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RESEARCH ARTICLE

Development and Evaluation of Combined Effect Buccal Films for Treatment of Oral Candidiasis

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Abstract

Buccal film formulations, including antifungal nystatin, anti-inflammatory agent hydrocortisone acetate, and local anesthetic lidocaine hydrochloride for pain relief, were developed. Bioadhesive films were fabricated with hydrophilic polymers, hydroxyethyl cellulose (HEC), and xanthan gum (XG) and dried in the incubator. Textural, swelling, and bioadhesive properties, physicochemical and *in vitro* release characteristics, and antifungal activities of bioadhesive films were evaluated. Bioadhesive films significantly extended nystatin release by prolonging retention time of the target area formulation while rapidly releasing hydrocortisone acetate and lidocaine HCl, reducing drug administration. The polymer type affected bioadhesion strength and erosion ratio, and XG formulations had more polymer suitability. Consequently, XT-O2 formulation that was prepared with xanthan gum and tween 80, was best for its highest antifungal film activity (20.00 ± 0.07 mm), released nystatin (44.296% ± 1.695), and lowest erosion matrix (36.719% ± 0.249). The selected formulation can be used for compatibility, stability and *in vivo* studies targeted oral candidiasis infections.

Keywords buccal drug delivery · hydrocortisone acetate · lidocaine hydrochloride · mucoadhesive film · nystatin · oral candidiasis · xanthan gum

Introduction

Candidiasis is by far the most common opportunistic infection among patients with HIV/AIDS infections due to the suppression of the immune system and, in particular, to the use of antitumor drugs among cancer patients. The majority of these infections are caused by *Candida albicans*. Oral candidiasis is a commonly occurring local candida infection [1]. During treatment, reducing and alleviating the pain and inflammation that occur are of utmost importance while also trying to suppress the cause of the disease. The combined treatment of antifungal, anti-inflammatory, and local anesthetic drugs is a promising treatment options for oral candidiasis.

Antifungal drugs are used in the treatment of oral candidiasis [2]. The often preferred and commonly used antifungal drugs administered orally in conventional treatment are amphotericin B and fluconazole [3]. However, some studies have identified the development of resistance to these drugs [4]. In addition, their systemic administration in treatment exposes the organism to toxicity due to the toxic properties of antifungal agents. Some studies have shown that local antifungal treatments deliver more effective healing of oral candidiasis than systemic treatment [5]. Nystatin is only used through local administration (i.e., 2–4 mg/kg daily dose) due to its poor oral absorption properties and toxicity which arises when used systematically[6]. Nystatin is used solely for oral fungal infections as it lacks absorption properties in the stomach. Therefore, both gel and oral suspension forms of nystatin are available. However, the fast release of the drug from the formulation in the mouth presents a disadvantage in treatment. For treatments with nystatin to be successful, its concentration in the saliva should be higher than the minimum inhibitory concentration. Therefore, we decided to use nystatin, a polyene macrolide derivative antifungal drug, topically to obtain local action in the buccal area in our study.

Thus, while providing antifungal treatment, the intention was to also treat other symptoms caused by the fungal

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infection. The chosen other active ingredients were hydrocortisone acetate for suppressing the *Candida albicans* inflammation occurring in the mouth and the local anesthetic lidocaine hydrochloride for pain relief. Lidocaine, which is a compound in a structure of amino-amides, has been used as a local anesthetic for many years. The efficacy profile of the drug as a local anesthetic, characterized by a rapid onset of action and its distribution over tissue with a prolonged, stronger effect, suggested that lidocaine was a good candidate for this study [7]. Used for its anti-inflammatory property, hydrocortisone is one of the most important natural glucocorticoids released by the adrenal cortex. Hydrocortisone is administered orally, parentally, and locally, and its anti-inflammatory properties represents its most important pharmacological activity [8].

This study focuses on the development of buccal bioadhesive formulations with increasing duration times of nystatin and other active ingredients (hydrocortisone acetate and lidocaine HCl) in the buccal area while quick onset of action was observed with lidocaine and hydrocortisone acetate. Drug release from buccal films, formulated with mucoadhesive polymers, were delayed as predicted [9]. Mucoadhesive polymers are particularly suitable for the development of bioadhesive formulations [10–12]. The present study was developed and optimized becoming the first combined buccal film formulation for *Candida albicans* by using xanthan gum (XG) and hydroxyethyl cellulose (HEC) as a matrix polymer.

The aim of our study is to improve and prolong the antifungal effect of nystatin, the inflammation suppressing effect of hydrocortisone, and the pain relief effect of lidocaine HCl The urgent need for a combined treatment model of oral candidiasis suitable for clinical use has been acknowledged. The objective in the next phase of this study is to conduct clinical studies on the best film formulation chosen and to prove its efficacy. As a result of these studies, the selected formulation is likely to find a place in the commercial market. This study is significant as it offers innovation in the treatment of oral *Candida albicans*.

Materials and Methods

Nystatin (PubChem CID: 71,308,475) was kindly provided by Deva Pharmaceutical Company (Istanbul, Turkey) while Embil Pharmaceutical Company (Istanbul, Turkey) supplied hydrocortisone acetate (PubChem CID: 5744). Lidocaine HCl (PubChem CID: 6314) was offered by the PharmaVision Pharmaceutical Company (Istanbul, Turkey). HEC (PubChem CID: 24,846,132) (250.000 Mw, 145 mPas, 1% in H_2O (20°C)) was purchased from Sigma-Aldrich (Germany), and XG (PubChem CID: 7107) (1000–1400 mPas, 1% in H2O (20°C)) solution was purchased from the Doğa Drug Company (Istanbul, Turkey). All other chemicals were of analytical reagent quality.

Preparation of Mucoadhesive Films

Our preliminary assessment determined that XG and HEC were the most suitable "candidate" polymers requiring detailed studies in regard to their bioadhesive suitability [13]. Table I displays the formulation used in the preparation of buccal films. To generate the films, different amounts of each film-forming polymer HEC (2.5 and 3.0%, w/v) and XG (2.8 and 3.0%, w/v) were gradually added to the required amount of water while stirring continuously. The medicated gel was left at room temperature overnight to ensure a clear, bubble-free gel. Lidocaine HCl (0.8%, w/v) was dissolved in distilled water. Nystatin (0.5%, w/v) and hydrocortisone acetate (0.4%, w/v) were dissolved in ethyl alcohol (8%, w/v). Tween 80 (6%, w/v) or Cremophor RH40® (2% and 6%, w/v) were chosen as formulation components to enhance the solubility of nystatin and were added to the alcohol phase. The plasticizing agent propylene glycol (PG, 6% and 10%, w/v) was also added to this solution. In the first phase, water was added to the polymeric solution, and then the mixture was combined with alcohol. The obtained gel (25 g) was cast into a glass petri dish ($r = 9$ cm) and allowed to dry at 40°C in the incubator until a flexible film was formed. After drying, the films were wrapped in aluminum foil, suspended in a desiccator at room temperature with a relative humidity of 40%, and then used for experiments within 24 h. Table I shows the formulation and the ingredients used to prepare the mucoadhesive buccal films.

Quantification of Nystatin, Hydrocortisone Acetate, and Lidocaine

A reversed-phase high-performance liquid chromatographic method which is able to detect nystatin, hydrocortisone acetate, and lidocaine was developed and validated for the quantification. SHIMADZU system equipped with photodiode array detector, auto sampler, quaternary pump, and column oven was utilized. The analysis was achieved using C18 column (150 mm × 4.6 mm, 5 µm) at 30° C. The mobile phase consisted of 60:40 mixture of methanol/0.1 M Na_2HPO_4 with diluted phosphoric acid to pH 4.5 at a flow rate of 1 mL min^{-1}. The injection volume was 10 µL and the detection wavelength was 230 nm. The method was validated for linearity, specificity, precision, and accuracy. [14].

Physicochemical Characterization of Buccal Films

The thickness, weight, and drug content of the buccal films were assessed based on at least 6 films, and the results are expressed as the mean and standard deviation.

The thicknesses of the films at five different locations (center and four corners) were measured using a digital micrometer (QLR digit, IP4, PRC), and the mean thickness

Table I The Formulation used in the Preparation of Mucoadhesive Buccal Films Included Nystatin, Hydrocortisone, and Lidocaine HCl (w/w %)

Formulation	Nystatin*	Hydrocortisone* acetate	Lidocaine HCl*	Hydroxyethyl cellulose*	Xanthan gum*	Propylene glycol*	Cremophor RH 40*	Tween 80*	Ethanol*
HC-O1	0.5	0.4	0.8	2.5	–	6	2	–	8
HC-O2	0.5	0.4	0.8	3.0	–	6	2	–	8
HC-O3	0.5	0.4	0.8	2.5	–	10	2	–	8
HC-O4	0.5	0.4	0.8	3.0	–	10	2	–	8
XC-O1	0.5	0.4	0.8	–	2.8	6	6	–	8
XC-O2	0.5	0.4	0.8	–	3.0	6	6	–	8
XC-O3	0.5	0.4	0.8	–	2.8	10	6	–	8
XC-O4	0.5	0.4	0.8	–	3.0	10	6	–	8
XT-O1	0.5	0.4	0.8	–	2.8	6	–	6	8
XT-O2	0.5	0.4	0.8	–	3.0	6	–	6	8
XT-O3	0.5	0.4	0.8	–	2.8	10	–	6	8
XT-O4	0.5	0.4	0.8	–	3.0	10	–	6	8

*(w/w) %

HC–O formulations have prepared with HEC and Cremophor RH40 and dried by oven, *XC-O* formulations have prepared with XG and Cremophor RH40 and dried by oven, *XT-O* formulations have prepared with XG and Tween 80 and dried by oven

was then calculated. The values were the average of three experiments. To determine the weight homogeneity, 6 different incisions with a diameter of 0.8 cm (0.502 cm^2) were taken from different regions of the film formulations and weighed. The average weight and standard deviation were calculated. Previously measured film was dissolved with simulated saliva. Simulated saliva included potassium dihydrogen phosphate (12 mM), sodium chloride (40 mM), and calcium chloride (1.5 mM), and the pH was adjusted to 6.75 using sodium hydroxide. Samples were filtered through membrane filters (0.45 µM, Millex LH, Billerica, MA, USA), and the concentration of the drug in the medium was assayed using a modified HPLC (Shimadzu LC 20, Kyoto, Japan) method at 230 nm (details given in Sect. 2.2) [14].

In Vitro Release Studies

In vitro release studies of films were evaluated using a USP 23 dissolution test apparatus 5 (paddle over disk) and a dissolution tester (SOTAX, AT7 Smart V 230-Switzerland). The dissolution medium consisted of 500 ml of simulated saliva (pH: 6.75) containing ethyl alcohol (50:1) stored at a temperature of 37 ± 0.5°C and subjected to paddle rotation at a speed of 50 rpm [15–17]. The film was cut into circular pieces with a radius (*r*) of 2 cm each and placed in a self-fabricated basket (50-mm diameter and 6-mm height) made from stainless steel with a sieve opening of 850 µm (size no. 20, USP 23). The basket containing the film was submerged into the dissolution medium. Filtered samples (0.5 ml) were manually collected at intervals of 0 to 8 h [16, 18]. The samples were compensated with an equal volume of simulated saliva suspended at the same temperature. The drug concentration released in the medium was assayed with the HPLC method at 230 nm (details given in Sect. 2.2) [14].

In vitro drugs release data from buccal films were evaluated kinetically using zero-order, first-order, Higuchi, and Korsmeyer–Peppas mathematical models [19–21].

Swelling and Matrix Erosion Studies

For each analyzed film, two separate indications were measured, namely, film swelling (also referred to as hydration) and erosion characteristics. Each film was divided into 4-cm^2 portions (2 × 2 cm), cut, weighed (W1), and immersed in simulated saliva at pH 6.75 for predetermined periods (5, 15, 30, 45, 60, 75, 90, 105, 120, 180, 240, 300, and 360 min) [14]. After immersion, excess surface water was removed from the films using filter paper, and the films were weighed (W2) [22]. Swollen films were dried at 60°C for 24 h, suspended in a desiccator for 48 h, and repeatedly weighed (W3) [23]. The swelling [24] and matrix erosion [25] percentages were calculated using the following equations:

$$\% \text{ Swelling} = \frac{W2 - W1}{W1} \times 100 \quad (1)$$

$$\%\text{Matrix Erosion} = \frac{W1 - W3}{W1} \times 100 \quad (2)$$

Mechanical Properties

The mechanical properties of buccal films were analyzed using a texture analyzer (TA.XT Plus, Stable Micro Systems,

Haslemere, UK) equipped with a 5-kg load cell [14]. Force and elongation were defined according to when the film broke based on a load cell speed of 0.5 mm/s. The film (1 × 3.5 cm) was held between two clamps positioned at a distance of 3 cm. The tensile strength and elongation at the point of breakage were calculated based on the following equations:

$$\text{Tensile Strength (N/mm}^2\text{)} = \text{Breaking force (N)/Cross sectional area of sample (mm}^2\text{)} \quad (3)$$

$$\text{Elongation at Break (\%)} = \left(\frac{\text{Increase in length at breaking point (mm)}}{\text{Initial length (mm)}}\right) \times 100 \quad (4)$$

In Vitro Bioadhesion Test

The bioadhesive strength of the films was evaluated by the Sezer *et al*. method. [26] The measurement was conducted with a texture analyzer (Stable Micro System, Haslemere, Surrey, UK). The bioadhesive strength of the films was measured using a texture analyzer equipped with a 5-kg load cell with bioadhesion test rig while bioadhesive force using porcine buccal mucosa as the model membrane [15, 27] The mucosal membrane was fitted on the bioadhesion test rig and hydrated with a phosphate buffer (pH 6.8) solution at 37°C. A circular piece of film ($r = 1.2$ cm) was attached to the P/10 cylindrical Perspex (Lucite International Ltd., Queens Gate, UK) probe with double-sided adhesive tape. The probe was lowered onto the tissue surface at a constant speed of 1 mm/s and a force of 1 N. After 30 s of contact, the probe was moved upwards at a constant speed of 1 mm/s. The work of adhesion formula (mJ/cm^2) was calculated using the Texture Exponent 2.0.6.0 software package from TA.XT Plus (Stable Micro Systems, Surrey, UK).

Antifungal Activity of Film Formulations Against Candida albicans

The antifungal activity of optimized nystatin-loaded buccal films was evaluated against *Candida albicans* by the disk diffusion method. Standardization of antifungal susceptibility testing has been an area of active research since the availability of reference methods for the testing of yeasts within Clinical and Laboratory Standards Institute guidelines [28]. Sabouraud dextrose agar medium was prepared and autoclaved at a pressure 15 lb^2/inch at a temperature of 121°C. The main culture was diluted to have aliquots corresponding to 10^8 CFU/ml. The sabouraud dextrose agar plates were seeded with the fungal strain (10^8) and allowed to stay on a leveled surface at 37°C for 3 h. Once the medium solidified, a well of 4-mm diameter was cut out of the agar using a sterile borer, and the film was cut into circular pieces, each with a radius (r) of 2 cm, and was placed into the well. The assay plates were incubated for 24 h at 37°C, and the diameter of the inhibition zone was measured. Voriconazole and fluconazole disk (A) is used as a positive control where blank disk is used as a negative control (Fig. 6) [29].

Statistical Analysis

Statistical analyses of *in vitro* studies were performed using parametric one-way ANOVA (GraphPad prism version 8.2). Post hoc analysis among the groups was performed using the Newman-Keuls Multiple Comparison Test. Results are reported as the averages ± SD and $p \leq 0.05$ was considered statistically significant.

Results and Discussion

Preparation and Characterization of Buccal Films

According to our preliminary studies, HEC- or XG-based films were chosen (Table I) [13]. The thickness of the films was between 0.039 and 0.042 mm (HC-O1 to HC-O4) for HEC-based formulations, whereas the thickness of the films was 0.066–0.095 mm (XC-O1 to XC-O4 and XT-O1 to XT-O4) for XG-based formulations (Table II). From these results, we can deduce that the thickness was affected by the viscosity and the type of polymer that was used.

i) Effect of polymer on the viscosity: There are studies that support that the viscosity is a critical process parameter for film thinning properties [30]. The results that were obtained from this study are related to initial gel formulations of XG that were higher (20000cp) than the HEC gel formulations (4400 cp) which is compatible with the literature [31]. Gels should have proper mechanical properties such as good flowability, pour-ability, and spreadability, which specify the viscosity [32]. Due to the higher viscosity of XG-based films, the gels spread out and a highly dense layer forms in the petri dish creating thicker films than HEC-based formulations.
ii) Effect of the polymer type: Although the presence of plasticizer is another factor that affects the thickness, this was shown to be untrue for HEC formulations (Table II). On the other hand, the thickness of XG formulations significantly increased ($p < 0.05$) with increasing amounts of PG (Table II). The reason for this is that the viscous XG becomes even more so with increased PG concentration which changes the flow properties. Similarly, a study performed by Noha *et al*. also compares the effect of polymer type and concentrations on the patch thickness. They also observed that there is a thickness difference among PVC (poly(vinyl chloride)), HEC, and chitosan [32]. The optimal thickness of buccal films is between 0.050- and 0.100-mm range [33, 34].

Thus, this study suggests that all the film formulations in this study are suitable for physical application in terms of thickness and function.

The weight of the formulation prepared with XG (0.128 ± 0.06 to 0.198 ± 0.023 mg) was significantly higher than the HEC formulations (0.076 ± 0.012 to 0.170 ± 0.012 mg). Polymer types caused significant weight differences ($p < 0.05$). For all formulations, the weight variation was found acceptable. These results correlate with current literature [33–35]. In all formulations, the amount of nystatin, hydrocortisone, and lidocaine ranged between 109.555% ± 0.322 and 90.141% ± 1.650 (Table II) that are consistent with recent literature [36, 37].

In Vitro Release Studies and Kinetic Models of Nystatin, Hydrocortisone Acetate, and Lidocaine HCL from Buccal Films

Nystatin Release and Kinetic Models from Buccal Films

Drug release from buccal films depends on polymer composition and nature are verified [9]. In terms of the release profile, nystatin release ranged from 5.328 ± 1.344 to 6.957 ± 1.669% in the first half an hour in HEC films (Fig. 1). By the end of 8 h, the release profile reached its maximum level (22.2 ± 2.130 to 33.037 ± 3.453%). Rapid hydration and gelation process of HEC affects the drug dissolution rate, and nystatin release was shown to be inversely proportional to polymer concentration [15, 38]. Conversely, XG-based films displayed a more sustainable nystatin release than HEC-based films.

Nystatin release from buccal films was between 10.619 ± 0.887% and 25.677 ± 2.241 for the first 30 min. Nystatin reached the maximum level after 4 h (29.539 ± 3.752 to 49.174 ± 2.227%) in the release profile and this level extended for 8 h (34.415 ± 5.365 to 51.246 ± 1.901) (Fig. 1). In addition, the high viscosity of XG affected the *in vitro* release behavior of the drug and this finding matches other literature [33, 39, 40]. The nystatin release of XG-based formulations increased with the highest amount of plasticizer (PG, 10% w/w) (Fig. 1), as PG was found to have a major effect on the release profile. Therefore, it appears that the extent to which the type of active surface agent (RH40 and Tween 80) affected nystatin release depended on the concentration of PG. In a study performed by Chun *et al*., similar findings were reported [41]. Other studies have also confirmed that the amount and type of polymer used with nystatin affects the release profile.

Nystatin release for all buccal film formulations is supported by both the Higuchi and Korsmeyer-Peppas correlations [19, 21]. For these kinetic models, film formulations exhibited strong linear correlations, with r2 values as high as 0.9413, except for XC-O3, XC-O4, XT-O3, and XT-04. The Korsmeyer-Peppas kinetic model is used especially when there are multiple release models for determining which model of release will fit better [21]. We decided to examine whether non-Fickian (diffusion and polymer control) or Fickian diffusion (controlled diffusion) control exists with this kinetic model. In one study performed by Dalia Abouhussein *et al*., depending on the polymer usage and the percentage, the formulations gave either a non-Fickian or Fickian mechanisms. Both mechanisms were possible, but for non-Fickian, the transport occurred as relaxation and diffusion of controlled drug release profiles [42]. Generally, for the Fickian diffusion, the n value equals to less than 0.5 whereas for non-Fickian release this given n value will be within 0.5–1.0 [42]. In our study, the nystatin release from film formulations HC-01, HC-O3, HC-04, and XC-O1 complied with the non-Fickian mechanism

Table II Physicochemical Properties, Drug Content, and Antifungal Activity of the Prepared Bioadhesive Buccal Films Drying by Oven. Values Represent the Mean ± SD ($n = 3$)

Formulations	Thickness (mm)	Weight (g)	Nystatin (%)	Hydrocortisone (%)	Lidocaine (%)	Disk diameter (mm)
HC-O1	0.039 ± 0.002	0.097 ± 0.008	98.069 ± 1.728	96.087 ± 0.87	99.282 ± 4.049	4.50 ± 0.71
HC-O2	0.040 ± 0.002	0.076 ± 0.012	95.699 ± 0.705	95.421 ± 2.139	102.372 ± 5.073	4.50 ± 0.71
HC-O3	0.041 ± 0.002	0.196 ± 0.014	96.189 ± 6.136	92.362 ± 5.108	102.934 ± 4.018	4.50 ± 0.71
HC-O4	0.042 ± 0.002	0.198 ± 0.023	91.113 ± 4.458	93.567 ± 3.816	94.691 ± 3.470	6.33 ± 0.58
XC-O1	0.069 ± 0.004	0.128 ± 0.006	96.443 ± 2.944	90.593 ± 2.829	96.528 ± 1.927	18.00 ± 0.00
XC-O2	0.066 ± 0.004	0.137 ± 0.015	97.647 ± 0.343	98.229 ± 1.150	97.596 ± 0.766	12.67 ± 0.58
XC-O3	0.090 ± 0.006	0.165 ± 0.017	92.493 ± 1.189	98.464 ± 1.927	99.294 ± 3.010	20.00 ± 2.52
XC-O4	0.095 ± 0.006	0.170 ± 0.019	91.428 ± 1.567	104.638 ± 6.024	102.282 ± 3.858	21.67 ± 2.08
XT-O1	0.069 ± 0.004	0.130 ± 0.004	93.154 ± 2.781	105.328 ± 2.331	109.878 ± 2.961	20.50 ± 0.71
XT-O2	0.066 ± 0.004	0.141 ± 0.012	93.136 ± 4.281	91.445 ± 1.007	98.975 ± 0.712	20.00 ± 0.07
XT-O3	0.090 ± 0.006	0.170 ± 0.012	91.367 ± 2.682	99.814 ± 1.127	102.106 ± 2.844	18.67 ± 1.15
XT-O4	0.095 ± 0.006	0.167 ± 0.013	90.036 ± 0.430	94.855 ± 3.762	94.583 ± 2.709	17.00 ± 1.00

while the remaining formulations complied with the Fickian release mechanism. In the case of non-Fickian diffusion, the swelling, diffusion, and slow erosion that occurs is the mechanism of release for the active substances [43]. In addition, this result suggests that nystatin partly diffuses through the swollen polymer matrix and the gradually expanding hydrated matrix with an increasing diffusion path length. Liquid diffusion and polymeric chain relaxation rates are among the important factors that affect the release kinetics of the polymeric chains. When liquid diffusion and polymer relaxation rates are of the same order of magnitude, anomalous, or non-Fickian diffusion is observed [44]. Singh reported similar observations using buccal bioadhesive film formulations of clotrimazole [34]. Lina Winarti *et al*. also mentions consistent characterization of non-Fickian diffusion release in their study for diltiazem hydrochloride mucoadhesive buccal films [45].

Hydrocortisone Acetate Release and Kinetic Models from Buccal Films

The range of hydrocortisone release in XG-based formulations was found to be higher (18.956 ± % to 23.552 ± 2.738%) than for HEC-based films (9.168 ± 4.910 to 16.20 ± 3.391%) in the first 30 min (Fig. 2). By the end of 5 h, the release profile reached its maximum level (43.472 ± 6.050 to 80.385 ± 8.651%) for all formulations, and this release level increased until the end of 8-h period. The amount of PG did not affect the hydrocortisone release for all film formulations. This may be due to the molecular weight of the active substance [46]. Similarly, it was observed that the surface agents (RH40 and Tween 80) within the film formulations did not affect the hydrocortisone release profile. Nevertheless, since the amount of PG used spaces apart the chains of polymers, they do have a crucial role in determining the flexibility of the films [46]. The release rates and determination coefficients of hydrocortisone films determined that all formulations complied with the Higuchi release kinetic [18] and the Korsmeyer Peppas kinetic ($r^2 > 0.9$) models. The determination of the hydrocortisone releases kinetic of the films showed that the formulations XC-O2 complied with the Fickian release mechanism while all other formulations complied with the non-Fickian mechanism. In terms of buccal formulations, literature findings have generally favored non-Fickian release mechanism to achieve controlled diffusion profiles [47].

Lidocaine HCl Release and Kinetic Models from Buccal Films

The lidocaine HCl release in all formulations was higher than 45.105% in the first 30 min and exceeded 81.269% within 3 h (Fig. 3). After 8 h, the release profile reached its maximum level (85.273 ± 5.146 to 98.386 ± 8.406%). This highest amount of lidocaine HCl release showed that increasing the water-soluble content within the release medium accelerated the dissolution ratio of the highly water-soluble drugs from the film formulations [20]. For patient compliance, higher amounts of the lidocaine HCl release are desired for treatment of oral candidiasis. Due to their fast release pattern, lidocaine films do not comply with any release kinetic.

Swelling and Matrix Erosion Studies of Buccal Films

The degree of the films' hydration influences mucoadhesive strength. The polymer chain structure such as relaxation and interpenetration capacity is defined by the hydration of the polymer within the films [12]. HEC is a hydrophilic cellulose ether polymer, and it swells in an aqueous solution.

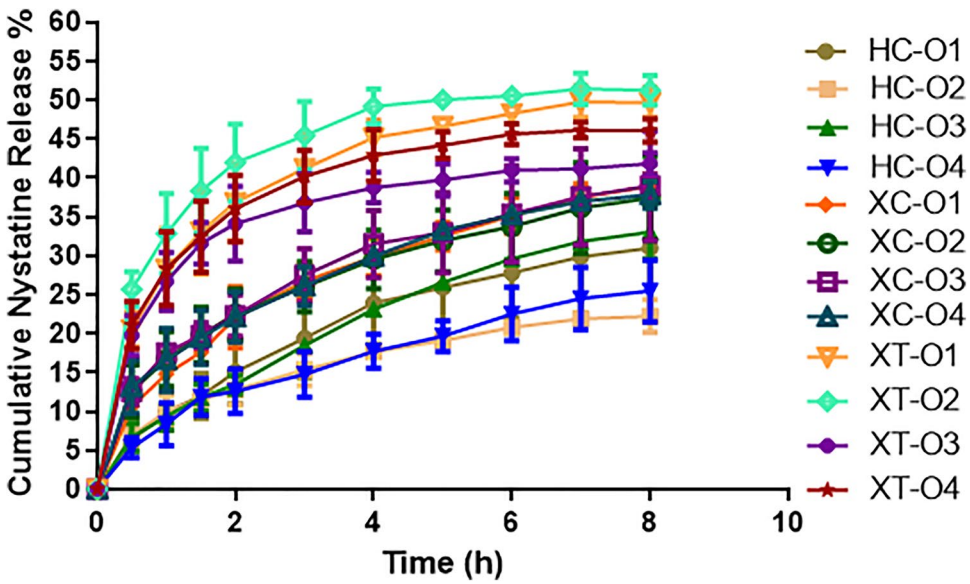

Fig. 1 Nystatin release from mucoadhesive films formulations prepared using HEC (HEC–O1 to HEC–O4) and Xanthan gum (XC-O1 to XC-O4 and XT-O1 to XT-O4) and dried by oven through 8 h. Each patch formulation contains the same amount of nystatin (50 mg) as active and different-ratio propylene glycol (6% and %10 PG, w/w) as the plastifian agent ($n = 3$)

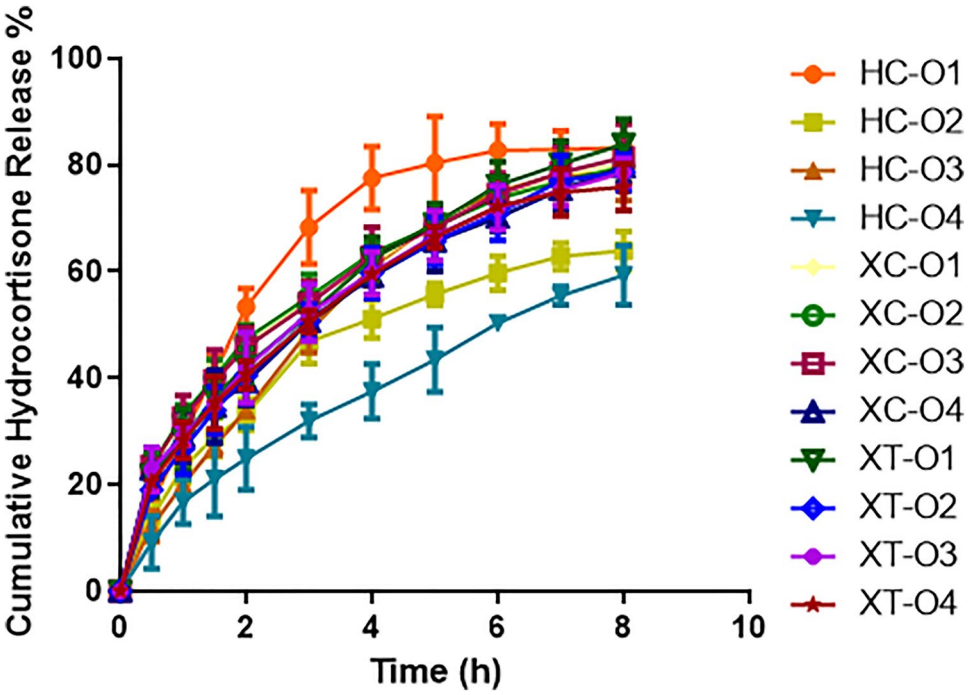

Fig. 2 Hydrocortisone release from mucoadhesive films formulations prepared using HEC (HEC–O1 to HEC–O4) and xanthan gum (XC-O1 to XC-O4 and XT-O1 to XT-O4) and dried by oven through 8 h. Each patch formulation contains the same amount of hydrocortisone (40 mg) as active and different-ratio propylene glycol (6% and %10 PG, w/w) as the plastifian agent ($n=3$)

HEC has also shown to have hydrogel-forming properties which in turn is a necessity to achieve a mucoadhesion character in the formulation [48]. The HEC-based and XG-based films reached a maximum swelling ratio of $87.53 \pm 3.58\%$ and 64.01 ± 2.05 for 5 min, respectively (Fig. 4). The swelling continued until the end of the 6 h for all the formulations (Fig. 4). This finding is consistent with the literature [33]. When the films are treated with water, first swelling starts then binding settings and finally adhesion appears. However, in some cases, the adhesion may decrease due to the disentanglement and deformation of the overhydrated polymers [49]. This study shows that HEC could cause the "disentanglement effect" in connection with hydration.

Film erosion is directly proportional to the excessive amount of swelling due to the fact that the optimum amount of water absorption is required. Matrix erosion (%) of the film formulations was similar for both polymer types (Fig. 5). On the other hand, the matrix erosion ratio increased by increasing the amount of PG for all formulations. The higher value of folding endurance is the presentation of flexible and soft films, which is directly affected by the type of PG and polymer used in the study [50]. There

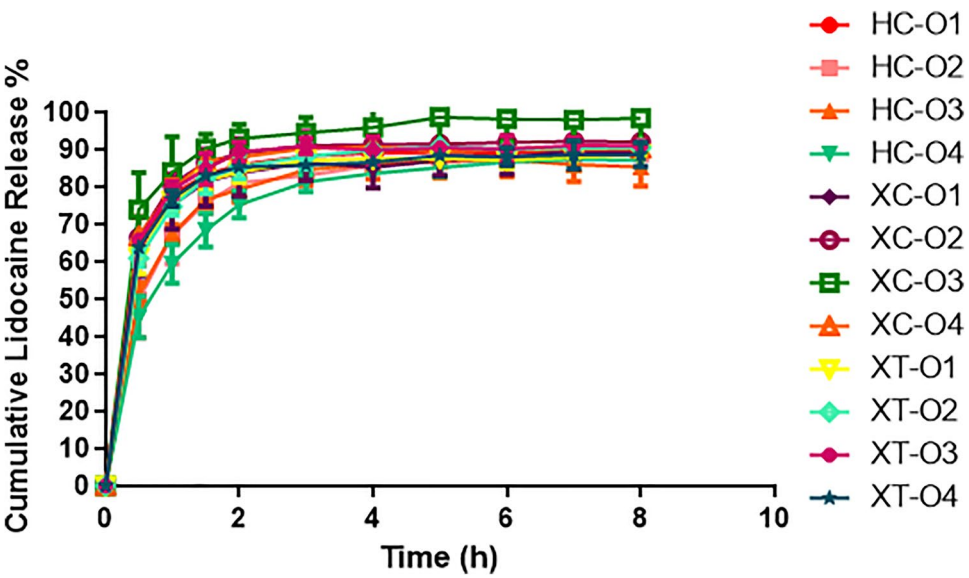

Fig. 3 Lidocaine HCl release from mucoadhesive films formulations prepared using HEC (HEC–O1 to HEC–O4) and xanthan gum (XC-O1 to XC-O4 and XT-O1 to XT-O4) and dried by oven through 8 h. Each patch formulation contains the same amount of lidocaine HCl (80 mg) as active and different-ratio propylene glycol (6% and %10 PG, w/w) as the plastifian agent ($n=3$)

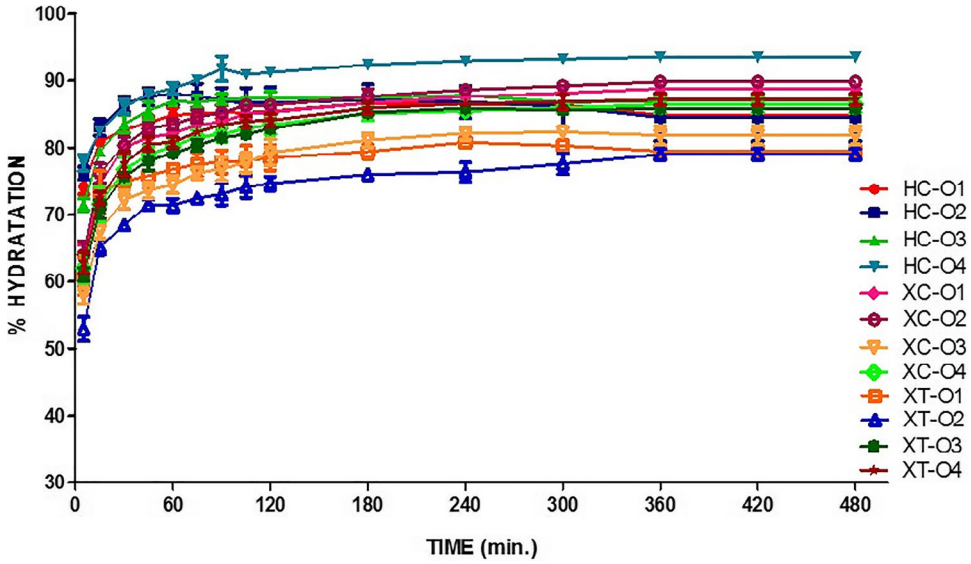

Fig. 4 Swelling index of mucoadhesive films prepared using HEC (HEC–O1 to HEC–O4) and xanthan gum (XC-O1 to XC-O4 and XT-O1 to XT-O4) and dried by oven through 8 h. The different-ratio propylene glycol (6% and %10 PG, w/w) was used as the plastifian agent. Each film was divided into 4 $cm.^2$ proportions (2 × 2 cm) and cut, weighed (W1), and immersed in simulated saliva fluid at pH 6.75 for predetermined periods of time. After immersion, the films were wiped off from the excess surface water using filter paper and weighed (W2) ($n = 3$)

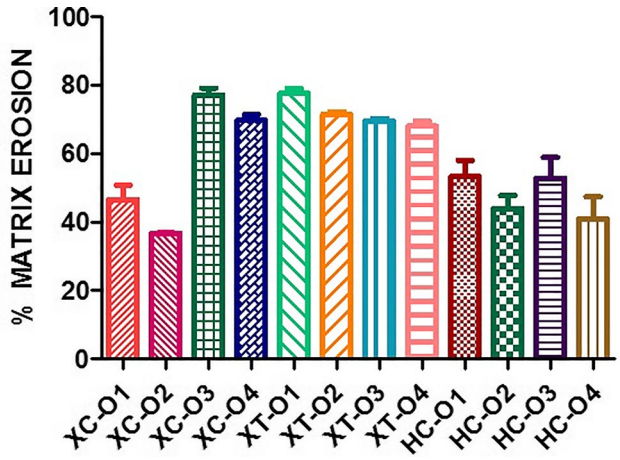

Fig. 5 Matrix erosion of these mucoadhesive films prepared using HEC (HEC–O1 to HEC–O4) and xanthan gum (XC-O1 to XC-O4 and XT-O1 to XT-O4) and dried by oven after 24 h. The difference-ratio propylene glycol (6% and %10 PG, w/w) was used as the plastifian agent. Each film was divided into 4 $cm.^2$ portions (2 × 2 cm) and cut, weighed (W1) and immersed in simulated saliva fluid at pH 6.75 for predetermined periods of time. After immersion, the swollen films were dried at 60°C for 24 h and kept in a desiccator over 48 h and weighted (W3) ($n = 3$)

are similar studies in the literature where use of different concentrations of PG has modified the mechanical properties of the films and cause noticeable variations in the overall texture [51].

Mechanical Properties of Buccal Films

The tensile strength is the stretching force necessary to induce a break [39]. In this study, XG-based films were shown to have higher mechanical strength (1.216 ± 0.018 to 2.507 ± 0.047 N/cm^2) than HEC-based films (0.611 ± 0.058 to 0.759 ± 0.069 N/cm^2) (Table III) due to the fact that they are more resistant to tension stress. The elongation at the break (EB) gives an idea about elasticity of films. It is estimated that maximum film length's changing before breaking [39]. The polymer types and plasticizing agent are influenced on the elongation percentage of the films [30]. The EB results indicate that elasticity value of the HEC films (5.340 ± 0.041 to 6.537 ± 0.025%) were approximately ten-fold higher than XG films 0.564 ± 0.089–1.587 ± 0.076% ($p < 0.05$) (Table III). The elasticity values were not directly proportional to the mechanical strength values of the formulations. Resistance to breakage or deformation decreased with increased elasticity. Baus *et al*. (2019) has utilized from the total work of adhesion, maximum detachment force, and deformation to failure parameters, in order to evaluate the mucoadhesive strength of the gel formulations prepared with HEC and xanthan polymers. This in turn has revealed that due to the adhesive properties of HEC, a higher mechanical strength and less deformation failure was observed. These findings are consistent with previous literature [52, 53]. The elasticity value of the films, which contained HEC as the polymer, was significantly ($p < 0.05$) higher (5.340 ± 0.041–6.537 ± 0.025%) compared with all the other formulations (Table III).

In Vitro Bioadhesion Test of Buccal Films

Determination of *in vitro* mucoadhesion parameters is great importance for buccal film formulations [34]. The work of adhesion is estimated by calculating the force which removed films from the tissue. The polymer types and concentrations are influenced to work of adhesion of the films [38]. Polymer-related factors are named as "intrinsic factors"

Table III Mechanical Properties of the Prepared Bioadhesive Buccal Films Drying by Oven. Values Represent the Mean ± SD ($n = 3$)

Formulations	Tensile strength (N/cm^2)	Elongation at break (%)	Work of adhesion (mJ/cm^2)
HC-O1	0.633 ± 0.047	6.537 ± 0.025	1.529 ± 0.022
HC-O2	0.759 ± 0.069	5.801 ± 0.055	1.777 ± 0.020
HC-O3	0.611 ± 0.058	5.340 ± 0.041	1.390 ± 0.026
HC-O4	0.514 ± 0.025	5.749 ± 0.154	1.385 ± 0.020
XC-O1	2.507 ± 0.047	0.904 ± 0.156	0.608 ± 0.002
XC-O2	1.586 ± 0.041	0.564 ± 0.089	0.585 ± 0.006
XC-O3	2.230 ± 0.037	1.095 ± 0.092	0.420 ± 0.002
XC-O4	1.883 ± 0.045	1.125 ± 0.064	0.474 ± 0.004
XT-O1	2.127 ± 0.065	0.927 ± 0.157	0.510 ± 0.004
XT-O2	2.211 ± 0.023	1.002 ± 0.127	0.586 ± 0.002
XT-O3	1.330 ± 0.013	1.203 ± 0.049	0.292 ± 0.003
XT-O4	1.216 ± 0.018	1.587 ± 0.076	0.293 ± 0.004

which are molecular weight, chain length, flexibility, cross-linking, presence of functional groups, and concentration that will affect the mucoadhesion properties of the final formulation [54]. The HEC-based films show higher bioadhesion (1.385 ± 0.020 to 1.777 ± 0.020 mJ/cm^2) when compared with XG-based formulations (0.292 ± 0.003to 0.608 ± 0.002 mJ/cm^2). This is because of the fact that HEC-based films are shown significantly higher elastic deformation than XG-based films. At the same time, their EB values are last larger and more durable. These findings are consistent with previous studies [55].

Antifungal Activity of Film Formulations Against Candida albicans

Antifungal susceptibility testing is an important *in vitro* parameter used to determine the antifungal activities of the prepared buccal films (Table II). We found that the disk diameter of XG-based formulations (12.67 ± 0.058 mm to 21.67 ± 2.08 mm) was significantly larger ($p < 0.05$) than that of HEC-based formulations (4.50 ± 0.71 to 6.33 ± 0.58 mm) (Table II). These results suggest that the antifungal activity rates are higher on XG-based formulations. Based on these results, the antifungal activity of the films may depend on polymer types. This may also be a result of the non-Fickian behavior of nystatin. The XG-based formulations were deemed to be sufficient inhibitors of *Candida albicans* growth (Fig. 6) [34]. Specifically, XC-O4, XT-O1, XT-O2, and XT-O3 show the best antifungal activity among the XG-based formulations.

Conclusion

The antifungal activity of the prepared mucoadhesive film formulation has been proven in this study. Additionally, the antifungal treatment of nystatin, the amount of lidocaine release, which increases patient compliance and provides local anesthesia, and hydrocortisone release, which eliminates inflammation accelerating the treatment, were at the intended rates. Thus, the aim was to provide antifungal treatment while also treating other symptoms caused by the fungal infection. Given the lack

Fig. 6 Voriconazole and fluconazole disk as positive control (**A**); empty film and blank disk as negative control (**B**); XT-O2 formulation disk (**C**) on lawn of 10^8 CFU of *C. albicans* after 24 h of incubation

of studies in the research literature, incorporating the combination of these three active ingredients and the prolonged effects of their profiles while providing the physicochemical properties that should be found in buccal formulations are the most important findings of this study. These studies show that the *in vitro* studies were mainly affected by polymer types, and amount of PG. For the reasons listed below, xanthan-based films are found suitable for the combined treatment of oral candidiasis. Firstly, as a result of the lower swelling index, xanthan-based films show lower matrix erosion. Secondly, they correlate to the Higuchi and Korsmeyer-Peppas model. Last but not least, xanthan films achieve more sustainable release, which is a fundamental advantage related to their polymeric structure and diffusion rate. Further studies will be conducted to determine the physicochemical and compatibility of a three-drug dosage form. As a result, the ideal formulation candidates will undergo stability and *in vivo* studies.

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Declarations

Conflict of Interest The authors declare no competing interests.

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