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Research article

Optimization and comparison of unidirectional lidocaine-loaded buccal patch with the articaine-loaded buccal patch to reduce injection pain and increment of patients' compliance in dental procedures: A double-blind randomized controlled trial

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ABSTRACT

Introduction: Nervous patients often postpone dental visits until they are in severe pain, exacerbating anxiety. Buccal patches provide a noninvasive method of delivering drugs between the upper gum and cheek, offering local and systemic effects. Prior research has demonstrated the effectiveness, safety, and reliability of topical lidocaine or articaine patches for oral anesthesia. Consequently, this study aimed to develop a three-layered buccal drug delivery system for topical anesthetics.

Methods: The first step was preparing and optimizing lidocaine-loaded three-layer patches using Design-expert software. The effects of ethylcellulose, Eudragit, and carbopol concentrations were investigated on patch characteristics, including mucoadhesion, Young's modulus, and Elongation-at-break. Subsequently, patches were fabricated according to the optimized formulation determined by the software, and their efficacy was studied in a randomized, double-blind clinical trial. Participants received either lidocaine or articaine-loaded compared with placebo in a split-mouth study. They evaluated their pain levels using the Visual Analogue Scale (VAS), and the onset and duration of action were recorded for each treatment.

Results: According to the results, increasing ethyl cellulose and Eudragit concentrations improved mucoadhesion force ($p < 0.05$) while increasing ethyl cellulose and reducing Eudragit concentrations increased Young's modulus ($p < 0.05$). Increasing Carbopol and decreasing Eudragit concentrations also raised elongation at break significantly in the patch ($p < 0.05$). Treatment with lidocaine-loaded patches resulted in lower VAS scores and faster onset of action in patients than articaine-loaded patches. However, the duration of the effect was longer in the former($p < 0.001$).

Conclusion: Based on the responses' analysis, the formulation of the 3-layered buccal patch was optimized. This formulation comprised 4.72 % ethyl cellulose, 2 % Carbopol, and 5 % eudragit. Clinical evaluation results showed that loading the optimized formulation with lidocaine was more efficient in controlling the injection pain than articaine.

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1. Introduction

Dental phobia is the predominant excuse for patients to refrain from attending dental appointments. Dental phobia may arise due to a multitude of factors, encompassing auditory and tactile stimuli derived from tooth-cutting instruments like dental handpieces, olfactory perception of pharmaceuticals or substances employed within the realm of dentistry, discomfort experienced during dental therapy, and unwarranted apprehension towards injection of localized analgesia [1]. The occurrence of dental fear and anxiety (DFA) manifests with significant variability, ranging from 6 to 20 % among European children, 20–50 % among Asian children, or assuming intermediate values of 28–31 % across all regions. It is postulated that younger children and females possess a heightened likelihood of exhibiting adverse conduct and that females generally exhibit higher rates of intense dental fear in comparison to males [2]. Therefore, pain management holds significant importance, specifically for each pediatric dentist [3].

A transdermal patch is an adhesive medicated patch that is applied onto the surface of the skin in order to administer a precise dosage of medication through the skin and into the bloodstream, with a predetermined rate of release to achieve distribution throughout the body. Currently, the most prevalent transdermal system available in the market is primarily based on semi-permeable membranes, commonly called patches. Transdermal drug delivery systems (TDDS), also known as "Transdermal patches" or "Skin patches," are pharmaceutical formulations specifically designed to deliver a therapeutically effective amount of medication across a patient's skin and into the bloodstream. The administration of drugs through the skin bypasses the risks and inconveniences associated with intravenous therapy, reduces the likelihood of dose fluctuation, facilitates easy discontinuation, and provides both localized and systemic therapeutic effects. Transdermal drug administration offers the opportunity to facilitate the attainment of a steady blood concentration profile, leading to a decrease in overall systemic adverse reactions and, in certain cases, an enhancement in therapeutic effectiveness compared to alternative dosage forms [4].

Topical anesthesia serves as a highly impressive tool in effectively managing pain in children. Acquiring knowledge regarding the appropriate choice of topical anesthetics holds great importance in the successful pain management in pediatric dentistry [3]. From a chemical standpoint, the local anesthetic agents currently utilized in clinical practice can be categorized into two main groups: (A) those containing esteric bonds and (B) those containing amide bonds. Among these, amide agents are is the most frequently employed local anesthetic drugs in pediatric dentistry. Lidocaine hydrochloride (HCl) 2 % with 1:100,000 epinephrine is preferred due to its minimal allergic reaction tendencies and enhanced potency at lower concentrations [5]. Lidocaine, an anesthetic of the amide class, exerts a nonselective blockade on sodium channels found in sensory afferents. This blockade encompasses both A-delta and C fibers, thereby diminishing the occurrence of ectopic discharge and hindering signal propagation [6].

The Noven DentiPatch ™ is an innovative pain management patch that offers a non-invasive approach to delivering anesthetics to specific sites. Currently approved by the FDA, the DentiPatch ™ system is indicated for the provision of mild topical anesthesia to the mucous membranes of the oral cavity before superficial dental procedures. The manufacturer highlights that this patch has the potential to alleviate the discomfort associated with injections into the gingiva. It contains either 46.1 mg or 23.1 mg of lidocaine, which gradually permeate the mucosal tissue [7]. The topical administration of lidocaine is highly beneficial in the context of dental therapy, as it alleviates dental anxiety, particularly in younger patients, by alleviating discomfort and pain and also diminishing the pain arising from needle penetration in the buccal mucosa. Recent literature has demonstrated the efficacy of lidocaine when applied at least 1 min prior to needle insertion, with concentrations ranging from 2 to 5% in gel and patches, the latter being more effective than the former, and 10 % in spray. The latter formulation yields superior outcomes, exhibiting minimal toxicity levels, thus ensuring its safe usage. It is important to note that lidocaine is associated with an unfavorable taste, which poses a substantial drawback in its application specifically within the field of pediatric dentistry [6].

Articaine, discovered in 1969, is a type of amide local anesthetic that is commonly employed in dental anesthesia. Its chemical composition contains an additional ester linkage, which contributes to its favorable safety profile by means of rapid metabolism by esterases (with an elimination half-life of less than 20 min), thereby allowing the potential of readministration during the dental procedure. It shares similar pKa and toxicity characteristics with lidocaine. In contrast to a benzene ring, articaine features a thiophene ring, enabling enhanced and expedited penetration to the cell membrane and bone. Concerns have been raised regarding the potential for persistent paresthesia, attributed to potential neurotoxicity [8].

The objective of this investigation was to design, optimize and compare the efficacy of mucoadhesive 3-layer patches that contained either lidocaine or articaine. These patches were unidirectional and the disagreeable taste of the medication was masked using sweeteners in the formulation. A randomized double-blind clinical investigation was conducted with a sample size of 40 individuals ranging in age from 20 to 35 years.

2. Materials and method

2.1. Materials

Lidocaine hydrochloride powder was obtained from Merck (Germany). Articaine hydrochloride was purchased from Exir

Pharmaceutical Company (Iran). Ethyl cellulose and Carbopol 934 were purchased from Samchun (South Korea). Eudragit L100-55 polymer was obtained from Rahavard Tamin (Iran). Plasticizers, including propylene glycol, glycerin, and triacetin, were purchased from Merck (Germany).

2.2. Preparation of the lidocaine patch

The lidocaine patch comprised three distinct layers: the backing layer, intermediate layer, and mucoadhesive layer.

The backing layer was prepared by gradually adding ethyl cellulose solution, with a concentration of 2–7% (w/v), to 95 % ethanol while utilizing a magnetic stirrer. This solution was subsequently plasticized with triacetin at a concentration of 30 % (w/w) and propylene glycol at a concentration of 5 % (w/w) based on the weight of the polymer. The resulted solution was thoroughly mixed on a stirrer for 1 h. The solution was subjected to sonication and refrigerated for 20–30 min to eliminate air bubbles. Finally, the solution was poured into a Polytetrafluoroethylene mold and settled to dry.

An ethanolic solution containing Eudragit L 100-55 was prepared, with a concentration ranging from 5 to 10 % (w/v). This solution was mixed on a magnetic stirrer and then plasticized with triacetin at a concentration of 20 % (w/w) and propylene glycol at 5 % (w/w) of the total polymer weight. The resulting solution was subjected to sonication and then placed in a refrigerator to eliminate the air bubbles. Subsequently, the solution was poured onto the previous layer, known as the baking layer and was settled to dry. This layer was added as a bridge between the backing and mucoadhesive layers.

The mucoadhesive layer was prepared by hydrating Carbopol in water for 24 h at a concentration of 0.5–2% (w/v). Subsequently, an ethanolic solution containing lidocaine was introduced. The concentration of the plasticizer, glycerol, was maintained at a constant level of 25 % (w/w) of Carbopol. The resulted solution underwent sonication and was then left on the stirrer for 1 h. Finally, the obtained solution was poured onto the two preceding layers.

The desiccated patches were separated from the molds and sliced into circular pieces with a diameter of 1 cm. Each circular shaped patch contained 240 mg of lidocaine. The drug dose was determined according to the therapeutic window of lidocaine [9].

2.3. Formulation experimental design

Design Expert software version 13 was utilized to study the effect of each variable on the characteristics of the resulted patches, using a 3-factor, 3-level, Box-Behnken study design. The independent and dependent variables investigated in the current study are summarized in Table 1 and each test was performed in triplicate. Design Expert software was also utilized to optimize the parameters for preparing drug-containing patches. The experimental data was subjected to statistical analysis using analysis of variance (ANOVA), and polynomial equations were generated. These mathematical equations were employed to explain the influence of independent variables on the characteristics of the formulation.

2.4. Evaluation of the prepared patches

2.4.1. Drug content

The patch samples were dissolved in 3 ml of ethanol. Then, 2 ml of HCl 37 % (w/w) was introduced to dissolve the drug. The ethanol was evaporated under gentle nitrogen steam. Subsequently, the obtained solution underwent centrifugation at a rate of 8000 rpm for 10 min, after which the absorbance of the supernatant was measured at the wavelength of 264 nm for lidocaine and 270 nm for articaine-containing patches.

2.4.2. Mucoadhesion

Each patch (1 cm × 1 cm) was positioned onto a piece of bovine buccal mucosa and subsequently inserted into the universal texture analyzer (Santam™, Iran). To assess the mucoadhesion force, an extension force at the speed of 10 mm/min was applied to each patch.

2.4.3. Elongation at break (E_{max}) and Young's modulus

Each patch (1 cm × 1 cm) was positioned vertically, between the upper and lower jaws of the universal texture analyzer (Santam™, Iran) and an extension force at the speed of 10 mm/min was applied to each patch. The determination of E_{max}, the maximum length at which the sample would be broken, was accomplished through the utilization of equation number 1 [10].

Table 1
Factors and responses considered to design the experiment.

Factors	(Range)	Responses
EC%	(2–7%)	Load
CBP%	(0.5–2%)	Mucoadhesion
EU%	(5–10 %)	Young's Modulus
		Elongation

EC: Ethyl cellulose.
EU: Eudragit.
CBP: Carbopol.

$$\mathbf{E_{max}} = \frac{\Delta L}{L0} \tag{1}$$

in which, ΔL is difference between final and initial length (cm), and L0 is initial length (cm) of the placed patch.

Young's modulus was also calculated for measuring patch stiffness. Young's modulus was calculated using equation number 2 [10].

$$\text{Young's modulus} = \frac{stress}{Emax} = \frac{F/A}{Emax} \tag{2}$$

in which F is the f*orce applied* (*N*) and A is the a*rea* (mm2) of the patch.

2.5. Determination of the optimal formulation

The ideal composition of the patch formula, ethyl cellulose, eudragit, and carbopol was determined considering the following criteria: maximum drug content, maximum mucoadhesion force, maximum Young's modulus, and maximum E_{max}. Using the optimal formulation defined through software analysis, patches containing lidocaine or articaine were prepared in an aseptic environment. The in vitro characteristics of these patches, including thickness and pH, moisture content, swelling, uniformity of content, FTIR spectrum, and drug release profile, were then assessed. Subsequently, clinical evaluations were conducted under the specified procedures.

To enhance the unpleasant flavor of lidocaine and articaine present in drug-loaded patches, 4.5 % (w/w) of a mixture of sucralose-acesulfame potassium (1:1) and 0.6 % (w/w) of orange essential oil were added to the formulation.

2.6. In vitro characterization of the optimal patch

After determining the optimal formulation, the lidocaine containing patch and the articaine containing patch were prepared, and their physicochemical properties were compared.

2.6.1. Thickness of prepared patches

The measurement of the thickness of the drug containing patch samples was conducted in multiple areas of each patch through the utilization of a Caliper device. Subsequently, the resulted average thickness of each sample was documented and reported. The test was performed in triplicate.

2.6.2. Surface pH of the drug-loaded patches

Three samples of each drug-loaded patch were immersed in 5 ml of simulated saliva fluid (SSF) to assess the pH. Subsequently, the pH of the SSF was measured after 5 min using a pH meter electrode (Metrohm, Switzerland).

2.6.3. Moisture content

Three samples of each patch were precisely weighed and subsequently placed in a crucible inside an oven set at 100 °C and weighed until each sample achieved a steady weight. The water content of each sample was calculated using equation number 3 [11].

$$Moisture\ (\%) = \frac{(W1 - W2)}{W1} \times 100 \tag{3}$$

in which, W1 is the weight (g) of sample before and W2 is the weight (g) of sample after the drying process.

2.6.4. Swelling test

Three samples from each patch were precisely weighed and positioned on an aluminum foil within a beaker that held 2 ml of SSF at 37 °C. Subsequently, at each time point, the liquid was gradually withdrawn using a pipette, any surplus water present on the patch's surface was eliminated using absorbent paper and this procedure was repeated until the weight of the patch became stable. The quantity of SSF uptaken by each sample was determined using equation number 4 [12].

$$SSF\ uptake = \frac{Wwet - Wdry}{Wdry} \times 100 \tag{4}$$

In which, Wwet represents the weight (g) of each sample after the test procedure and Wdry represents its initial weight (g).

2.6.5. Content uniformity test

Three patches were precisely weighed and solubilized in 3 ml ethanol and 2 ml hydrochloric acid. The ethanol component was removed by evaporation, and the resultant solution underwent centrifugation. The absorbance of the supernatant was measured at 264 nm for lidocaine and 270 nm for articaine-containing patches.

2.6.6. Drug release study

Three samples of lidocaine-containing patches and three samples of articaine-containing patches were accurately weighed. Based on the saturation solubility of each drug and sink condition (maximum concentration 10–15 % of saturation solubility of each drug),

the approximate weight of each sample was determined according to the volume of the Franz cells. These samples were then placed in the Franz cell, with a volume of 25 ml, utilizing bovine buccal mucosa as the membrane and SSF as the release medium. At predetermined time intervals, samples were collected from the receiver compartment of the Franz cell and replaced with fresh SSF. Following centrifugation (at 8000 rpm for 10 min) and filtration of the solution using 0.22 μm syringe filters, the absorbance of each sample was measured at either ƛ max of 264 nm or ƛ max of 270 nm for lidocaine or articaine-loaded samples, respectively. The percentage of drug released at each time point and the drug release efficiency were subsequently calculated.

2.6.7. Investigation of patches morphology using scanning electron microscopy (SEM)

The morphology of the optimized patches was examined using scanning electron microscopy (SEM) (JSM-6010LA; JEOL, Peabody, MA, USA). A layer of gold was applied to the samples, and the formation of separate layers in the structure of patch samples was investigated in sections of the patch.

2.6.8. Differential scanning calorimetry (DSC)

The solid-state and thermal characteristics of the unprocessed active drug substances and the formulations were examined using DSC (DSC822e; Mettler Toledo, Columbus, OH, USA). A heating rate of 10 °C per minute was employed within a temperature range of −25 °C–250 °C while maintaining an inert nitrogen atmosphere to obtain thermograms of the lidocaine-containing patch and the articaine-containing patch.

2.6.9. Fourier transform infrared (FTIR) spectroscopy

The FTIR spectra of pure lidocaine, lidocaine-loaded patch, pure articaine, articaine-loaded patch, and drug-free patch were analyzed by FTIR spectroscopy instrument (Jasco, Japan) to assess the possibility of covalent bonding between the active pharmaceutical ingredient and excipients. FTIR spectra were scanned in the range of 4000–350 cm-1.

2.7. Clinical method

A randomized, double-blinded clinical trial was conducted from January 2023 to July 2023 at the Maxillofacial Surgery Department of Prof TorabiNejad Dentistry Research Center. All patients provided written informed consent before their inclusion in the trial, demonstrating their voluntary participation and confirming their comprehension of the study's objectives and procedures.

A total of 40 adult patients within the age range of 20–35 years who had received injections in the area of the upper 4th and 5th teeth were selected as participants. These individuals possessed the necessary eligibility criteria, including the absence of systemic diseases such as cardiovascular diseases and diabetes, as well as physical and mental ailments. Furthermore, they had no allergies to lidocaine and articaine, dental phobia, inflammation, abscess, or history of surgery at the injection site. Additionally, they had not taken any painkillers or corticosteroids within the past week. Any patients who experienced an emergency during the injection process and were unable to complete the procedure were excluded from the study. Likewise, the study did not include individuals who reported pain during their visit. Qualified individuals were categorized into two distinct groups. In each group, the split-mouth method was implicated.

Patients were randomly assigned treatment groups using a random number table, and the project manager distributed the patches to ensure both the dentist and the patient remained unaware of the treatment assignment.

The first group received a patch containing 240 mg of lidocaine on one side of the oral cavity and a drug-free patch (placebo) on the opposite side. The second group received a patch containing 240 mg of articaine on one side of the mouth and a drug-free patch (placebo) on the other. The selection of participants was executed through a random process. The patients were then administered patches, either containing or lacking the medication. Following a 15-min interval, the dentist removed the patch and performed a supra periosteal lidocaine injection using a 27-gauge needle near the upper fourth and fifth teeth, with a lidocaine concentration of 2 %.

Subsequently, the patients were requested to assess the level of pain they experienced on a VAS (visual analog scale) ranging from 0 to 10, as well as the onset time and duration of the local anesthesia. Also, patients tracked the start and duration of the patch's effects. Patients were assessed for any potential outcomes 24 h after the intervention.

The participants were presented with a VAS score (Fig. 1), where they were guided to indicate the intensity of their pain by marking

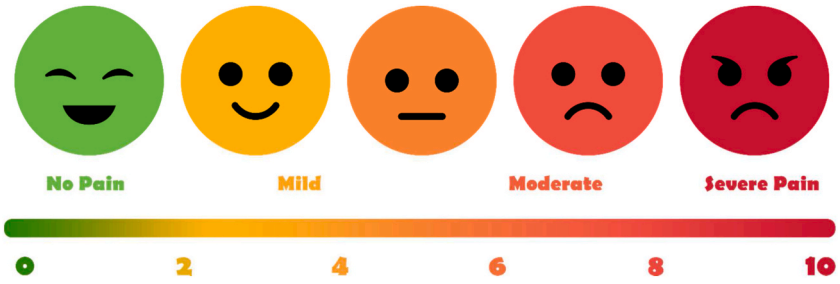

Fig. 1. Visual Analogue Scale for assessment of patient's pain perception.

a position on the line. The VAS system employed a scoring range from 0 to 10, with higher scores indicating greater severity of pain.

2.8. Statistical analysis

Equation number 5 was used to determine the sample size.

$$n = \frac{\left(z_{1-\frac{\alpha}{2}} + z_{1-\beta}\right)^2 \left(\sigma_1^2 + \sigma_2^2\right)}{d^2} \quad (5)$$

in which n is the sample size, α error equals 5 %, β error equals 80 %, d equals 1.5, and σ is the standard deviation and equals 1.67.

n = (1.96 + 0.84)2 × ((1.67)2 + (1.67)2) / (1.5)2 = 20

Statistical studies were performed using SPSS software (ver.26). The Kolmogorov-Smirnov test was used to determine the data distribution. The non-parametric Mann-Whitney test was used to analyze quantitative data with a non-normal distribution. Finally, the results were expressed as mean ± standard deviation, and values with a P-value less than 0.05 were considered significant.

2.9. Data sharing plan statement

The data associated with this manuscript is available upon request from the corresponding author.

3. Results

The resulted patches had a semi-transparent appearance and only two distinct layers could be visually observed in the patches.

3.1. Investigation of the effect of the studied independent variables on characteristics of the prepared patches

The results of the dependent variables measured for each formulation designed by Design Expert software are presented in Table 2. This information was analyzed by the software to investigate the effect of each independent variable on the dependent variable and determine the optimal formulation.

3.1.1. Drug content

The Drug content of the designed studies was obtained between 28.64 and 95.35 % for different patch formulations. Equation number 5 shows the mathematical relationship between the drug content and the independent variables.

Drug content = 1.41A - 2.47B - 12.22C + 3.42AB - 7.59AC - 13.69BCE - 15.77 A2 + 10.99 B2 + 0.3612C2 (5)

Table 2
The results of the dependent variables of the formulations designed for lidocaine loaded patch by Design Expert software (n = 3, mean ± SD).

Study Design	Variables			Responses			
	EC (%)	CBP (%)	EU (%)	R1: Drug content (%)	R2: Mucoadhesion (N)	R3: Young's modulus N/mm^2	R4: Elongation at break (%)
D1	2	2	7.5	48.68 ± 9.45	0.44 ± 0.07	0.04 ± 0.005	130.00 ± 5.00
D2	7	0.5	7.5	51.77 ± 2.79	0.31 ± 0.05	0.06 ± 0.008	153.00 ± 7.63
D3	4.5	1.25	7.5	58.43 ± 1.78	3.65 ± 0.08	0.03 ± 0.002	83.00 ± 2.82
D4	7	1.25	5	53.81 ± 2.51	0.32 ± 0.04	0.09 ± 0.005	126.00 ± 5.65
D5	4.5	1.25	7.5	58.43 ± 1.78	3.65 ± 0.08	0.03 ± 0.002	83.00 ± 2.82
D6	2	1.25	5	41.79 ± 1.41	1.16 ± 0.12	0.08 ± 0.009	125.00 ± 10.00
D7	7	1.25	10	29.07 ± 1.99	2.06 ± 0.12	0.02 ± 0.002	120.00 ± 10.00
D8	4.5	1.25	7.5	58.43 ± 1.78	3.65 ± 0.08	0.03 ± 0.002	83.00 ± 2.82
D9	2	0.5	7.5	49.82 ± 1.58	0.59 ± 0.05	0.02 ± 0.003	150.00 ± 5.50
D10	4.5	1.25	7.5	58.43 ± 1.78	3.65 ± 0.08	0.03 ± 0.002	83.00 ± 2.82
D11	4.5	2	10	28.64 ± 7.23	0.76 ± 0.08	0.04 ± 0.009	120.00 ± 5.00
D12	4.5	2	5	95.35 ± 11.38	2.68 ± 0.09	0.11 ± 0.005	173.00 ± 2.82
D13	4.5	1.25	7.5	58.43 ± 1.78	3.65 ± 0.08	0.03 ± 0.002	83.00 ± 2.82
D14	4.5	0.5	10	71.59 ± 8.19	0.71 ± 0.13	0.05 ± 0.002	120.00 ± 10.00
D15	4.5	0.5	5	83.55 ± 6.4	0.78 ± 0.13	0.14 ± 0.011	100.00 ± 10.00
D16	7	2	7.5	64.33 ± 1.33	0.66 ± 0.1	0.04 ± 0.009	156.00 ± 5.65
D17	2	1.25	10	47.41 ± 1.27	0.49 ± 0.01	0.08 ± 0.007	100.00 ± 10.00

EC: Ethyl cellulose.
CBP: Carbopol.
EU: Eudragit.

In the equation provided, the variables A, B, and C represent the values for the concentration of Ethylcellulose, Carbopol, and Eudragit, respectively. When two parameters are changed simultaneously, phrases composed of two factors indicate the interaction terms, revealing how the response changes. The inclusion of the squared term allows for the consideration of non-linear relationships between variables. In the equation, the negative or positive sign before the coefficients of each factor indicates whether the response decreases or increases with changing the factor levels. The magnitude of the coefficients reflects the extent of the term's impact on the response.

Fig. 2 and the software analysis performed with the Quadratic model showed that the simultaneous increase in the amount of Carbopol and decrease in the amount of Eudragit caused a significant increase in the amount of drug content ($p < 0.05$). Other independent variables had no significant effect on the percentage of drug content ($p < 0.05$).

3.1.2. Mucoadhesion

The mucoadhesion of the designed studies varied between 0.31 and 3.65 N for different patch formulations. Equation number 6 shows the mathematical relationship between the mucoadhesion and the independent variables.

$$\text{Mucoadhesion} = 0.0879A + 0.2688B - 0.1137C + 0.1263AB + 0.6079AC - 0.4612BCE - 1.69\ A2 - 1.47\ B2 - 0.9531C2 \quad (6)$$

In the equation provided, the variables A, B, and C represent the coded values for the concentration of Ethylcellulose, Carbopol, and Eudragit, respectively. When two parameters are changed simultaneously, phrases composed of two factors indicate the interaction terms, revealing how the response changes. The inclusion of the squared term allows for the consideration of non-linear relationships between variables. In the equation, the negative or positive sign before the coefficients of each factor indicates whether the response decreases or increases with changing factor levels. The magnitude of the coefficients reflects the extent of the term's impact on the response.

Fig. 3-a and the software analysis results fitted into the Quadratic model showed that the simultaneous increase of ethyl cellulose up to 4.5 % and Eudragit up to 7.5 % caused a significant increase in patch mucoadhesion ($p < 0.05$). Also, with the simultaneous increase of Eudragit up to 7.5 % and Carbopol up to 1.25 %, the mucoadhesion force increased ($p < 0.05$) (Fig. 3-b).

3.1.3. Elongation at break (E_{max})

The E_{max} value of the patch formulations ranged from 83 to 173 %. Equation number 7 shows the mathematical relationship between the E_{max} and the independent variables.

$$E_{max} = 6.25A + 7.00B - 8.00C + 5.75AB + 4.75AC - 18.25BCE + 26.88\ A^2 + 37.38\ B^2 + 7.88C^2 \quad (7)$$

In the equation provided, the variables A, B, and C represent the values for the concentration of Ethylcellulose, Carbopol, and Eudragit, respectively. When two parameters are changed simultaneously, phrases composed of two factors indicate the interaction terms, revealing how the response changes. The inclusion of the squared term allows for the consideration of non-linear relationships between variables. In the equation, the negative or positive sign before the coefficients of each factor indicates whether the response decreases or increases with changing factor levels. The magnitude of the coefficients reflects the extent of the term's impact on the response.

Fig. 4 and the software analysis performed with the Quadratic model showed that E_{max} increased significantly ($p < 0.05$) with the simultaneous increase of carbopol from 1.25 % and a decrease of eudragit from 7.5 %. Other independent variables had no significant effect on E_{max} ($p < 0.05$).

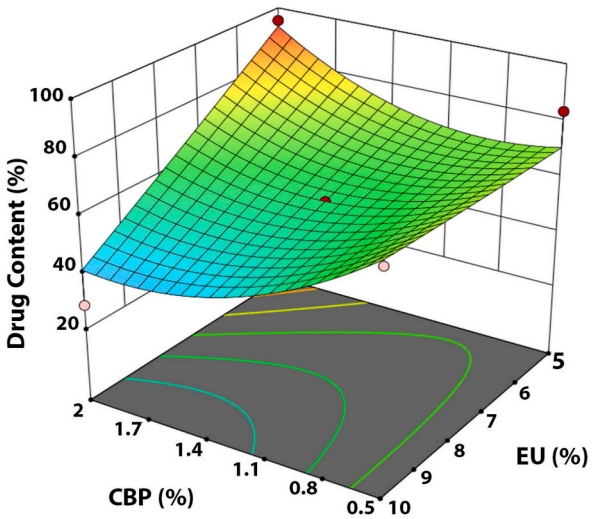

Fig. 2. Simultaneous effect of carbopol and eudragit on drug content.

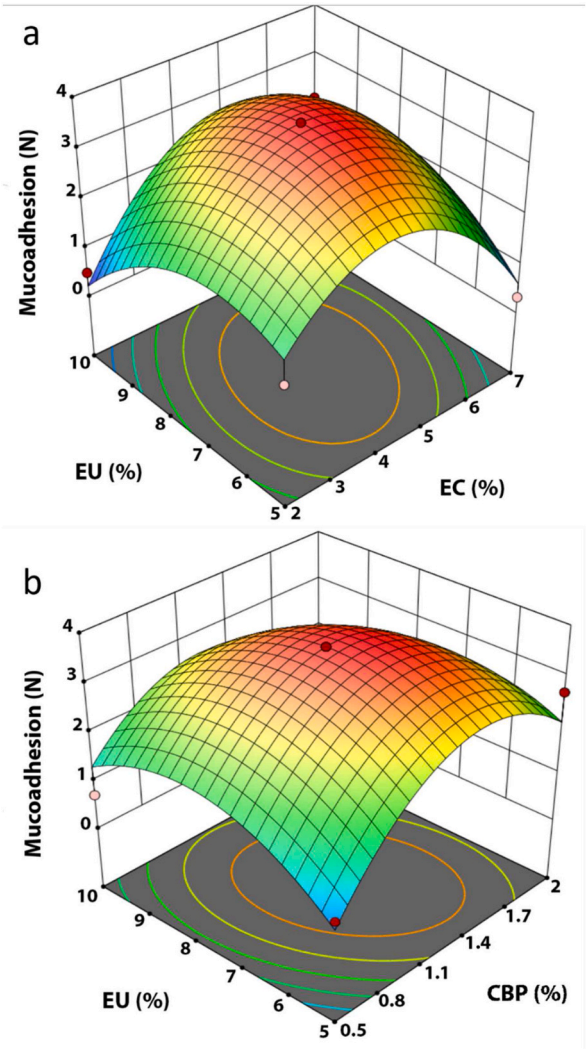

Fig. 3. a) Simultaneous Effect of **a)** Eudragit and Ethylcellulose, **b)** Eudragit and Carbopol on Mucoadhesion force.

3.1.4. Young's modulus

The Young's modulus of the patch formulations was reported to range from $0.20*10^5$ to $1.41*10^5$ N/mm^2. Equation number 8 shows the mathematical relationship between Young's modulus and the independent variables.

$$\text{Young's modulus} = -0.0052A - 0.0348B - 0.2892C - 0.0833AB - 0.1963AC + 0.0521BCE - 0.0517\,A^2 + 0.1350\,B^2 + 0.3921C^2 \quad (8)$$

In the equation provided, the variables A, B, and C represent the values for the concentration of Ethylcellulose, Carbopol, and Eudragit, respectively. When two parameters are changed simultaneously, phrases composed of two factors indicate the interaction terms, revealing how the response changes. The inclusion of the squared term allows for the consideration of non-linear relationships between variables. In the equation, the negative or positive sign before the coefficients of each factor indicates whether the response decreases or increases with changing factor levels. The magnitude of the coefficients reflects the extent of the term's impact on the response.

Fig. 5 and the software analysis results fitted into a Quadratic model showed that with the simultaneous increase in the percentage of ethyl cellulose and decrease in the percentage of ethyl eudragit, the value of Young's modulus increased significantly ($p < 0.05$). Other independent variables did not significantly affect Young's modulus($p < 0.05$).

3.2. Formulation optimization for drug-containing patches

The data was fit to a quadratic model for analysis. Optimization of the patch was performed based on factors such as maximum drug content, maximum mucoadhesion, maximum Young's modulus, and maximum E_{max}.

The values of the dependent variables predicted by the software were compared with experimentally achieved ones and the corresponding results were presented in Table 3. Based on the calculations, it was observed that the prediction error was notably high

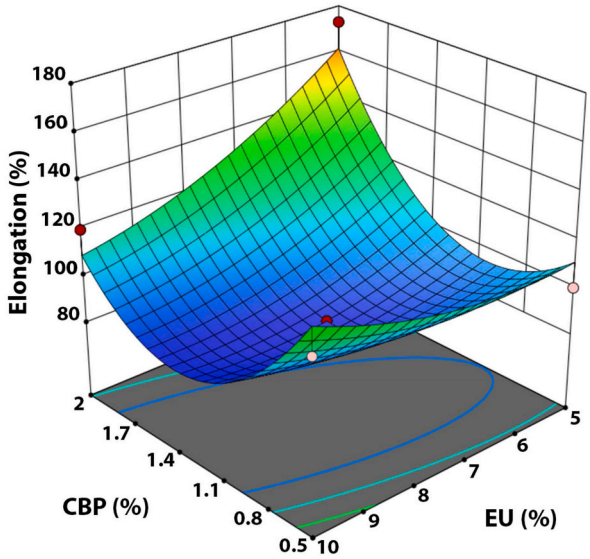

Figure 4. Simultaneous effect of carbopol and eudragit on elongation at break.

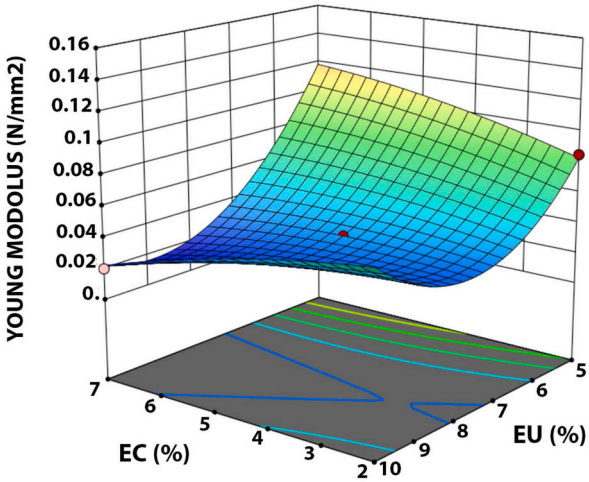

Fig. 5. Simultaneous effect of ethylcellulose and eudragit on Young's modulus.

for mucoadhesion, while in other cases, it remained around 6 % or lower.

3.3. Comparison of properties of lidocaine and articaine patch

After preparing the optimal formulation of patches, either containing lidocaine or articaine, the in vitro properties of these two were measured and compared. The results can be seen in Table 4.

3.3.1. Drug release profile

After evaluating the release profile of lidocaine and articaine from the optimal patch formulation, the release profiles are

Table 3
Comparison of predicted and practical for dependent variables of optimal formulation.

	MUCOADHESION (N)	YOUNG MODOLUS (N/mm2)	Elongation at break (%)	Drug content (%)
Values Predicted by The Software	2.029	0.110	162.39	94.205
Values Obtained Experimentally	2.680 ± 0.095	0.113 ± 0.005	173.000 ± 2.828	95.353 ± 11.386
Error %	32.084	2.727	6.533	1.218

represented in Fig. 6. The percentage of release efficiency for lidocaine from the patch was 41.69 ± 13.10, while for articaine, it was 13.30 ± 3.60. The results indicated that 96.74 % of the lidocaine content was released within 25 min, and 41.78 % of the articaine content was released within 30 min of the patches.

3.3.2. The morphology of patches investigated using scanning electron microscopy (SEM)

The SEM microscope imaging revealed a three-layered structure of both lidocaine and articaine-loaded patches (Fig. 7).

3.3.3. DSC thermal analysis

In the thermal analysis conducted for lidocaine hydrochloride powder and the patch containing this API, shown in Fig. 8, it is evident that the pure lidocaine powder has a sharp endothermic melting peak at 80 °C. However, this peak is absent in the patch containing lidocaine. Instead, a curve was observed in the spectrum, indicating alteration of the drug from crystalline to amorphous phase [13].

Similarly, in the thermal analysis performed for articaine hydrochloride powder and the corresponding patch, represented in Fig. 9, the pure articaine powder exhibits a sharp endothermic melting peak at 173 °C. However, in the graph of the patch containing articaine, a curve was observed instead of this peak, indicating the alteration of the drug from crystalline to amorphous [14].

3.3.4. Fourier transform infrared spectroscopy

Infrared spectrum analysis was conducted to confirm the absence of any chemical interaction between the formulation components and the active pharmaceutical ingredients. The FTIR spectrums of the analyzed samples, including pure lidocaine, lidocaine-loaded patch, pure articaine, articaine-loaded patch, and drug-free patch, are illustrated in Fig. 10.

The FTIR spectrum of pure lidocaine hydrochloride (Fig. 10-a) exhibited distinctive peaks arising from the N–H stretching bonds at 3452 and 3387 cm^{-1}, the C–H stretching bonds within the ring at 3187 cm^{-1}, and a series of peaks ranging from 3034 to 2920 cm^{-1} indicates the combined effects of C–H bonds. The presence of vibration at 1657 cm^{-1} indicated the existence of a C=O stretching bond, while the peaks at 1544 and 1477 cm^{-1} were associated with the C–C stretching bonds in the aromatic ring. The zone encompassing peaks in the 1000–1250 cm^{-1} range reveals the interconnections between the C–N and N–H groups within the amide compounds [15]. The stretching bonds of the N–H, C–H, C=O, C–C, C–N, and N–H amides in the lidocaine HCl patch (Fig. 10-b) were observed at 3383, 3177, 1649, 1547, and 1473 cm^{-1} respectively. These spectroscopic values indicated lack of any intermolecular interactions among the functional groups.

In the FTIR spectrum of pure articaine hydrochloride (Fig. 10-c), the peaks of ester and carbonyl amide stretching bonds were observed at 1725 and 1702 cm^{-1}, respectively. The peak at 3199 cm^{-1} is associated with the amide N–H stretching bond, and 3413 cm^{-1} is associated with the amine N–H stretching bond. The peak at 1474 cm^{-1} showed the existence of a C=C stretching bond. A 3094 cm^{-1} peak is related to the C–H aromatic ring. The C–S stretch bond participating in the aromatic ring was observed at 697 cm^{-1} [16]. The mentioned peaks were also observed in the articaine patch (Fig. 10-d). The presence of the C=O, C=C, secondary amine, secondary amide, C–S, and aromatic C–H of the articaine HCl patch (Fig. 10-d) were observed at the respective wavelengths of 1722, 1700, 1482, 3415, 3204, 698, and 3114 cm^{-1}. This observation indicated that no chemical interaction was occurred between the active drug and the formulation excipients.

3.4. Results of clinical studies

Fig. 11 illustrates the process of conducting the clinical trial. A total of 43 patients were evaluated in January 2023–July 2023, out of which, 43 patients had the inclusion criteria. Among them, 40 patients agreed to participate and were randomly divided into two groups, receiving either lidocaine or articaine loaded patches.

Table 5 displays the fundamental demographic and clinical features of the enrolled patients in the study. The analysis indicated no statistically significant difference between the two groups concerning demographic variables, including age, weight, gender distribution, and pre-existing medical conditions ($p > 0.05$).

Following the evaluation of data distribution normality, using the Kolmogorov-Smirnov test for variables including VAS score, onset, and duration of action, it was established that the data did not conform to a normal distribution. Consequently, a non-parametric Mann-Whitney test was used for analysis.

Fig. 12 illustrates the comparative analysis of average Visual Analog Scale (VAS) scores among three groups: those receiving the lidocaine-containing, articaine-containing, and drug-free patches. The graph illustrates that the group treated with the lidocaine-containing patch exhibited significantly lower average VAS scores than those receiving the articaine-containing patch and the

Table 4
Comparison of Invitro properties of Lidocaine-loaded and Articaine-loaded patches.

Drug	Thickness (mm)	Surface pH	Drug content (%)	Moisture content (%)	Swelling (%)	Drug content Standard deviation (%)	Release efficiency (%)
Lidocaine	3.01 ± 0.16	4.83 ± 0.35	97.47 ± 2.37	18.00 ± 0.70	27.00 ± 1.41	10.14	41.69 ± 13.10
Articaine	3.35 ± 0.12	3.60 ± 0.53	92.81 ± 3.71	15.00 ± 1.52	7.50 ± 0.70	10.44	13.30 ± 3.60

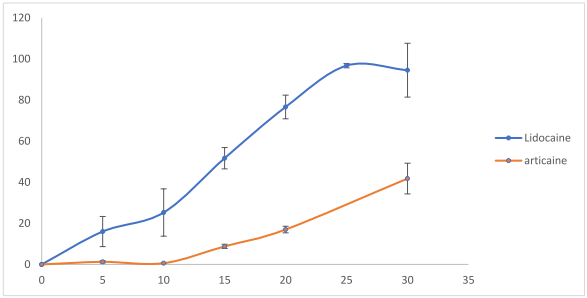

Fig. 6. Release profile of lidocaine from lidocaine loaded patch and articaine from articaine loaded patch.

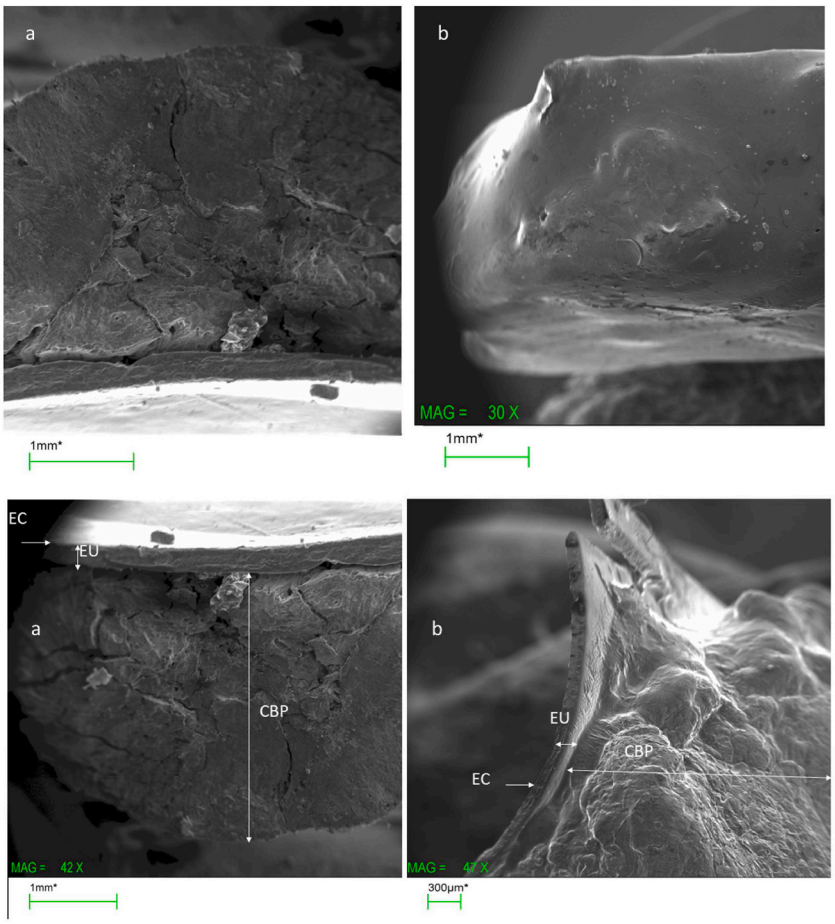

Fig. 7. Scanning electron microscopy micrograph of **a)** lidocaine loaded patch, **b)** articaine loaded patch; EC: Ethylcellulose; EU: Eudragit; CBP: Carbopol. Arrows show three separate layers of patches.

drug-free patch ($p < 0.001$). Furthermore, a significant distinction was observed between the VAS score of the subjects receiving the articaine-containing patch and the drug-free patch ($p < 0.001$).

A non-parametric test was used to compare the onset and duration of action among different groups. As indicated in Fig. 13, the onset of action for the lidocaine-loaded patch was significantly lower than that of the articaine-loaded patch ($p < 0.001$).

According to Fig. 14, the articaine-loaded patch's duration was significantly longer than the lidocaine-loaded patch ($p < 0.001$). The duration of action of each drug-containing patch was significantly longer than the drug-free patch that only received lidocaine injection ($p < 0.001$).

The patch was well-tolerated by patients, with no significant adverse events observed. Only two patients experienced mild inflammation at the buccal patch application site.

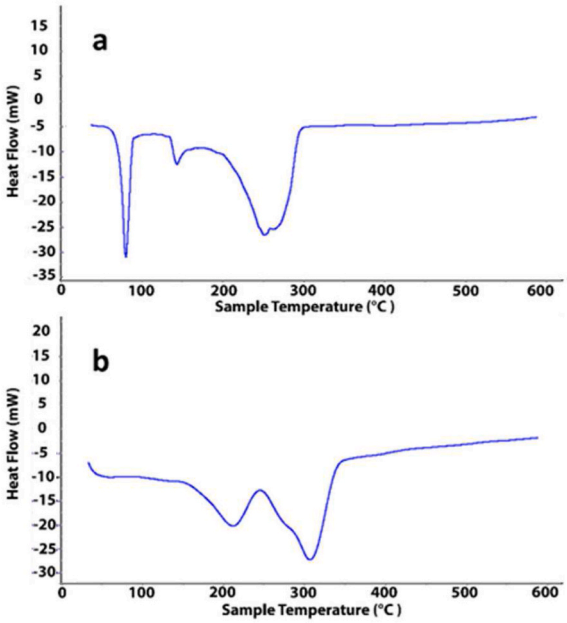

Fig. 8. DSC thermograms of **a)** lidocaine powder, **b)** lidocaine-loaded patch.

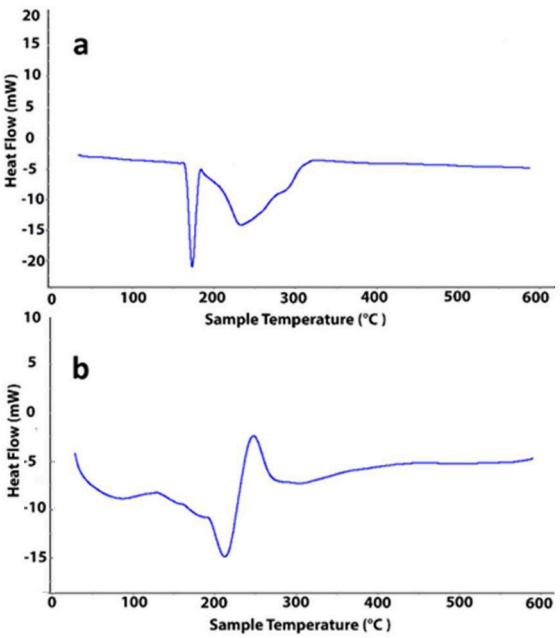

Fig. 9. DSC thermograms of **a)** articaine powder, **b)** articaine-loaded patch.

4. Discussion

4.1. Selection of lidocaine and articaine as local anesthetics

In the current study, the utilization of a buccal drug delivery system for anesthetics was studied as a desirable aid for DFA, considering the following benefits: (A) buccal drug delivery is non-invasive and well-received by patients, as the buccal cavity is conveniently accessible for self-administration and removal of drug delivery devices. (B) The buccal mucosa is characterized by its abundant blood supply, excellent permeability, and relatively low enzymatic activity compared to other mucosal tissues. (C) Drugs administered through the buccal pathway may experience rapid absorption, avoiding hepatic first-pass metabolism and pre-systemic

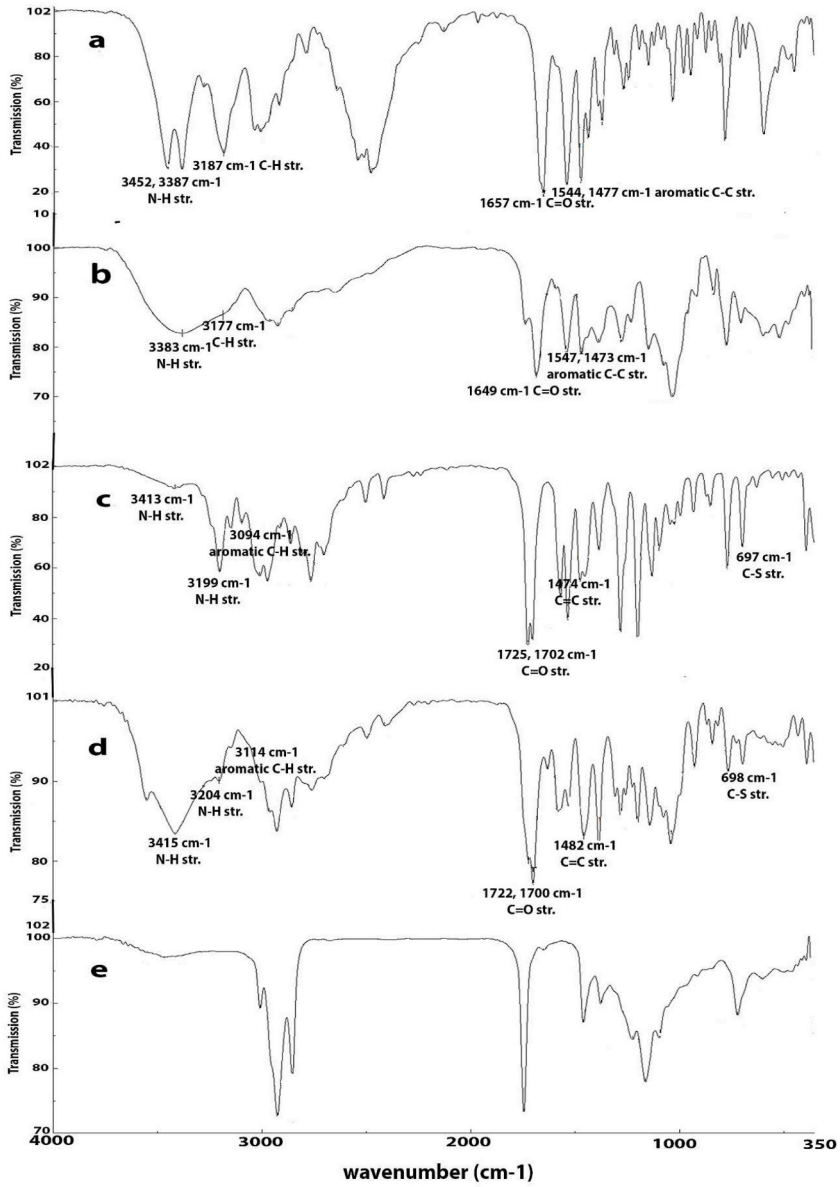

Fig. 10. FTIR spectra of **a)** lidocaine powder, **b)** lidocaine-loaded patch, **c)** articaine powder, **d)** articaine-loaded patch, **e)** drug-free patch.

elimination in the gastrointestinal tract. Buccal drug delivery leads to an enhanced extent of drug bioavailability while minimizing adverse effects. Recent advancements have yielded mucoadhesive dosage forms, including tablets, gels, and films. Nevertheless, mucoadhesive buccal patches (MBPs) are often selected over mucoadhesive tablets due to their compact size, appropriate thickness, flexibility, and comfort. Furthermore, MBPs exhibit resistance to elimination by saliva, unlike oral gels [11]. Therefore, buccal patches were chosen as the drug delivery system in the current study.

Articaine has a thiophene ring, enhancing lipid solubility and penetration across membranes. Additionally, it contains an ester group that allows for hydrolysis in plasma through nonspecific cholinesterases. Regarding maxillary infiltration anesthesia, no notable contrasts in the onset and duration of anesthesia were observed between articaine and lidocaine. Although there have been reports on the safety of articaine compared to lidocaine in both adults and children, a potential correlation between paresthesia and articaine has been proposed. The etiology of paresthesia remains inconclusive, although it may be associated with an augmented level of local anesthetic agent. Given the potential complications associated with paresthesia, the utilization of high-concentration anesthetic formulations for nerve block anesthesia is restricted despite the presence of viable alternatives [17].

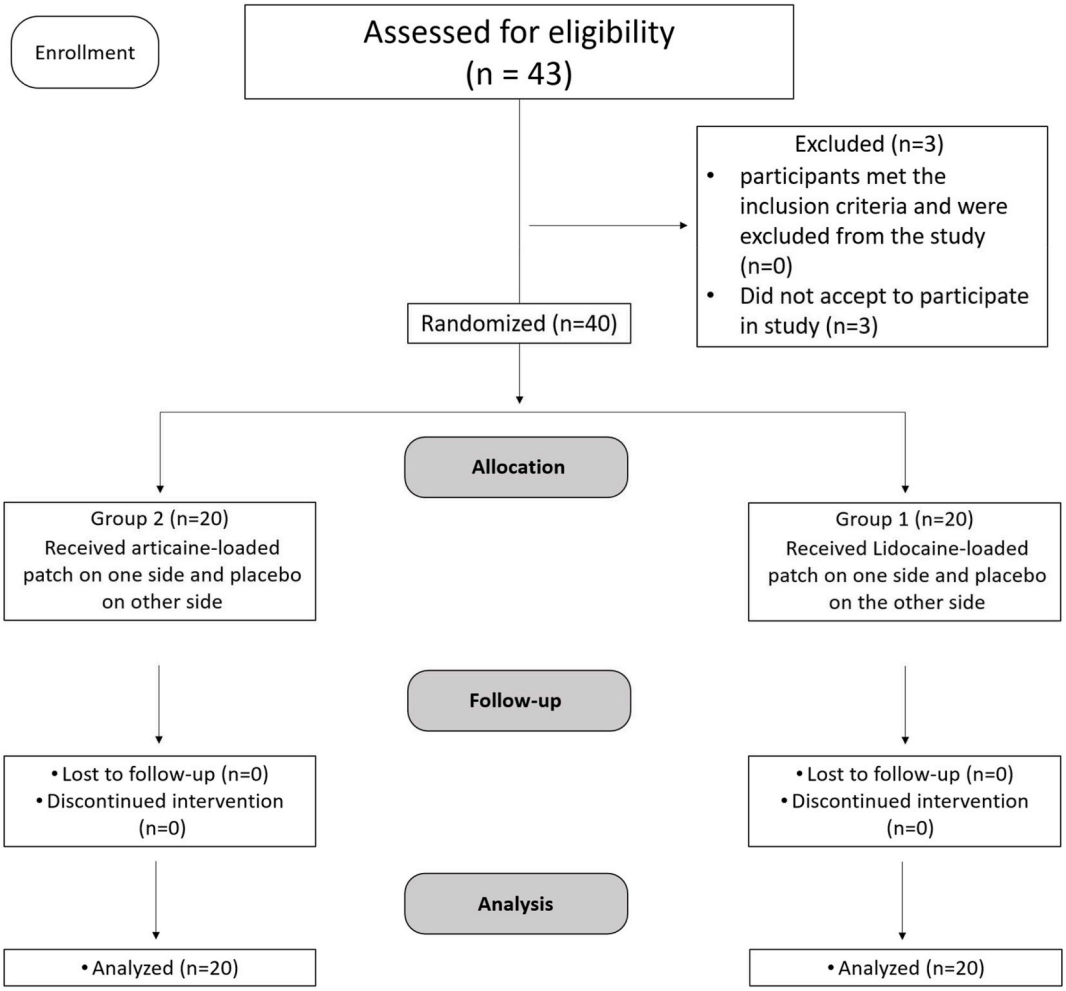

Fig. 11. The CONSORT diagram of the clinical trial study.

Table 5
Comparison of demographic information between the two groups.

Demographic data	Group 1	Group 2
Gender (n, %)		
Male	11 (55 %)	12 (60 %)
Female	9 (45 %)	8 (40 %)
Age (years)	26.57 ± 3.62	25.83 ± 3.37
Weight (Kg)	72.25 ± 23.49	71.17 ± 20.55
Systemic disease (n, %)		
Healthy	18 (90 %)	19 (95 %)
Cardiovascular disease	0	0
Hypothyroidism/hyperthyroidism	2 (10 %)	1 (5 %)

Note: data are expressed as mean ± SD or the number of people (n).
Group 1: treated with lidocaine-loaded patch on one side and placebo patch on the other side.
Group 2: treated with articaine-loaded patch on one side and placebo patch on the other side.

4.2. Selection of ethylcellulose polymer as the backing layer

Since the main objective of the current investigation was to achieve unidirectional medication administration in the buccal region, patches consisting of three layers were designed. Thus, a non-water-soluble backing layer was included to restrict the diffusion of drug molecules into the oral cavity. Instead, it directed the diffusion of the API towards the desired area. In the current study, ethylcellulose was utilized due to its recognized characteristics of being non-toxic, non-allergenic, non-irritating, and generally acknowledged as

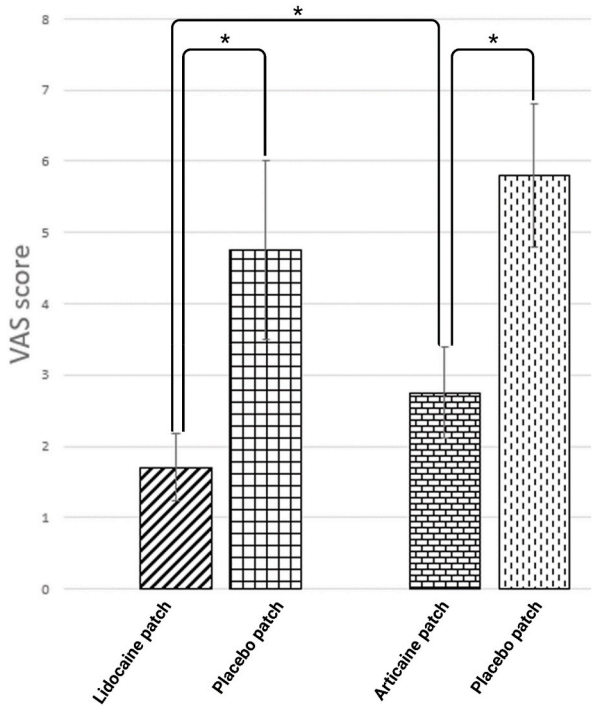

Fig. 12. VAS scores in the studied groups (*: significant difference between the lidocaine-loaded and articaine-loaded patches ($p < 0.001$); #: lidocaine-loaded patch vs. drug-free patch ($p < 0.001$); ^: articaine-loaded patch vs. drug-free patch ($p < 0.001$)).

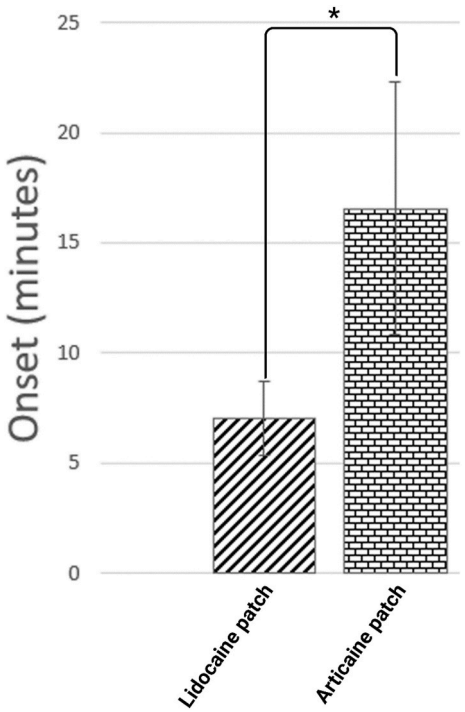

Fig. 13. The onset of action in the studied groups (*: significant difference between the lidocaine-loaded and articaine-loaded patches ($p < 0.001$)).

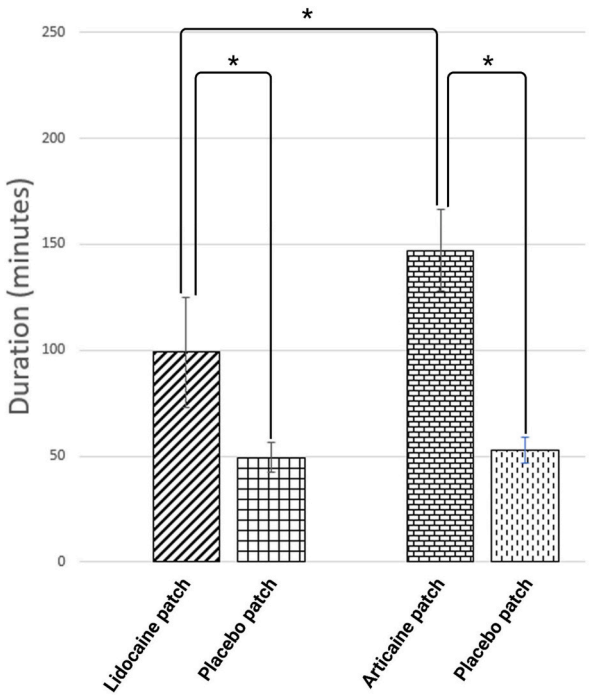

Fig. 14. Duration of action in the studied groups (*: significant difference between the lidocaine-loaded and articaine-loaded patches ($p < 0.001$); #: lidocaine-loaded patch vs. drug-free patch ($p < 0.001$); ^: articaine-loaded patch vs. drug-free patch ($p < 0.001$)).

safe. Additionally, ethylcellulose maintains promising film-forming properties that allow for the creation of thin and uniform patches [18]. The formation of tri-layered patches was confirmed via microscopic visualization of the samples with SEM. Apart from increasing the efficiency of drug delivery to the target point, directing drug diffusion using unidirectional patches would also result in reduced drug distribution within the oral cavity and help reduce the contact of drug molecules with gustatory receptors and sensation of the drug taste inside the oral cavity. Considering the unpleasant taste commonly associated with many local anesthetics like lidocaine and articaine, it is essential to prevent the drug from spreading in the oral cavity. In the study conducted by Salale et al. aspartame was utilized as a sweetener in the oral formulation of the amide local anesthetic (Bupivacaine) to mask its bitter taste, ultimately leading to improved patient compliance [19]. Also, Based on the study conducted by Boddu et al. a mixture of sweeteners and citrus flavors has been used to mask the bitter taste of local anesthetics such as lidocaine [20]. Thus, considering the extremely unpleasant taste of lidocaine, several strategies, including unidirectional drug delivery and the addition of sweeteners and flavors, were implicated simultaneously in the current study.

4.3. Selection of eudragit L100-55 polymer as the intermediate layer

Eudragit polymers are extensively used as a coating material in various pharmaceutical formulations [21]. It was observed that the longest adhesion time and the convenient bio-adhesion strength reflect the different behavior of Eudragit, which, in addition to its role as a film-forming polymer, possesses non-negligible mucoadhesive properties that enhanced mucoadhesion and facilitate the adhesion of the support layer to the mucoadhesive layer [11,22,23].

4.4. Selection of carbopol polymer as the mucoadhesive layer

Moreover, implementing a mucoadhesive polymer as the inner layer of the patch enhanced the infiltration of the drug payload into the mucosal membrane. Carbopol, as a polymer, exhibits mucoadhesive properties and offers several advantages in drug delivery. These include superior mucoadhesion, resulting in the formulation's extended adhesive residence time. Moreover, Carbopol enhances drug permeation and facilitates prolonged drug release. Additionally, it demonstrates pH compatibility with all mucosal sites, exhibits biocompatibility, and displays pseudoplastic behavior when formulated. Consequently, incorporating Carbopol can be an effective mucoadhesive agent for topical drug delivery systems [24].

4.5. Effect of the studied independent variables on characteristics of the prepared patches

4.5.1. Drug content

The significant drug content of lidocaine patches and articaine patches demonstrated that the medication was adequately

incorporated within the mucoadhesive layer. By increasing carbopol concentration from 1.25 % and reducing eudragit from 7.5 %, the percentage of drug content was increased. The observed results could be attributed to the method utilized to determine the drug content in patch samples. As described previously, in order to measure the actual drug content, the polymer layers were first dissolved in ethanol, and the active substance was released; then, HCl solution was added, and ethanol was evaporated, so the drug was dissolved in the acidic solution. In this process, eudragit and ethyl cellulose precipitation may occur after the evaporation of ethanol, and some of the drug molecules may also be trapped within the layers of polymer chains. Cavallari et al. studied lidocaine multiparticulate buccal patch showed that carbopol binds to lidocaine physically and improves drug loading. Lidocaine is a weak base (pKa 7.92), while carbopol is a weak acid (pKa 6.0), and the interaction between the two compounds significantly improves the solubility of the drug in water [25]. Therefore, higher carbopol concentrations, due to the affinity of this polymer to the drug, prevent the penetration of the drug into the deposited layers of EC and EU. Also, reducing the amount of eudragit resulted in increased binding of the drug molecules to the carbopol layer.

4.5.2. Mucoadhesive force

The study by Deore et al. showed that increasing polymer concentration would increase the bioadhesive force [26]. The present study revealed that by increasing ethyl cellulose concentration up to 4.5 %, the mucoadhesion force raised because ethyl cellulose could act as a protective layer and prevent the rapid dissolution of the carbopol layer in saliva. This outcome demonstrated that since the hydrophobicity of ethyl cellulose reduced the hydration and swelling of the film, the mucoadhesion force decreased with a further increase in ethyl cellulose concentration [27]. In addition, in the current study, it was observed that by increasing the eudragit concentration by two-fold (from 7.5 %), a 38.5 % reduction in the mucoadhesion force was observed, which was comparable to the results of the article by Kumria et al. in which, it was found that increasing the amount of eudragit by two-fold resulted in 28.5 % reduction in mucoadhesion force. Decreased mucoadhesion could be attributed to the hydrophobic nature of eudragit, which reduces the chance of binding to mucin. Also, it was reported that by increasing the amount of carbopol in the prednisolone buccal patch, the mucoadhesion force also increased [28]. The reason could be related to the high hydrophobicity of prednisolone, which prevents binding to carbopol polymer chains. However, In the current study, due to the use of lidocaine, the interaction between lidocaine and carbopol was more influential than the mucoadhesion force of patch to mucin hence, increasing the amount of Carbopol reduced the mucoadhesion force. The observed decrease in mucoadhesion force can be attributed to the interaction between lidocaine, a basic drug, and the acidic carboxylic groups of carbopol. This interaction shielded the negative charge of the carboxylic group, reducing the repulsion forces between carboxylic groups. Consequently, the Carbopol may undergo a recoiling effect, making it challenging for the drug to diffuse out of the system, thereby hindering the formation of secondary chemical bonds with biological tissues [29].

4.5.3. Elongation at break (E_{Max})

In this study, with the simultaneous increase of Carbopol (over 1.25 %) and the decrease of Eudragit (from 7.5 %), E_{max} increased. In an article by Anupam et al. it was reported that with a 50 % increase in the amount of carbopol, E_{max} increased by 16.7 % [30]. In the current study, with the same percentage increase of carbopol from 1.25 % (w/v), E_{max} increased by 30.83 %. In the mentioned article, the percentage of plasticizers was the same in all formulations. However, in the current study, the plasticizer percentage was determined according to the polymer weight. So, it increased in different formulations based on incrementing polymer weight. Thus, a more influential increase in E_{max} percentage was observed. The article by Sampaopan et al. reported that the percentage of E_{max} decreased with the increase of eudragit in pectin mucoadhesive film. In the present study, a decrease in E_{max} with a slight slope was observed with increasing eudragit concentration [31].

4.5.4. Young's modulus

In the present study, the value of Young's modulus increased by increasing the percentage of ethyl cellulose and decreasing the percentage of eudragit. This phenomenon might be caused by the higher elasticity of eudragit polymer compared to ethyl cellulose, which led to decreased Young's modulus. The amphiphilic nature of Eudragit and the hydrophobic properties of ethyl cellulose are distinct characteristics of these polymers. The presence of hydrophilic propylene glycol and hydrophobic triacetin as plasticizers affects the elasticity of the Eudragit layer in the film. Conversely, triacetin exerts a more pronounced impact on film elasticity in the ethyl cellulose layer. In the current investigation, the amount of plasticizer in each formulation was determined based on the polymer weight, leading to a more substantial influence of eudragit concentration on elastic properties and a more significant effect of the ethyl cellulose layer on plastic properties. Consequently, an increase in the concentration of ethyl cellulose and a decrease in eudragit concentration resulted in the elevation of Young's modulus [32]. According to a study by Sadeghi et al. the incorporation of plasticizers like triacetin and propylene glycol into eudragit was found to decrease both tensile strength and Young's modulus [33].

4.6. Surface pH

Although the low pH level of the patches could enhance the permeability of the formulation, it resulted in a mild irritation of the mucosal layer, as reported by the subjects of the study. According to the research conducted by Talal Sulaiman et al. the pH becomes acidic when the concentration of carbopol increases as a result of the acidic properties of this polymer [34].

4.7. DSC

In the analysis of the patches containing each drug, it was evident from the graphical representation that the melting endothermic

peak of the drug underwent notable shape transformation alongside a slight leftward shift. This shift could be attributed to the overlap between the drug and peak corresponding to ethyl cellulose within the patch sample. The presence of ethyl cellulose in the formulation influenced the thermal characteristics of the patch, resulting in the observed shift in the melting peak of the drug. This observation highlighted the interaction between the drug and ethyl cellulose, which affected the thermal behavior of the patch formulation. The transition temperature of ethyl cellulose is reported in the literature to be 130–133 °C [35]. However, increasing the distance between the ethyl cellulose polymer chains by the plasticizer could have made the polymer chains slide more easily on each other and thus move at lower temperatures. Therefore, the transition temperature was reduced to about 85–115, which had overlap with the location of the peak related to the drugs incorporated in the patches.

4.8. Clinical study

Considering the indication of the patches designed in the current study, a short onset time would be favorable since the dentist could start the procedure consequently. Thus, lidocaine was found to be more suitable for the preparation of a buccal patch due to its faster onset of action compared to articaine. Additionally, patients reported experiencing less pain with the lidocaine patch as opposed to the articaine patch. Based on the findings of the drug release profile study comparing lidocaine-loaded patches and articaine-loaded patches, it was observed that within a 15-min period, approximately 50 % of lidocaine was released from the patch, while only 8 % of articaine was released. This could justify the superior efficacy of the lidocaine-loaded patch during the 15-min interval.

In a study by Oliveria et al. no significant differences in palatal pain sensitivity were observed between the two solutions 5 min after injection. The VAS score values for articaine and lidocaine were recorded as 2.3 and 2.7, respectively. This study did not provide evidence to support the assertion that articaine exhibits superior diffusion compared to other local anesthetics commonly used in dentistry [36].

The current study also demonstrated that the duration of the effect of the articaine patch was significantly longer than that of the lidocaine patch ($p < 0.001$). This finding could be attributed to the superior penetration of articaine compared to lidocaine, which is facilitated by the higher log P value of articaine (3.24) compared to lidocaine (2.44) [37,38]. This enhanced penetration allows for better blockade of deeper sensory. Besides, when the drug molecules penetrate deeper into the buccal layers, it would increase the chance of drug accumulation in the fat tissue and decrease its removal via blood circulation, leading to a longer duration of action [39].

A study conducted by Snoeck et al. cautioned against using articaine in children below the age of seven. The findings of their clinical trial indicate that the 4 % articaine solution does not offer any distinct advantages over the 2 % solution [40]. Consequently, considering that one of the objectives of the present research was to develop a buccal patch for pediatric use, it is preferable to utilize lidocaine instead. The study by Sampaopan et al. measured patients' pain levels during dental procedures using the VAS score and assessed their anxiety through a questionnaire. The study revealed a significant correlation ($p < 0.001$) between the level of pain experienced by the patients and their anxiety levels. Although the level of anxiety was not investigated in the current study, it could be anticipated that the patients treated with lidocaine patches might have experienced less anxiety since they had reported pain VAS scores less than 2 [31]. The findings of this study are applicable to individuals of all ages, particularly children and older adults who may experience discomfort from injections.

This study was limited by ethical restrictions that prevented investigation in specific populations, including pregnant women and children.

5. Conclusion

Regarding the formulation, it was demonstrated that 3-layered patches were fabricated and optimized to obtain appropriate mechanical characteristics and drug release profiles. Lidocaine, a well-established anesthetic drug, and articaine, a more hydrophobic drug with the same indication, were loaded to compare the efficacy of each formulation in healthy volunteers. The optimized formulation loaded with lidocaine showed a higher clinical effect on the prevention of pain sensation during the injection compared to the articaine-loaded formulation. Moreover, it was observed that the onset of the effect of the lidocaine patch was significantly lower than that of the articaine patch ($p < 0.001$). This phenomenon can be attributed to the higher saturation solubility of lidocaine compared to articaine, as evidenced by the higher release of lidocaine relative to articaine within the same period. Thus, the lidocaine-loaded 3-layered patches are suggested for further evaluations to provide an effective means of reducing the patients' pain, hence, the fear and hesitation from dental processes. Thus, it could be specifically advantageous in pediatric dentistry.

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Ethics and informed consent

This trial was prospectively registered with research ethics committee of Isfahan university of medical sciences (registration number: IR.MUI.RESEARCH.REC.1401.130) on June 13, 2022. All participants provided written informed consent prior to their enrollment in the trial, signifying their voluntary involvement and allowing for the publication of the collected clinical data. The study population consisted solely of adults.

Data availability statement

The data that support the findings of this study are available and could be provided upon reasonable request. The data are not publicly available due to privacy restrictions.

CRediT authorship contribution statement

Elham Panahandeh: Writing – review & editing, Writing – original draft, Software, Investigation, Formal analysis. **Erfaneh Ghassami:** Writing – review & editing, Writing – original draft, Validation, Supervision, Software, Project administration, Investigation, Data curation, Conceptualization. **Milad Etemadi Sh:** Writing – review & editing, Visualization, Supervision. **Jaleh Varshosaz:** Writing – review & editing, Visualization, Supervision.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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