Journal of Oral Hygiene & Health
ISSN: 2332-0702
Stucchi, J Oral Hyg Health 2022, 10:8
Short Communication Open Access

In Vitro Evaluation of the Filmogenic and Barrier Retention Capability of a 3D Cross-linked Formulation Based on a Novel Sodium Hyaluronate Lipoate Medical Device in Gel Form

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Abstract

Aphthous stomatitis (canker sore) is painful ulcerations of the oral mucosa that can affect the quality of life of affected people. The use of medical devices in gel form has become a valuable alternative to drug-based approaches in the treatment of aphthous stomatitis (canker sores). The presented study aimed to investigate the filmogenic capability and the barrier retention of a 3D cross-linked formulation based on a novel sodium hyaluronate lipoate medical device gel formulation, produced by BMG PHARMA. To investigate its efficacy in forming and retaining a barrier effect over time, an in vitro approach based on the well-established Franz cell system was applied. In particular, the BMG gel (BMG0725) product was compared with two commercial formulations available on the Italian market, Alovex® Gel and Tantum® Verde SOS Afte Gel. According to our results, the sodium hyaluronate-based gel of BMG products line showed a better barrier retention compared to the two commercial formulations: indeed, while the barrier efficacy for BMG gel medical device (BMG0725) was observed for up to 18 h, for the other two formulations the barrier efficacy lasted up to 6 h. All tested formulations readily form a barrier following application. Within the limitation of our experimental design, it can be concluded that the barrier forming sodium hyaluronate-based formulation of BMG line is effective in the treatment of aphthous stomatitis, since it protects the aphthae from the oral environment for a long period following application, limiting its application frequency while increasing the patient's compliance as a consequence.

Keywords: Aphthae; Aphthous stomatitis; Sodium hyaluronate; Gel; Filmogenic/Barrier capacity

Introduction

Aphthous stomatitis, also known as aphthae, represents a very common and unpleasant oral mucosal disease that can significantly affect patient's quality of life due to painful and stinging sensations during daily activities like speaking, eating or even drinking [1]. Caused by physical trauma, chemical injury, and microbial infection (bacterial, viral, and fungal), aphthae generally appear on non-keratinized oral mucosa areas (i.e., soft palate, inner lips, inner cheeks, floor of the mouth and ventral surface of the tongue). While a complete healing is usually reached in 10-14 days [2-4], treatments such as anti-inflammatories, corticosteroids, analgesics, antimicrobial, and lubricating agents are used to accelerate the healing process while lessening the pain [4-8]. This approach may lead to unwanted side effects, such as ranging from somnolence to nausea and gastrointestinal symptoms [9]. A potential solution to this problem comes from film-forming formulations that create a temporal physical barrier on ulcerous lesion, protecting it from oral traumas while reducing pain and fostering the healing process, without side effects [10-13]. These formulations are required to be applied several times during the day to keep up the barrier effect. Indeed, film/barrier retention in the oral cavity is mediated and influenced by both the formulation composition and administrations ways (topical gel, spray or mouth rinse). To improve patient's compliance of film/barrier forming formulations for aphthae treatment, it is necessary to increase barrier effect duration so reducing the number of applications. With this aim, BMG PHARMA developed a new sodium hyaluronate-based medical device gel formulation (BMG0725) for aphthae treatment. In the present work, the filmogenic capability and the barrier effect of the BMG medical device is evaluated by mean of a Franz cell-based in vitro approach, and the efficacy of the gel formulation is also compared with two commercially available formulations, Alovex® Gel and Tantum® Verde SOS Afte Gel.

Materials and Method

Formulation tested

The barrier effect of a cross-linked sodium hyaluronate lipoate based gel-medical device for aphthae treatments of BMG products line, was compared with two commercially available formulations, Alovex® Gel and Tantum® Verde SOS Afte Gel. Tested formulations are described in Table 1. Alovex® Gel and Tantum® Verde SOS is registered trademark of Recordati SpA and Angelini SpA respectively.

Methods

Evaluation of the medical device filmogenic capability and barrier effect retention: The barrier effect experiments were conducted using Franz cell diffusion apparatus (PermeGear) (20 mm diameter orifice, 10 mL acceptor chamber, flat ground joint, clear glass) with

Table 1: List of tested medical devices.

Formulation	Application Method
BMG Gel (BMG0725 Gel)	Gel
Alovex® Gel	
Tantum® Verde SOS Afte	

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Received: 18-Jul-2022, Manuscript No: JOHH-22-69437, **Editor assigned:** 21-Jul-2022, PreQC No: JOHH-22-69437(PQ), **Reviewed:** 04-Aug-2022, QC No: JOHH-22-69437, **Revised:** 09-Aug-2022, Manuscript No: JOHH-22-69437(R), **Published:** 16-Aug-2022, DOI: 10.4172/2332-0702.1000329

Citation: Stucchi L (2022) In Vitro Evaluation of the Filmogenic and Barrier Retention Capability of a 3D Cross-linked Formulation Based on a Novel Sodium Hyaluronate Lipoate Medical Device in Gel Form. J Oral Hyg Health 10: 329.

Whatman 5 filter paper (GE Healthcare) as the membrane between the donor and acceptor chambers. Briefly, 500 µL of tested medical device was applied on the filter paper and evenly distributed. Then, the filter paper was placed between the donor and the acceptor chambers (water was used to fill the acceptor compartment) and left to equilibrate for 20 min. Once the equilibration step was concluded, 500 µL of a 0.5 % Trypan Blue solution were added to the donor chamber. Aliquots from the acceptor chamber were collected at pre-determined time intervals (from 0 up to 24 h depending on tested formulation) for the spectrophotometric evaluation of the presence of penetrated Trypan Blue (reading at 540 nm). The entire Franz cell system was maintained at 37.0 °C ± 0.5 °C throughout the experiment.

Statistical Analysis: Results were statistically analyzed by t-test (t-test for paired sample), using Origin Lab software (Origin Lab Corporation, Northampton, MA, US). Experiments on the gel medical device were performed in triplicate on a single batch, while, for mouth rinse and spray, two different batches in triplicate were considered. The obtained results were presented as average ± standard deviation. A p-value of ≤ 0.05 was considered significant.

Results

BMG gel medical device (BMG0725) and commercial formulations filmogenic capability and barrier effect retention

As mentioned before, aphthae are common, small, light-coloured, painful punched-out sore in the mucous membrane of the mouth, causing significant discomfort linked to the pain provoked by the continuous contact with tongue, teeth or food. As such, the simplest and more effective way to reduce the pain, while reducing the healing time, is by creating a film/barrier on the aphthae and limiting the potential contact. However, this barrier not only need to form quickly but it should also last as long as possible, to decrease the formulation application frequency. As shown in **Figure 1, Table 2 and Table 3**, all tested gel formulations are able to readily form an impermeable barrier. While the cross-linked sodium hyaluronate lipoate-based gel formulation (BMG0725 GEL) retains its barrier effect up to 8 h (Figure 1, Table 2 and Table 3), a significant increase in Trypan Blue absorption and a decrease in barrier retention is observed after 6 h for both tested

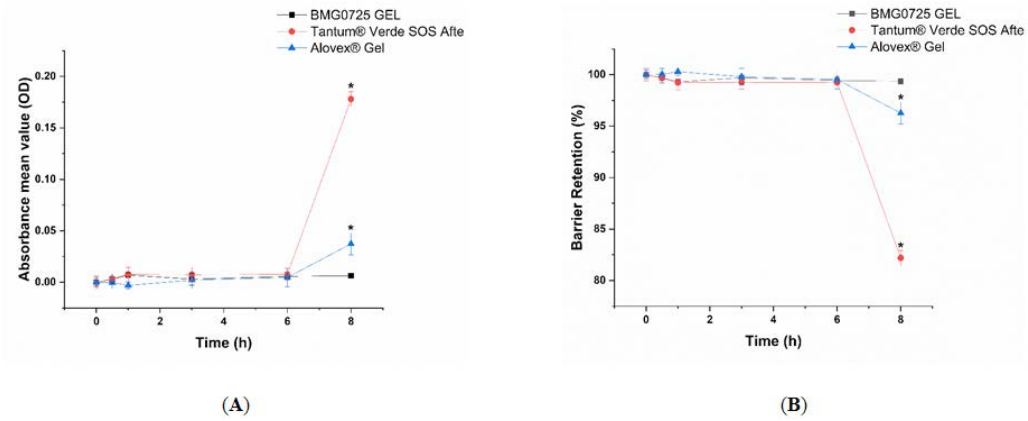

Figure 1: Evaluation of the barrier effect of tested gel medical devices. (A) Absorption kinetic of 0.5 % Trypan Blue solution permeated in the acceptor chamber through the film/barrier and (B) barrier retention over time of tested gel medical devices. BMG0725 GEL (Black Square and line), Tantum® Verde SOS Afte (red circle and line) and Alovex® Gel (blue triangle and line). * p < 0.05

Table 2: Absorbance values of 0.5 % Trypan Blue solution permeated in the acceptor chamber.

	Trypan Blue Absorbance (OD)		
Time (h)	**BMG0725 Gel**	**Tantum® Verde SOS Afte**	**Alovex® Gel**
0	0.000 ± 0.004	0.000 ± 0.006	0.000 ± 0.005
0.5	0.003 ± 0.005	0.003 ± 0.002	0.000 ± 0.006
1	0.007 ± 0.002	0.008 ± 0.007	-0.003 ± 0.003
3	0.003 ± 0.006	0.007 ± 0.006	0.002 ± 0.008
6	0.006 ± 0.002	0.008 ± 0.006	0.005 ± 0.009
8	0.006 ± 0.003	0.178 ± 0.007	0.037 ± 0.011
Spectrophotometric readings of acceptor chamber medium aliquots collected at selected time points (0, 0.5, 1, 3, 6 and 8 h). The results are reported as mean ± standard deviation.			

Table 3: Barrier retention over time of tested gel medical devices.

	Barrier Retention (%)		
TIME (h)	**BMG0725 Gel**	**Tantum® Verde SOS Afte**	**Alovex® Gel**
0	100.0 ± 0.3	100.0 ± 0.6	100.0 ± 0.5
0.5	99.9 ± 0.3	99.7 ± 0.2	100.0 ± 0.6
1	99.6 ± 0.5	99.2 ± 0.7	100.3 ± 0.3
3	99.8 ± 0.5	99.3 ± 0.6	99.8 ± 0.8
6	99.6 ± 0.1	99.2 ± 0.6	99.5 ± 0.9
8	99.3 ± 0.2	82.2 ± 0.7	96.3 ± 1.1
Barrier retention of tested formulation at selected time points (0, 0.5, 1, 3, 6 and 8 h), expressed as percentage (%). The results are reported as mean ± standard deviation.			

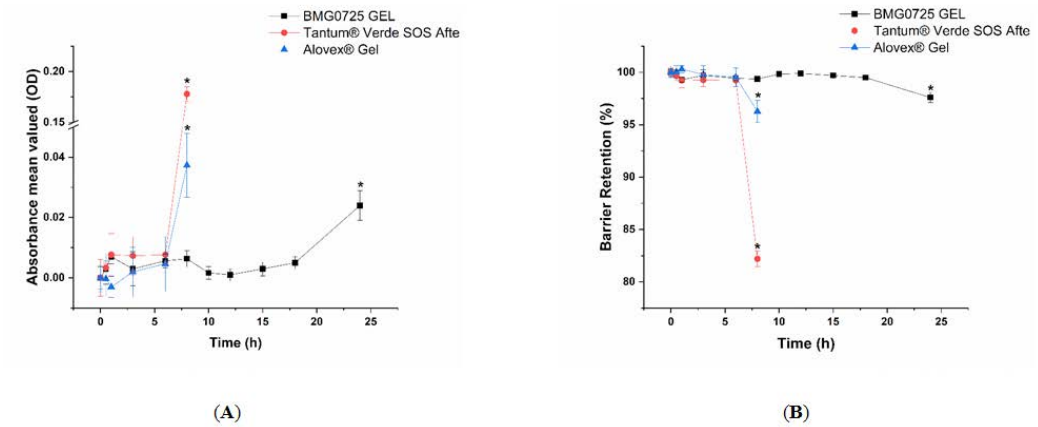

Figure 2: Determination of the BMG0725 formulation film-forming effect duration. (A) Absorption kinetic of 0.5 % Trypan Blue solution permeated in the acceptor chamber through the film/barrier and (B) barrier retention over time of tested gel medical devices, BMG0725 GEL. The results obtained up to 8 h for the two commercial formulations, Tantum® Verde SOS Afte e Alovex® Gel, are reported for comparison reason * $p < 0.05$

Table 4: Absorbance values of 0.5 % Trypan Blue solution permeated in the acceptor chamber and barrier retention over time of tested gel medical device.

Time (H)	BMG0725 Gel	
	Trypan Blue Absorbance (OD)	Barrier Retention (%)
0	0.000 ± 0.004	100.0 ± 0.4
10	0.002 ± 0.002	99.8 ± 0.2
12	0.001 ± 0.002	99.9 ± 0.2
15	0.003 ± 0.002	99.7 ± 0.2
18	0.005 ± 0.002	99.5 ± 0.2
24	0.024 ± 0.005	97.6 ± 0.5

Spectrophotometric readings of acceptor chamber medium aliquots and barrier retention, expressed as percentage (%), of BMG0725 at selected time points ((0, 10, 12, 15, 18 and 24 h)). The results are reported as mean ± standard deviation.

commercial formulations, with Tantum® Verde SOS Afte Gel endowed with the worst overall barrier retention efficiency **(Figure 1 and Table 2).** Consequently, BMG gel formulation ensures a longer barrier effect and a longer barrier retention compared to the considered commercial formulations, reducing its application frequency while increasing its patient's compliance.

Since no permeation of Trypan Blue was observed up to 8 h, the barrier-forming ability of BMG0725 was investigated at longer times. As highlighted by Figure 2 and Table 4, a significant increase in Trypan Blue permeation is observed after 18 h, indicating that BMG0725 was able to retain its barrier effect up to 18 h (Figure 2 and Table 4)**.**

Discussion and Conclusions

The aphthous stomatitis, usually called aphtha, is the most common form of oral ulcers and are associated with painful sensation, that worsen during normal daily activities (i.e., speaking, eating, etc.). While pharmacological treatments do exist, they are not devoid of side-effects. As such, side effects-free film/barrier forming formulations represent an interesting solution for aphthae treatment. Indeed, once the barrier/film is formed, the aphthae is physically protected from the oral cavity environment, limiting the painful contact with the tongue, the teeth or oral microbiota. However, given the specific action of these formulations, multiple applications during the day is necessary to maintain an effective barrier, limiting in part their patient's compliance. Results of the study indicate that the cross-linked sodium hyaluronate lipoate-based formulation produced by BMG PHARMA readily form a physical barrier on the application site effective up to 18 h. In particular, the barrier formed following the application of BMG gel formulation is effective for a longer period of time compared to that of two well-known commercial products, reducing the needed application as a consequence. In conclusion, BMG gel formulation guarantees an effective aphthae treatment with fewer applications (i.e., better patient's compliance), reducing the pain and accelerating their healing compared to the other two formulations Alovex® Gel and Tantum® Verde SOS Afte Gel.

References

1. MA Woods, AR Mohammad, JE Turner, HH Mincer (1990) Oral ulcérations 21.
2. Ship JA, Ann Arbor M (1996) Recurrent aphthous stomatitis. Oral Surg Oral Med Oral Pathol Oral Radiol Endod 81: 141-147.
3. Thakrar P, Chaudhry SI (2016) Oral Ulceration: An Overview of Diagnosis and Management. Prim Dent J 5: 30-33.
4. Scully C, Porter S (2008) Oral mucosal disease: Recurrent aphthous stomatitis. Br J Oral Maxillofac Surg 46:198-206.
5. De Wazieres B, Gil H, Vuitton DA, Dupond JL (1999) Treatment of recurrent oro-genital ulceration with low doses of thalidomide. Clin Exp Rheumatol 17: 393.
6. Macario-Barrel A, Tanasescu S, Courville Ph, Redonnet M, Cordel N, et al. (2001) Ulcérations buccales chez un malade recevant du tacrolimus. Ann Dermatol Venereol 128: 1327-1329.
7. Gilden D (1995) Thalidomide and aphthous ulcers. GMHC Treat Issues 9: 12.
8. Bousvaros A, Mueller B (2001) Thalidomide in gastrointestinal disorders. Drugs 61: 777-787.
9. Dalessandri D, Zotti F, Laffranchi L, Migliorati M, Isola G, et al. (2019) Treatment of recurrent aphthous stomatitis (RAS; Aphthae; canker sores) with a barrier forming mouth rinse or topical gel formulation containing hyaluronic acid: A retrospective clinical study. BMC Oral Health 19:1-10.
10. Casale M, Moffa A, Vella P, Rinaldi V, Lopez PA, et al. (2017) Systematic review: The efficacy of topical hyaluronic acid on oral ulcers. J Biol Regul Homeost Agents 31: 63–69.
11. Lee JH, Jung JY, Bang D (2008) The efficacy of topical 0.2% hyaluronic acid gel on recurrent oral ulcers: Comparison between recurrent aphthous ulcers and the oral ulcers of Behçet's disease. J Eur Acad Dermatology Venereol 22: 590-595.
12. Nolan A, Baillie C, Badminton J, Rudralingham M, Seymour RA (2006) The efficacy of topical hyaluronic acid in the management of recurrent aphthous ulceration. J Oral Pathol Med 35: 461-465.
13. Koray M, Ofluoglu D, Senemtasi A, Íssever H, Yaltirik M (2016) The Efficacy of Hyaluronic Acid Gel in Pain Control of Recurrent Aphthous Stomatitis. Int J Dent Oral Sci 3: 273-275.