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Research Article

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Evaluating the efficacy of triamcinolone acetonide chewing gum in treating recurrent aphthous stomatitis: A randomized clinical study

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Abstract

Recurrent Aphthous Stomatitis (RAS) is a prevalent inflammatory disorder that affects the mouth and is defined by painful ulcers. The precise cause of the condition is still unknown, and the major approach to treatment is mainly centered around managing the symptoms. Triamcinolone acetonide (TA) is a commonly used medication for several conditions. However, due to its potential benefits, there is growing interest in exploring novel drug delivery systems, such as medicated chewing gum (MCG). This study introduces a novel MCG formulation containing TA (T-MCG). We investigated its in vitro drug release and content uniformity before conducting a clinical trial comparing the efficacy of T-MCG versus placebo in patients with RAS. The T-MCG formulation exhibited a sustained release of TA for 120 minutes. The clinical findings demonstrated a notable decrease in the ulcer's size and the mean wound healing period. The results suggest that T-MCG not only improves the effectiveness of TA treatment by releasing the drug over a longer period and allowing it to stay in the mouth longer but also increases patient adherence due to its pleasant composition.

Keywords: Triamcinolone acetonide; Recurrent aphthous stomatitis; Drug delivery; Oral; Chewing gum.

1. Introduction

RAS, a prevalent inflammatory disease of the oral cavity [1, 2], is caused by viral and bacterial infections [3], allergies [4], deficiencies in vitamins or microelements [5, 6], and stress [7]. However, the exact etiology of RAS occurrence is unknown. RAS is common in women and patients between 10-40 years old [8]. It is characterized by developing small and painful ulcers on the oral mucosa, which spread into the lips, cheeks, gums, and tongue. RAS treatment primarily focuses on managing symptoms and reducing pain, ulcer size, healing time, and inflammation [9, 10]. Topical glucocorticoids, such

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as TA, are often the first choice for RAS treatment. TA decreases RAS symptoms through its anti-inflammatory and immunosuppressive effects [11]. To date, TA oral paste [12], ointment, mouthwash [13], and topical gel [14] have been used for aphthous treatment. Chewing gum (CG) is a potential drug delivery system representing emerging progress and development in current research. CG can deliver either pharmaceuticals or nutrients defined as medicated chewing gum (MCG) and non-MCG. MCG is a prolonged-release dosage form that continuously releasing its content [15]. This consumer-friendly formulation has been used for either topical or systemic administration through the oral cavity [16]. When nicotine CG was prepared for the first time, MCG gained significant attention as a drug delivery system [17]. However, to date, MCG has been developed for calcium carbonate, caffeine, fluoride, chlorhexidine, and dimenhydrinate [18]. Due to its high patient compliance, ease of carry, feasible administration, good taste, and beneficial health outcomes, MCG came into the spotlight and generated significant academic interest [19]. Being acceptable for children [16], the capability to bypass the first-pass effect [15], and inducing the saliva flow in the mouth [20] are other advantages of MCGs. Moreover, MCG is suitable for patients with difficulty swallowing [15]. In this study, for the first time, a novel MCG formulation containing TA (T-MCG) was prepared. In vitro, drug release and content/weight uniformity were investigated. Then, the clinical efficiency of prepared T-MCG was investigated in patients with RAS. The lesion diameter and duration of wound healing were compared between patients treated with T-MCG and those treated with placebo.

2. Materials and Methods

2.1. Materials

Triamcinolone acetonide powder (Crystal Pharma, Spain), Ethanol 96% (Merck, Germany), Gum base (Shirin Asal, Tabriz, Iran), Potassium dihydrogen phosphate (Chem-lab NV, Belgium), Disodium hydrogen phosphate (Merck, Germany), Glycerin (Merck, Germany), Distilled water.

2.2. Synthesis

2.2.1. Calibration curve of Triamcinolone acetonide

A calibration curve was first plotted to measure the TA concentration in the prepared formulation and study the drug release. First, a stock solution with TA in ethanol and PBS was prepared. Then the prepared stock solution was diluted to 1.638, 3.125, 6.25, 12.5, and 25 µg/ml. Consequently, a calibration curve was prepared by the UV absorbance of 5 solutions of TA at 240 nm.

2.2.2. Preparation of T-MCG formulation

TA (100 mg) was dissolved in the ethanol. The chewing gum formulation consisted of gum base (5.8 g), sorbitol powder (3.5g), glycerin (0.5 g), and TA was prepared using a fusion method [21]. The gum base was melted, and other components of CG (sorbitol and glycerin) were added to it. Finally, TA solution was added to the mixture, and ethanol was evaporated due to the hot temperature of the mixture. T-MCG was then allowed to cool.

2.2.3. In vitro drug release

The *in vitro* drug release from T-MCG was performed using chewing simulator CS-4.2 (Feldkirchen-Westerham, Germany). 100ml PBS (pH=6.8) was used as a release medium. The release chamber was surrounded with circulating water to maintain the chamber temperature at 37 ºC. The chew rate was 60 strokes/min [22]. The samples with a volume of 1 ml were taken at times of 15, 30, 60, 90, and 120 minutes and replaced with 1 ml PBS. The UV absorbance of samples at 240 nm was determined.

2.2.4. The effect of glycerin on drug release

The same procedure as the last part was used to investigate the effect of glycerin on the *in vitro* drug release profile of TA from prepared T-MCG.

2.2.5. Weight uniformity of the prepared T-MCG

According to the pharmacopeia, the maximum deviation from the average weight should be less than 5% [23]. Twenty randomly chosen T-MSCs were weighted.

2.2.6. Content uniformity of the prepared T-MCG

Based on pharmacopeia guidelines, content uniformity is calculated by measuring the drug content in 10 random MCGs. Each single MCG should have a drug content within the 85% to 115% range [23]. A total of ten randomly selected T-MCGs were dissolved in a mixture of ethanol and PBS with a volume of 50 ml. The

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solutions were then centrifuged at 50 ºC and 1500 rpm. Samples were taken from each beaker containing the T-MCGs and analyzed using a UV-VIS spectrophotometer.

2.2.7. Efficacy Index

The efficacy indices (EI) of the ulcer diameter were determined using the formula below [24, 25]. V3 represents the values measured at the day 3 visit, whereas V1 represents the baseline value determined prior to the study participation):

$$EI = ([V3-V1] \div V1) \times 100\%$$

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

2.3. Subjects and study design

A total of 30 subjects were recruited from the dental clinic of Tabriz University of Medical Sciences for prospective, double-blind trial clinical evaluation. The ethical committee approved the proposal and consent form (IR.TBZMED.REC.1400.617). All patients included in the study were aged between 20 and 50 and met the same specific criteria for inclusion and exclusion, as outlined in **Table 1**. Before the trial, all patients signed a consent form and were informed of their right to withdraw from the study at any time. The patients were divided into two groups. The first group (15 patients) was treated with T-MCG, and the second group (15 patients) was treated with a placebo (CG without TA). Participants were instructed to use the MCG 4 times daily for 3 days. It is worth knowing that patients were not allowed to use any other medications during the trial.

2.4. Clinical evaluation

The MCGs were packed and coded, making it impossible to differentiate between T-MCG and placebo. Then, the MCGs were given to the patients. The lesion diameter, duration of wound healing, and patient satisfaction were compared between the two groups. All of these parameters were evaluated before the application of MCGs and on day 3 after the administration.

Table 1. Criteria for selection

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 five 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.

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The ulcer diameter was determined by measuring the distance between two opposite edges of the ulcer border using 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. 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 a dental clinician. No severe adverse effect was seen in any of the participants.

2.5. Statistical methods

All data were analyzed using SPSS software, and the level of significance was established at 0.05 ($P \geq 0.05$). The one-way ANOVA test was used to compare the duration of wound healing and lesion diameter between the two groups. In addition, the Chi-square test was used to compare the improvement rate and satisfaction level between the two groups.

3. Results and Discussions

3.1. Synthesis

3.1.1. In vitro drug release

The release of TA from T-MCG is shown in **Figure 1**. The cumulative release percentages were calculated using data obtained from the calibration curve. Approximately 49.87% of TA was released from the prepared formulation after 30 minutes. After 120 minutes, nearly all of the drug was released from the formulation.

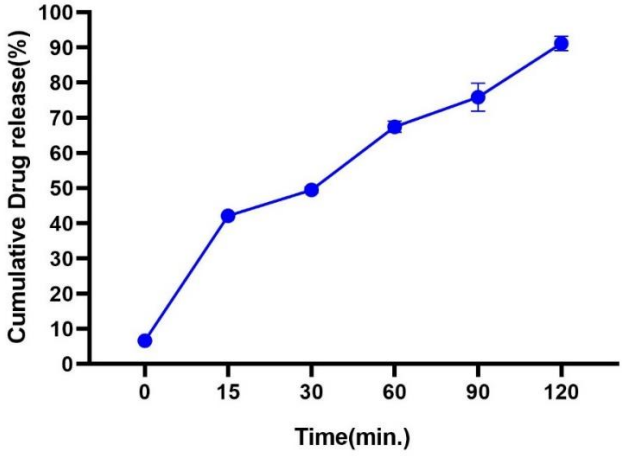

Figure 1. The release profile of TA from T-MCG.

3.1.2. The effect of glycerin on drug release

Figure 2 indicates the effect of glycerin on the release profile of TA from the MCG formulation. Only 51% of TA was released from glycerin-free T-MCG formulation after 120 minutes. Therefore, excluding glycerin from the formulation is not recommended as it may reduce therapeutic effectiveness. This is likely because TA is sparingly soluble in water, while glycerin is a hydrophilic substance. Thus, when glycerin was in the formulation, TA leaked out from the T-MCG. This result follows previous studies.

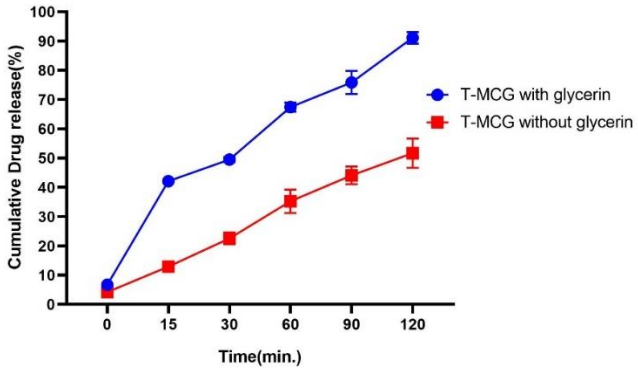

Figure 2. The release profile of TA from T-MCG with glycerin and T-MCG without glycerin

3.1.3. Weight uniformity of the prepared T-MCG

The weight of T-MCGs ranged from 0.840 to 0.921 g, with an average weight of 0.892 ± 0.032 g and a RSD of 3.59%. This is acceptable based on pharmacopeia guidelines.

3.1.4. Content Uniformity of the prepared T-MCG

The average content of TA in T-MCG was 29.75 ± 1.09 mg, with an RSD of 3.69%. This is acceptable based on pharmacopeia guidelines.

3.2. Clinical evaluation

3.2.1. Before the application of MCGs

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

The patients were treated with T-MCG or placebo. The frequency of different genders in the two groups, pain, and the lesion diameter in the patients with RAS are shown in **Table 2**. The lesion diameter was less than 4 mm in most of the participants.

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Table 2. The frequency of participants based on gender, pain, and lesion diameter

Baseline characteristics	T-MCG group(n=15)	Placebo group(n=15)
Genders (n)		
Male	9 (60%)	8 (53.3%)
Female	6 (40%)	7 (46.6%)
Age (y)		
Mean ± SD (n)	41.21 ± 9.61 (15)	39.81 ± 9.21 (15)
Range	23-50	20-47
Lesion diameter		
Mean ± SD (n)	4.02 ± 0.41 (15)	3.9 ± 0.32 (15)
Pain (VAS)		
Mean ± SD (n)	8.9 ± 0.76 (15)	9.2 ± 1.02 (15)

3.2.2. After the application of the MCGs
Lesion diameter and pain

The lesion diameter was reported by clinicians on days 0 and 3. The mean diameter of the ulcer and p-value are shown in **Table 3**. At the beginning of the experiment, the lesion diameter had no significant difference between the two groups (p-value > 0.05). After 3 days of treatment, the lesion diameter was significantly lower in patients treated with T-MCG compared to those treated with a placebo (p-value < 0.05).

3.2.3. *Pain scale*

Most patients experienced no pain (VAS = 0) 3 days after applying the new formula. A notable disparity was observed between the test and placebo groups, with a p-value of less than 0.0001(**Table 3**).

3.2.4. Duration of wound healing

The duration of wound healing is shown in **Table 3**. After 7 days of treatment with T-MCG or placebo, the wound healing duration was significantly lower in the T-MCG group. The mean value of healing duration in the T-MCG group was 5.07±1.93 days. These findings confirm topical TA's efficacy in the RAS treatment, consistent with previous studies [26, 27].

Table 3. Mean ± standard deviation of lesion diameter, pain (VAS), and duration of wound healing in the T-MCG group and placebo group and their P value.

Parameter	T-MCG		Placebo		P-value	
Lesion diameter	Day 0	4.021 ± 0.41	Day 0	3.96 ± 0.32	Day 0	0.839
	Day 3	1.76 ± 0.12	Day 3	2.10 ± 0.28	Day 3	0.038
Pain	Day 0	8.91 ± 0.76	Day 0	9.21 ± 1.021	Day 0	0.37
	Day 3	2.11 ± 0.31	Day 3	5.61 ± 0.62	Day 3	< 0.0001
Duration of wound healing	3.53 ± 1.31		5.47 ± 1.85		0.008	

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3.2.5. Patient Satisfaction

A questionnaire compared the overall satisfaction with both T-MCG and placebo in patients. The satisfaction survey results are shown in **Table 4**. 80% of patients who applied T-MCG noted that the treatment was good or excellent. However, this percentage was only 14% in patients who applied a placebo. Moreover, the T-MCG group's satisfaction level was statistically higher (p-value=0.026). This is likely due to the high patient compliance, more feasible dosage application of T-MCG formulation, and the ability of T-MCG to reduce the ulcer size [19].

3.2.6. Efficacy Index

On day 3, the improvement rates of both T-MCG and placebo were compared (**Table 5**). The improvement rate in the T-MCG group was significantly higher than in the placebo group (p-value= 0.001).

3.3. Discussion

Recurrent aphthous stomatitis is a prevalent inflammatory disease of the oral cavity, and it is characterized by the development of small, punched-out, painful ulcers on the oral mucosa [28]. Corticosteroids are the first-line treatment for RAS. Accordingly, topical corticosteroids such as triamcinolone, dexamethasone, and betamethasone have been used to manage RAS [29, 30]. MCG is a favorable drug delivery system for home treatment. In previous studies, herbal MCGs have been used to treat mouth ulcers [31]. In addition, Sarath et al. have successfully prepared the MCG formulation containing methylprednisolone. Approximately all of the drugs have been reported to be released from the MCG after 30 minutes[32]. In the present study, for the first time, an MCG formulation containing TA that could successfully prolong the release of TA for 120 minutes (**Figure 1**) was prepared. Plasticizers, such as glycerin, are commonly used in MCG to provide flexibility and a soft and pliable texture [33]. They can transform a hard, brittle gum base into a soft, flexible product [34]. It has been confirmed that soluble drugs are easily released from MCG. However, the release of drugs with low water solubility, such as TA, depends on the chewing time and components of the formulation [35-37]. So, excluding glycerin from the MCG formulation resulted in a decreased percentage of TA release. This can lead to reduced therapeutic effectiveness (**Figure 2**).

Based on the study by Shrivastava and co-workers, the oral paste of triamcinolone could reduce the ulcer size from 4 mm to 2.9 mm after 3 days of application (a 1.4-fold reduction) [12]. However, the findings of our clinical study revealed that the application of T-MCG 4 times a day could decrease the ulcer size by about 2.2-fold after 3 days of application (**Table 3**). Also, most patients qualified for no pain (VAS = 0) 3 days after applying the new formula (**Table 3**). It was confirmed in an investigation that after 4.9 days of topical administration of TA gel, 3 times a day, the wounds were completely healed. In our study, the duration of wound healing after administration of T-MCG 4 times a day was 3.5 days (**Table 3**). According to previous studies, the extended residence time of the formulation in the mouth leads to a suitable drug release rate and the preservation of drug concentration for better therapeutic efficiency. It has also been reported that CG's residence time is higher than that of lozenges [38]. Thus, the higher reduction in ulcer size and healing time observed in our study is likely due to the extended release of TA from T-MCG and the higher residence time of the formulation in the oral cavity compared to conventional gels and pastes.

Table 4. The patient satisfaction percentages in the T-MCG group and placebo group

Satisfaction level	Excellent	Good	Acceptable	Dissatisfaction
T-MCG group (Percentage of patients)	47%	33%	13%	7%
Placebo group (Percentage of patients)	7%	7%	33%	53%

Table 5. The improvement rate in the T-MCG group and placebo group

Group	T-MCG (Number of patients)	Placebo (Number of patients)
Marked improvement (70% ≤ EI <100%)	2	0
Moderate improvement (30% ≤ EI <70%)	12	14
No improvement (EI <30%)	1	1

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Furthermore, patient satisfaction and EI were significantly higher in the T-MCG group compared to the placebo group (**Tables 4** and **5**). Conventional topical treatments suffer from poor patient compliance, bad taste, and the need for several applications [39, 40]. The use of T-MCG addresses the mentioned challenges and offers a user-friendly alternative that can be administered conveniently, can result in prolonged release of the drug, and provides high EI in patients with minor RAS. There is excellent potential for expanding the application of MCG for treating diseases related to the oral cavity. Our study provides compelling evidence that T-MCG is a beneficial treatment for minor RAS. The prepared novel formulation holds promise for ameliorating the management of RAS by significantly reducing ulcer size and wound healing duration while enhancing patient satisfaction and EI.

Conclusion

The topical application of T-MCG led to decreased ulcer diameter and wound healing duration in patients with minor RAS. The constructed T-MCG demonstrated high patient satisfaction, consistent with the reported high level of patient compliance observed in MCGs. Looking at it in its entirety, the developed T-MCG effectively extended the release of TA and resulted in a significant improvement rate in patients with minor RAS.

Abbreviations

TA: Triamcinolone Acetonide
RAS: Recurrent Aphthous Stomatitis
MCG: Medicated Chewing Gum
VAS: Visual Analog Scale

Declarations

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 (IR.TBZMED.REC.1400.617)

Availability of data and material

All data generated or analyzed during this study are included in this published article.

Competing interests

The authors declare there is no conflict of interest

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Authors' contributions

Saba Bagherzadeh: Writing – original draft. **Fatemeh Soltanmohammadi**: Writing – review & editing. **Haleh Rezaee**: Writing – review & editing. **Nikzad Shahidi**: Conceptualization, Supervision, Writing – review & editing. **Adel Mahmoudi Gharehbaba**: Writing – review & editing. **Yousef Javadzadeh:** Conceptualization, Supervision, Writing – review & editing.
All authors have read the journal's authorship agreement and the manuscript has been reviewed by and approved by all named authors.

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Using artificial intelligence chatbots

There was no use of artificial intelligence in the making of this article.

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