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Research Article

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Comparison of the Efficacy of Tetracycline and Triamcinolone Mucoadhesive Gels in Treating Recurrent Aphthous Stomatitis: A Preliminary Study

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Abstract

Recurrent Aphthous Stomatitis (RAS) is a widespread oral condition characterized by painful lesions on the oral mucosa, affecting about 20-25% of the population, with a higher occurrence in females. The etiology remains unclear, but factors such as infections, nutritional deficiencies, and stress have been implicated. Current treatments often focus on symptom relief, and while topical formulations are common, their efficacy is limited by poor retention at the site of action. Mucoadhesive buccal gels are formulations designed for localized drug delivery in the oral cavity, enhancing adhesion and prolonging contact time with the buccal mucosa. This study aimed to develop a mucoadhesive gel containing Tetracycline (TC) and evaluate its effectiveness in treating RAS compared to a Triamcinolone (Tri) gel. Sixty participants aged between 20-50 with RAS were recruited for a randomized, double-blind clinical evaluation. Two groups of patients were formed, one of which received TC-gel and the other Tri-gel. Gel formulations were prepared using carboxymethyl cellulose (CMC) and Carbopol, with pH, in vitro drug release, mucoadhesive strength, and residence time assessed. Clinical evaluations included measuring ulcer diameter, pain intensity via the Visual Analogue Scale (VAS), and patient satisfaction over a 10-day treatment period. The TC-gel demonstrated a mean pH of 6.63 ± 0.15 and released 95.74% of TC after 240 minutes. The mucoadhesive strength was 544.44 ± 17.77 ($dyne/cm2$), with a residence time of 78 ± 1.61 minutes. Both gels significantly reduced ulcer diameter and pain levels by day 10, with no significant differences between groups. Patient satisfaction was high, with 73% reporting excellent or good outcomes for both gels. The TC-gel was an effective treatment for RAS, comparable to Tri-gel, with promising mucoadhesive properties and patient satisfaction. These findings support the potential of TC-gel as a viable therapeutic option for managing RAS symptoms.

Keywords: Mucoadhesive gel; Recurrent aphthous stomatitis; Tetracycline; Pain scale; Lesion diameter; Triamcinolone.

1. Introduction

Recurrent Aphthous Stomatitis (RAS) is a widespread ailment of the oral cavity, manifested by the formation of small, painful lesions on the oral mucosa [1, 2]. It has been estimated that 20-25% of the population experiences RAS [3], with

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a greater incidence in women than in men [4]. Heredity has also been found to be a part of RAS's development [5, 6]. The exact cause of RAS is yet unknown. However, viral and bacterial infections[1], deficiencies in vitamins and microelements such as iron, B12, vitamin D, and folic acid [7-9], mucosal injury [10], imbalance in estrogen/ progesterone hormone levels [11, 12] and stress [13] have all been proposed as possible causes of the RAS incidence. Accordingly, most of the time, treatment focuses on reducing the symptoms. RAS is a chronic, recurrent inflammatory disease that appears as a sore on the oral mucosa and usually spreads inside the lips, cheeks, gums, and tongue [14]. After 6-24 hours, a small, round ulcer with a diameter of 3-9 mm appeared. The ulcer is enclosed by a red inflammation area [15]. There is no certain treatment for RAS, and thus, the management includes reducing the severity, duration, and symptoms of RAS [2]. Topical formulations are often the first-line treatment for RAS due to their effectiveness, safety, and low cost. However, the treatment with topical dosages is limited because of the rapid rinse of applied dosage and, thus, low retention time at the site of action [16]. Topical antibiotics such as tetracycline (TC) [17] and doxycycline [18], as well as topical corticosteroids such as hydrocortisone [19], triamcinolone (Tri) [20, 21], and betamethasone [22] are the first-line therapy for RAS. However, atrophy, striae, rosacea, perioral dermatitis, acne, Tinea incognito, and purpura are some of the most prevalent side effects of topical corticosteroids such as Tri [23, 24]. Collagenase tissue levels have been reported to be increased in the inflammatory diseases. In addition to its antibacterial effect, TC has been proven to inhibit the collagenase [25]. Thus TC can be a good choice for topical treatment of RAS and has been used in form of liquid mouthwash [20], capsules [26], and topical application of TC crushed tablets [27]. Gel formulations have some advantages over other topical formulations. They spread easily throughout the mucosa [28] and make intimate contact with its membrane [29]. Accordingly, these non-irritable formulations exhibit high patient compliance [28, 30, 31]. However, the gels suffer from low retention time in the applied site and leading to need for frequent administration of the formulation [32]. So bio-adhesive components such as carboxymethyl cellulose (CMC) are suggested in order to prepare bio-adhesive gels [33, 34]. Mucoadhesive gels have been used for the treatment of mucositis due to their appropriate residence time at the desired cite. For instance, Salman pour et al., prepared a mucoadhesive gel containing carbopol-934 and chitosan for the treatment of chemotherapy-induced oral mucositis [35].

Mucoadhesive buccal gels are innovative pharmaceutical formulations designed for localized drug delivery within the oral cavity, providing a sustained release of therapeutic agents while enhancing bioavailability and patient compliance. The unique properties of mucoadhesive gels stem from their ability to form strong interactions with mucosal tissues, prolonging the active ingredients' contact time. This characteristic is particularly beneficial in treating oral conditions such as recurrent aphthous stomatitis, where localized therapy can significantly alleviate symptoms and promote healing [36].

This research focuses on creating a mucoadhesive gel containing TC (TC-gel), evaluating its effectiveness in treating RAS, and comparing it to a gel containing Tri (Tri-gel). The duration of ulcer healing, pain intensity measured by the Visual Analogue Scale (VAS), patient satisfaction, and ulcer diameter were compared between patients treated with TC-gel and those treated with Tri-gel.

2. Materials and Methods

2.1. Materials

TC powder (ScienceLab Inc., USA), CMC, Carbapol 934, EDTA, Sodium phosphate monohydrate, HCl, Triethanolamine, Carboxy methyl cellulose 90Kda (Merck, Germany), Triamcinolone (Loghman, Iran), Ethanol 96% (Jahan Alcohol Teb, Iran), Sheep mucus, Distilled water.

2.2. Preparation of the Formulations

Two types of gel formulations were prepared. Gels contain CMC and Carbopol (Dual formulations), including A1, A2, and A3, and those containing just one of the polymers (Single), including B1, B2, B3, and B4. 1.25 mg of TC was dissolved in a mixture of 10 ml ethanol and 10 ml DW to prepare dual formulations.CMC and carbopol were first dispersed in 20 ml of distilled water (DW) while stirring. The drug solution was slowly added to the mixture. Then, 10 ml of DW was added to bring the gel volume to 50 ml. After that, a few drops of triethanolamine were added to the mixture, followed by 0.5 ml of EDTA solution. The mixture was left at room temperature for 24 hours to evaluate its stability. Single formulations were prepared with CMC or carbopol. To prepare the B1 formulation, 0.5 0f carbopol was dispersed in 30 ml of DW while stirring. A TC or Tri solution was made by dissolving 1.25 mg of TC in 10 ml ethanol plus 10 ml DW or by dissolving 1.25 mg of Tri in 20 ml ethanol and was slowly added to the dispersed carbopol.

After that, a few drops of triethanolamine were added to the mixture, followed by 0.5 ml of EDTA solution. The mixture was left at room temperature for 24 hours to evaluate its stability. The gel was formed a biphasic gel after 24 hours. Consequently, just CMC was used as a polymer for the remaining single formulations. Furthermore, in B3 and B4 formulations, the drug solutions were prepared by adding 1.25 mg TC to 20 ml of DW. The same procedure was used for the preparation of B5 to B6 formulation. The drug solutions were prepared by adding 1.25 mg Tri to 20 ml of ethanol.

2.3. pH determination

The pH of each gel formulation was determined using a pH meter, which was calibrated before each use with a buffer solution at different pH levels.

2.4. In vitro drug release

The USP-recommended dissolution apparatus was utilized to conduct the in vitro release studies (USP apparatus III) [37-39]. A 50 ml solution of PBS with a pH of 6.8 was used as the dissolution media. Three samples of the formulations were located on a glass surface and then added to the beaker. The temperature of the apparatus was set to 37 °C, and the speed was set to 50 rpm. Sampling intervals were 5, 10, 15, 20, 30, 45, 60, 90, 120, 180, and 240 minutes, and in each sampling, 5 ml of the TC-gel or Tri-gel was withdrawn. After each sampling, 5 ml of fresh PBS (pH=6.8) was added to the beaker. The drug concentration in each sample was determined by measuring the absorbance at a wavelength of 275 nm for TC-gel and 240 nm for Tri-gel using a spectrophotometer

2.5. Measuring mucoadhesive strength of TC-gel

The mucoadhesive strength of TC-gel and Tri-gel was measured by sheep mucous and a mucoadhesive force-measuring apparatus. A modified physical balance method was used for this experiment [40]. Before being used, the sheep mucus segments had been brought to room temperature after being frozen in PBS at pH 6.8. The sheep mucous was placed in the lower vial with the mucosa layer facing outward. The vial was then filled with PBS (pH=6.8). The TC-gel was placed in the upper vial, then on top of the lower vial. Pressure was used to certify contact between the sheep mucous and prepared gels. Weights were added to the other side of the scale to separate the two vials.

2.6. Determination of in vitro residence time

A locally modified USP apparatus investigated the in vitro residence time [41, 42]. 500 ml PBS (pH=6.8) was used as medium, and the temperature was set to 30 ºC. A piece of sheep mucous was fixed on a glass slab. Then 0.5g of TC-gel or Tri gel was fixed on the slab so that it came into contact with the mucosal membrane. The glass slab was permitted to move up and down after being fastened vertically to the device. The gel was fully submerged in the PBS at the lowest point, and at the highest point, it was exposed. It was noted how long it took for the gel to erode off the mucosal surface.

2.7. Efficacy Index

The efficacy indices (EI) of the ulcer diameter were determined using the formula below [43, 44]. V10 represents the values measured at the day 10 visit, whereas V1 represents the baseline value determined prior to the study participation[43, 44]:

$$EI = ([V10-V1] \div V1) \times 100\%$$

The EI was evaluated on a 4-rank scale:
Heal: EI=100%, Marked improvement: 100%>EI≥70%, Moderate improvement: 70%>EI ≥30%, and No improvement: EI <30%

2.8. Subjects and study design

A total of 60 subjects were recruited from the Tabriz University of Medical Sciences dental clinic for randomized, double-blind clinical evaluation [45]. The ethical committee approved the proposal and consent form (TBZMED.REC.1394.424). All patients involved in the study were aged between 20 and 50 and met the same specific criteria for inclusion and exclusion as the following:

Inclusion criteria:

1. Individuals between the ages of 20 and 50, regardless of gender.
2. Voluntary engagement and agreement to complete the informed consent documents.
3. The patient has 1 to 5 aphthous ulcers, each with a diameter of no more than 5 mm, that have been present for less than 48 hours.
4. The anticipation that their ulcers typically require 5 or more days to heal without any medical intervention.
5. Typical perception of pain without anesthesia or abnormal sensations.

Exclusion criteria:

1. Documented instances of severe medication allergies.
2. Pregnancy and breastfeeding (Urine positive for human chorionic gonadotropin).
3. Simultaneous medical disorders that could potentially endanger the health of the participants, such as severe liver, renal, and heart dysfunctions.
4. A chronicle of an immunological issue.
5. Ulcers can occur due to systemic diseases such as ulcerative colitis, Crohn's disease, Behçet's syndrome, or severe anemia.
6. Administration of systemic corticosteroids or other immunomodulatory drugs within 1 month prior to the start of the research.
7. Prior consumption of nonsteroidal anti-inflammatory medicines or oral antihistamines within one month before the start of the research.
8. Administration of any ulcer treatment or medicine within 72 hours prior to study enrollment
Prior to study admission.
9. The patient received systemic antibiotics within less than 2 weeks.
10. Exclude participants who have participated in any other clinical studies within 3 months before study admission.

Before the trial, all patients signed a consent form and were informed of their right to withdraw from the study at any time. Two groups of participants were formed. Tri-gel was administered for patients in the first group (30 patients) and TC-gel for patients in the second group (30 patients). Participants were guided to use the gel at the ulcer site 3 times a day for 10 days. They were also advised to moisten the gel with saliva after each application and to refrain from eating for 30 minutes after applying the gel. It is essential to note that patients were not permitted to use any other medications during the trial.

2.9. Clinical evaluation

The gels were packaged and coded in a way that made it impossible to distinguish between TC-gel and Tri-gel. It is worth knowing that the B4 formulation was used. The clinician then randomly assigned the gels to the patients. The lesion diameter, duration of ulcer healing, and patient satisfaction were compared between the two groups. The ulcer diameter was established by measuring the length between two opposing edges of the lesion border with a periodontal probe. A visual analog scale (VAS) was employed to assess pain, utilizing a 10-cm horizontal line with endpoints representing no pain (origin) and terrible pain. The following cut points on the pain VAS have been recommended: no pain (0-4 mm), mild pain (5-44 mm), moderate pain (45-74 mm),

and severe pain (75-100 mm) [46, 47]. Participants were instructed to indicate the current level of pain for the ulcer by marking a vertical line at the corresponding site. All the patients were monitored at each visit by the dental clinician. No severe adverse effect was seen in any of the participants.

2.10. Statistical methods

All data were analyzed using SPSS software, and the significance level was established at 0.05 (P≥0.05). The Mann-Whitney test compared the two groups' pain scale and lesion diameter. Furthermore, Levene's test was used to study the equality of variances.

3. Results and Discussion

3.1. Preparation of the Formulations

Topical steroids have been widely used for the treatment of RAS. Nevertheless, when applied to the oral mucosa, these medications may lead to the occurrence of adverse effects, including oral candidiasis along with a burning sensation in the oral cavity and hypogeusia, hypersensitivity reactions to the corticosteroid, and suppression of the hypothalamic-pituitary-adrenal axis, leading to secondary adrenal insufficiency [48]. Thus, TC has been used to treat RAS and prevent these side effects. In addition to the antibacterial effect, TC has been confirmed to decrease the severity and pain level in patients with RAS [17]. It was also found that TC can decrease collagen degradation by inhibiting collagenase activity. In individuals with periodontitis, the local administration of TC has demonstrated a decrease in IL-1B, C-reactive protein, and TNF levels [49]. Crushed tablets [50], oral pastes [51], and mouthwashes [52] have been used for the treatment of Ras. However, these formulations do not have enough retention time in the applied site, and this causes frequent administration of the formulations [32]. Hence, a mucoadhesive TC-gel was prepared in this study, and its effectiveness in managing minor RAS was assessed. Natural, semisynthetic, and synthetic polymers can prepare polymeric gels. Anionic polymers such as poly(acrylic acid), poly(methacrylic acid), carboxymethylcellulose, sodium alginate, and poly[(maleic acid)-co-(vinyl methyl ether)], cationic polymers such as chitosan63 and some synthetic polymethacrylates, and amphoteric polymers such as gelatin and N-carboxymethyl chitosan, are the most common polymers that have been used in mucoadhesive gels [53-55]. All the formulations illustrated in **Table 1** were rejected due to the formation of a biphasic gel after 24 hours.

The Single formulations are shown in **Table 2**. In the B4 formulation, which contains TC, to increase the viscosity of the prepared gel, the amount of CMC was increased to 2 g. As a result, this formulation was used for further experiments. Similarly, the B7 formulation containing Tri was used for the following evaluations.

Table1. Dual polymer formulations.

Formulation	Carbopol (g)	EDTA (ml)	Alcohol (ml)	Drug(g)	CMC(g)	Approve or reject
A1	1.5	0.5	10	1.25	1	×
A2	0.25	0.5	10	1.25	1	×
A3	0.25	0.5	10	1.25	1	×

Table2. Single polymer formulations.

Formulation	Carbopol (g)	EDTA (ml)	Alcohol (ml)	Drug(g)	CMC(g)	Approve or reject
B1	0.5	0.5	10	1.25	-	✕
B2	-	0.5	10	1.25	1.5	✕
B3	-	0.5	٠	1.25	1.5	✓
B4	-	0.5	٠	1.25	2	✓
B5	0.5	0.5	20	1.25	-	✕
B6	-	0.5	20	1.25	2	✓
B7	-	0.5	20	1.25	2	✓

3.2. pH determination

It has been confirmed that the pH value of saliva is 5.5 to 8 [29]. The formulations applied to the mouth should not disrupt the acid-base balance in the mouth. The disruption of this balance leads to tissue damage in the oral cavity and affects its bacterial population [56-58]. In previous studies, the pH value of gels prepared for use in the oral cavity has been found to fall within the range of 6 to 7 [54, 59]. Our experiment showed that the pH value of the prepared TC-gel (6.63±0.15) was similar to the pH of saliva, indicating no potential for tissue damage.

3.3. Drug release profile

Initial data from the calibration curve were obtained to determine the percent of drug release. **Figure 1** shows the release profile of TC from TC-gel. 80.07% of TC was released from the prepared gel after 120 minutes, and after 240 minutes, 95.74% of the drug was released from the prepared formulation. **Figure 2** shows Tri-gel's release profile. 90.25% of Tri was released from the prepared gel after 120 minutes.

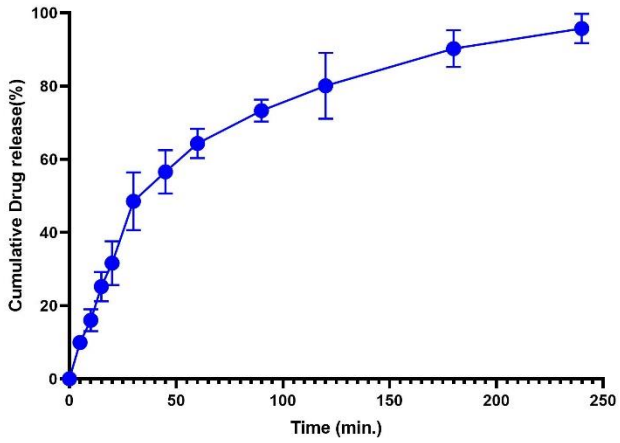

Figure 1. The release profile of TC from TC-gel.

Conventional drug delivery systems do not persist in the mouth for an extended duration, rendering them incapable of delivering drugs to the desired site in effective concentrations. Harish et al. prepared a muco-adhesive gel with HPMC and carbopol-containing clotrimazole to treat oral candidiasis. This muco-adhesive gel could sustain the release of the clotrimazole for up to 4 hours [54]. Similarly, the prepared TC-gel, which was composed of CMC, could successfully prolong the release of TC for approximately 4 hours.

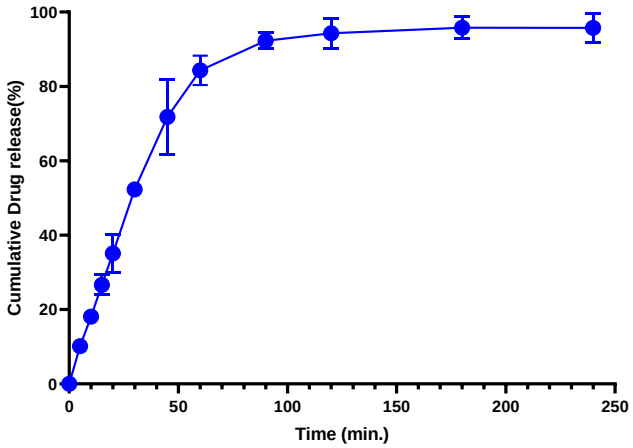

Figure 2- The release profile of TC from Tri-gel.

3.4. Measuring the mucoadhesive strength

The modified physical balance method was used to measure detachment force. The added weight was calculated by excluding the weight of each vial (8.9 g). The m*ucoadhesive strength* made by each weight was calculated by the below equation:

$$\text{M}ucoadhesive\ strength\ (dyne/cm^2) = m\ g\ /\ \text{A}$$

Where A is the area of the bottom of the vial, the detachment forces are shown in **Table 3**. The mean value of mucoadhesive strength of TC-gel was determined to be 544.44 ± 17.77 ($dyne/cm^2$). The same method was used to measure the mucoadhesive strength of Tri-gel. The mean value of the mucoadhesive strength of TC-gel was determined to be 537.18 ± 49.1.

Table 3. Mucoadhesive strength of TC-gel

Number of the measurement	The amount of added weight (g)	M*ucoadh esive strength* (*dyne/cm2*)
1	4.8	**522.67**
2	5	**544.44**
3	5.2	**566.22**

3.5. Determination of in vitro residence time

The modified USP apparatus method based on Nafee et al. [41, 42] was used to determine the residence time of prepared TC-gel. The experiment was repeated three times to achieve accuracy. The mean value of the time needed for deformation of prepared TC-gel was 78 ± 1.61 minutes, and the residence time of Tri-gel was 84 ± 2.3.

Based on previous studies, the residential duration of gels upon contact with the oral mucosa is restricted owing to the removal of the formulation due to the washing effect of saliva and mechanical stress. Thus, the residence time for most mucosal routes is less than an hour [60]. Furthermore, the liquid retention duration in the oral cavity is short, generally ranging from 5 to 10 minutes [61]. In a current study, TC crushed tablets were used topically to treat RAS. This treatment did not reduce the ulcer size and had a minor effect on the reduction in pain level [27]. This is likely because of the short residence time of TC crushed tablets in the oral cavity. In this study, a mucoadhesive TC-gel was prepared to enhance the formulation's residence time in the mouth. The prepared gel could prolong the residence time to more than 1 hour. The reason is that CMC, a cellulose derivative polymer, interacts with mucin and binds to the mucus layer in the oral cavity [62].

3.6. Clinical evaluation

3.6.1. Before the application of gels

The frequency of participants based on gender, pain, and lesion diameter

The patients were treated with TC-gel or Tri-gel. The frequency of different genders in the two groups, pain, and the lesion diameter in the patients with RAS are shown in **Table 4**. The lesion diameter was less than 4 mm in most participants, and the VAS score was 7.53 ± 0.34 and 7.23 ± 2.12 in the TC-gel and Tri-gel groups, respectively.

Ulcer occurrence time intervals are shown in **Table 4**. The time intervals of ulcer occurrence were 1.26 ± 0.71 and 1.11 ± 0.49 in the TC-gel and Tri-gel groups, respectively.

The wound healing duration was 9.81 ± 1.42 and 11.16 ± 0.81 days in the TC-gel and Tri-gel groups, respectively.

Table 4. The frequency of participants based on gender, pain, and lesion diameter

Baseline characteristics	TC-gel group(n=30)	Tri-gel group (n=30)
Genders (n)		
Male	17 (56.6%)	16 (53.3%)
Female	13 (43.3%)	14 (46.6%)
Age (y)		
Mean ± SD (n)	41.61 ± 7.3 (30)	40.18 ± 9.2 (30)
Range	22-50	23-47
Lesion Diameter		
Mean ± SD (n)	3.42 ± 2.340 (30)	4.20 ± 1.932 (30)
Pain (VAS)		
Mean ± SD (n)	7.53 ± 0.34 (30)	7.23 ± 2.12 (30)
Ulcer Occurrence Time(M)		
Mean ± SD (n)	1.26 ± 0.71 (30)	1.11 ± 0.49 (30)
Range	>1-3	>1-3
Duration of wound healing(d)	9.81 ± 1.42 (30)	11.16 ± 0.81 (30)
Mean ± SD (n)		
Range	4-14	4-16

3.6.2. After the application of the gels

Lesion diameter

Clinicians reported the lesion diameter on days 0 and 10. The mean diameter of the ulcer and P value is shown in **Table 5**. The decrease in the diameter of lesions was significant in both groups from day 0-day 10. At the same time, there were no significant differences in ulcer diameter between the TC-gel and Tri-gel groups.

Mohd et al. [27] used crushed TC tablets to treat RAS. However, after 7 days, there was no significant change in the lesion size. In a separate study [26], 250 mg TC capsules were given, which resulted in the complete healing of a 2.3 mm ulcer after 9 days. In our experiment, the prepared TC-gel could significantly decrease the ulcer size from 3.42 ± 2.340 to 1.76 ± 0.973.

Table 5. Mean ± standard deviation of lesion diameter in TC-gel and Tri-gel groups and their P value.

Day	TC-gel	Tri-gel	*P* value
0	3.42 ± 2.340	4.20 ± 1.932	0.42
10	1.76 ± 0.973	1.40 ± 1.430	0.13

Pain scale

VAS scores assessed the pain level on days 0, 3, and 6. After applying both gels, the pain score decreased in the participants. On days 0 and 6, the two groups had no statistically significant difference in pain levels (**Table 6**). However, on day 3, the pain level was significantly reduced in patients treated with Tri-gel. Together, these data indicate that the prepared mucoadhesive TC-gel efficiently reduces pain level in RAS patients. In a study, crushed TC tablets were used for RAS treatment, and the VAS score decreased from 7.52±1.17 to 3.82±1.33, indicating some improvement in pain [27]. In another research study, administration of 250 mg TC capsules decreased the pain scale from 5±2.3 to 0 after 9 days of taking the TC capsules [26]. In our study, the pain score was decreased from 7.53±0.34 to 0.13±0.66 after 6 days of application. These data support the conclusion that TC-gel could decrease lesion diameter and pain score in patients with minor RAS. This is probably because the prepared TC-gel could remain in the mouth for over 1 hour. Additionally, the formulation could prolong the release of TC for approximately 4 hours.

Table 6. Mean value ± standard deviation of pain scale in TC-gel and Tri-gel groups and their P value.

Day	TC-gel	Tri-gel	*P* value
0	7.53 ± 0.34	7.23 ± 2.12	0/09
3	0.86 ± 2.12	0.33 ± 0.66	0.03
6	0.13 ± 0.66	0.10 ± 0.30	0.07

Patient Satisfaction

The overall satisfaction with both TC-gel and Tri-gel in patients was evaluated by a questionnaire [63]. The findings of the satisfaction survey are shown in **Table 7** and **Table 8**. Overall, the patient reported a high level of satisfaction in both groups. 73% of participants who applied TC-gel reported it as excellent or good. Similarly, 73% of patients who applied Tri-gel reported excellent or good. The reason is the decrease in ulcer diameter, ulcer healing time, and pain level after the treatment with each of the gels.

Table 7. The satisfaction level in the TC-gel group.

Satisfaction level	Excellent	Good	Acceptable	Dissatisfaction
Percentage of patients	7%	66%	17%	10%

Table 8. The satisfaction level in the Tri-gel group.

Satisfaction level	Excellent	Good	Acceptable	Dissatisfaction
Percentage of patients	4%	69%	14%	13%

Efficacy Index

At day 10, the improvement rates of both TC-gel and Tri-gel were compared. Marked improvement was observed in 6 patients after TC-gel application and moderate improvement in 22 patients. However, 2 of them exhibited no improvement. Only 2 patients exhibited marked improvement in the Tri-gel group, and 25 exhibited moderate improvement. Three of the patients reported no improvement after the application of Tri-gel.

There was no significant difference in the efficacy index between the TC-gel and Tri-gel groups (p-value= 0.243).

4. Conclusion

Our experiment digs into the clinical evaluation of TC-gel and Tri-gel, representing their potential as an effective formulation for RAS treatment. The novel TC-gel could sustain the drug's release for up to 4 hours after application. Along with that, the mucoadhesive strength of the TC-gel was high enough to keep the formulation in the oral cavity for over an hour. Our clinical evaluation revealed no significant differences in pain level, lesion diameter, or patient satisfaction between the two formulations. Given the potential side effects of Tri-gel, our study suggests that TC-gel may be an expedient alternative treatment for RAS.

Ethics approval and consent to participate

The proposal and consent form were approved by the ethical committee of the Faculty of Pharmacy at Tabriz University of Medical Science (TBZMED.REC.1394.424).

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Conflict of interest

The authors declare there is no conflict of interest.

Data availability

Not applicable.

Athors Contributions

Farzaneh Davoudvandi: Writing – original draft. Fatemeh Soltanmohammadi: Validation, Writing – review & editing. Nasim Nourani: Writing – review & editing. Adel Mahmoudi Gharehbaba: Validation, writing– review & editing. Anali Aliakbari: Writing– review & editing. Firouz Pouralibaba: Conceptualization, Writing – review & editing. Yousef Javadzadeh: Conceptualization, supervision, Writing – review & editing.

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