E15 decreased from 450 mg in F1 to 300 mg in F4, whereas chitosan increased from 150 mg to 300 mg. This approach allowed the influence of polymer composition on patch characteristics to be explored. The importance of selecting an appropriate combination of film-forming and mucoadhesive polymers has also been demonstrated in previous buccal-film research. Mahapatra et al. reported that HPMC and chitosan combinations could produce films with satisfactory physical characteristics, mechanical strength, and controlled drug release [11]. Similarly, Thorat and Sarankar observed that polymer composition influenced the mechanical characteristics and drug-release behaviour of chitosan-containing buccal films [12]. In the present study, F3 was selected as the optimized formulation,

suggesting that a balanced proportion of HPMC E15 and chitosan may provide a suitable combination of flexibility, strength, and extract release.

The extraction process produced 8.12 g of dried extract from 40 g of powdered citrus peel, corresponding to a yield of 20.3% w/w. The extract was described as dark brown, citrus-scented, and semisolid. It was slightly soluble in water and freely soluble in ethanol and methanol. These characteristics provide preliminary information about the physical nature and solvent compatibility of the extract, which are relevant when selecting an extraction method and preparing a polymeric formulation. Liu et al. investigated citrus peel extracts obtained using different food-compatible solvents and reported that the extract composition and antifungal performance varied with citrus species and extraction conditions [13]. Their findings support the importance of standardizing the source material and extraction procedure when developing citrus-derived preparations. In the present study, the reported absorption maximum of 517 nm and calibration-curve equation (\(y = 0.0024x + 0.0542\), \(R^2 = 0.9983\)) indicate a strong linear relationship across the tested calibration range.

Qualitative phytochemical screening indicated the presence of alkaloids, glycosides, flavonoids, saponins, tannins, phenols, proteins or amino acids, and carbohydrates. The detection of flavonoids and phenolic compounds is particularly relevant because these classes include substances that have been investigated for biological activities, including antimicrobial and antioxidant effects. Liu et al. reported that citrus peel extracts contained phenolic constituents and that antifungal activity differed according to the extraction solvent and the composition of the resulting extract [13]. This provides a possible rationale for further investigation of citrus peel extract as a component of a local oral formulation. However, the positive qualitative tests in the present study do not identify individual molecules, quantify their concentrations, or demonstrate which compounds contribute to antifungal activity. In addition, the presence of a phytochemical class should not be considered proof of effectiveness against Candida albicans.

The physicochemical evaluation demonstrated that all four formulations possessed measurable weight, thickness, moisture content, surface pH, folding endurance, tensile strength, percentage elongation, and extract content. The patch weight ranged from 171.2 ± 3.1 mg to 179.3 ± 2.7 mg, while thickness increased from 0.21 ± 0.01 mm in F1 to 0.36 ± 0.02 mm in F4. This increase occurred alongside the progressive rise in chitosan content, although the present data alone cannot establish that chitosan was the sole cause. Moisture content decreased from 5.21 ± 0.19% to 4.13 ± 0.13%, while surface pH ranged from 6.45 ± 0.04 to 6.68 ± 0.04. These pH values are close to neutral and may be favourable for buccal application, although direct mucosal-irritation testing would be needed to establish tolerability. Hassan et al. demonstrated that polymer grade and concentration can influence film thickness, moisture content, mechanical strength, and mucoadhesive performance [14]. Nair et al. also emphasized the importance of assessing surface pH, flexibility, folding endurance, and drug content when developing buccal films [15].

Folding endurance increased from 228 ± 5 folds in F1 to 290 ± 8 folds in F4. Similarly, tensile strength increased from 1.48 ± 0.05 MPa to 2.34 ± 0.05 MPa, and percentage elongation increased from 24.2 ± 1.1% to 35.4 ± 1.3%. These findings indicate that the formulations containing higher proportions of chitosan exhibited greater resistance to repeated folding and improved measured mechanical performance. Thorat and Sarankar likewise reported that chitosan concentration influenced the mechanical properties of mucoadhesive films [12]. Hassan et al. also identified polymer concentration as an important factor affecting film quality [14]. Nevertheless, a mechanically stronger patch is not automatically the most suitable for oral use; flexibility, comfort, adhesion, residence time, and ease of removal should also be considered. The drug-content values ranged from 96.12 ± 0.91% in F1 to 98.91 ± 0.65% in F4, with F3 showing 98.53 ± 0.73%.

The in vitro release results showed a progressive increase in cumulative release over the eight-hour observation period. F1 released 15.8% at 0.5 hours and 99.2% at eight hours, whereas F4 released 9.8% and 92.8% at the corresponding time points. F3 showed 11.4% release at 0.5 hours, increasing to 95.1% at eight hours. The comparatively slower initial release from formulations with higher chitosan content may reflect differences in hydration, polymer-network structure, and diffusion pathways. This interpretation is consistent with research showing that the composition and concentration of polymers can modify release from buccal films. Mahapatra et al. demonstrated matrix-controlled release from HPMC–chitosan films [11], while Nair et al. reported that the combination of film-forming and mucoadhesive polymers influenced the release behaviour of rizatriptan buccal films [15]. The present results suggest that the citrus peel extract could be released progressively from the prepared patches under the tested in vitro conditions.

The optimized F3 patch produced a reported zone of inhibition of 20.9 ± 0.7 mm against Candida albicans, compared with 25.4 ± 0.6 mm for the clotrimazole standard. The blank patch produced no inhibition. The absence of inhibition with the blank formulation suggests that the observed activity was associated with the extract-containing formulation rather than the patch base alone, although this interpretation depends on the adequacy of the controls and the experimental method. The smaller inhibition zone for F3 than for clotrimazole indicates that the patch did not produce an equivalent zone of inhibition under the reported test conditions.

Liu et al. reported antifungal activity from citrus peel extracts against Aspergillus flavus, with differences according to citrus type, extraction solvent, and phenolic composition [13]. Because A. flavus is not C. albicans, that study provides only indirect support for the biological potential of citrus-derived extracts. Siregar et al. investigated a different fruit-peel extract against C. albicans, illustrating the broader research interest in evaluating peel-derived materials as possible antifungal agents [16].

Taken together, the findings indicate that citrus peel extract could be incorporated into HPMC E15–chitosan buccal patches with satisfactory measured physicochemical properties, high extract content, progressive in vitro release, and preliminary antifungal activity. F3 showed a combination of relatively high extract content (98.53 ± 0.73%), 95.1% cumulative release at eight hours, and an inhibition zone of 20.9 ± 0.7 mm. These results support its selection for further investigation, but do not establish clinical effectiveness. The study did not report statistical comparisons or p-values, so differences between formulations should be described as observed trends rather than statistically significant effects.

Begum and Alqahtani also reported satisfactory physical characteristics and release behaviour in polymer-based bilayer buccal films, supporting the need to assess multiple formulation parameters rather than relying on a single outcome [17]. Jin et al. demonstrated the feasibility of developing mucoadhesive patches for targeted delivery in the oral cavity, although their formulation and therapeutic target differed from the present study [18]. Research on other polymeric buccal-film systems has further emphasized the relationship between polymer composition, film performance, and drug-release characteristics [19,20].

CONCLUSION

The present study successfully formulated and evaluated citrus peel extract-loaded buccal patches for the potential management of oral candidiasis. Four formulations (F1–F4) were prepared using varying proportions of HPMC E15 and chitosan. The extraction process yielded 20.3% w/w, and preliminary phytochemical screening revealed the presence of flavonoids, phenols, tannins, and other phytochemical constituents. The prepared patches demonstrated acceptable physicochemical characteristics, with drug content ranging from 96.12% to 98.91%, surface pH between 6.45 and 6.68, and satisfactory mechanical properties. Formulation F3 was selected as the optimized formulation, exhibiting 98.53 ± 0.73% drug content and 95.1% cumulative release at eight hours. It also demonstrated antifungal activity against Candida albicans, producing an inhibition zone of 20.9 ± 0.7 mm. These findings indicate promising preliminary potential for localized antifungal delivery.

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