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In Vitro Evaluation of the Filmogenic and Barrier Retention Capability of Sodium Hyaluronate-Based Medical Devices in Gel, Spray and Mouth Rinse Forms

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Abstract

Objective: 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, spray and mouth rinse 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 three sodium hyaluronate-based medical devices: a gel, a spray and a mouth rinse formulation, produced by BMG PHARMA.

Methods: To investigate their 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 (BMG0722) product was compared with two commercial formulations available on the Italian market, Alovex® and Tantum® Verde SOS Afte Gel.

Results: According to our results, the sodium hyaluronate-based gel of BMG products line showed a better barrier retention compared to the two commercial formulation: indeed, while the barrier efficacy for BMG gel medical device (BMG0722) was observed for up to 8 h, for the other two formulations the barrier efficacy lasted up to 6 h. Regarding the other formulations of BMG line, the mouth rinse (BMG0721) performance is compatible with BMG0722 gel formulation (8 h), while the spray formulation (BMG0723) loses part of its barrier retention starting from 3 h after application. All tested formulations readily form a barrier following application.

Conclusion: Within the limitation of our experimental design, it can be concluded that the barrier forming sodium hyaluronate-based formulations of BMG line are effective in the treatment of aphthous stomatitis, since they protect the aphthae from the oral environment for a long period following application, limiting their application frequency while increasing the patient's compliance as a consequence.

Keywords: Aphthae; Aphthous stomatitis; Sodium hyaluronate; Gel; Spray; Rinse; Filmogenic 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 invented a line of medical devices for aphthae treatment, composed of three sodium hyaluronate-based products: a gel formulation (BMG0722), a mouth rinse (BMG0721) and a spray formulation (BMG0723). In the present work, the filmogenic capability and the barrier effect of BMG medical devices are 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 Methods

Formulations tested

The barrier effect of a sodium hyaluronate-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. A mouth rinse and a spray formulation, belonging to BMG products line and based on sodium hyaluronate, were also tested for their barrier effect with the same in vitro approach. Tested formulations are described in Table 1. Alovex® Gel and Tantum® Verde SOS Afte Gel is registered trademark of Recordati SpA and Angelini SpA respectively.

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Table 1: List of tested medical devices.

Formulation	Application Method
BMG Gel (BMG0722 Gel)	Gel
BMG Rinse (BMG0721 Rinse)	Liquid
BMG Spray (BMG0723 Spray)	Spray
Alovex® Gel	Gel
Tantum® Verde SOS Afte Gel	

Methods

Evaluation of the medical devices' 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 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 (0, 0.5, 1, 3, 6, and 8, h) 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 (BMG0722) 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 **Figures 1A and 1B, Table 2** and **Table 3**, all tested gel formulations are able to readily form an impermeable barrier. While the sodium hyaluronate-based gel formulation (BMG0722 GEL) retains its barrier effect up to 8 h (Figure 1, Tables 2 and 3), a significant increase in Trypan Blue absorption and a decrease in barrier retention is observed after 6 h for both tested commercial formulations, with Tantum® Verde SOS Afte Gel endowed with the worst overall barrier retention efficiency **(Figure 1 and Table 2).** Consequently, BMG products line gel formulation ensures a longer barrier effect and a longer barrier retention compared to the considered commercial formulations, reducing their application frequency while increasing their patient's compliance.

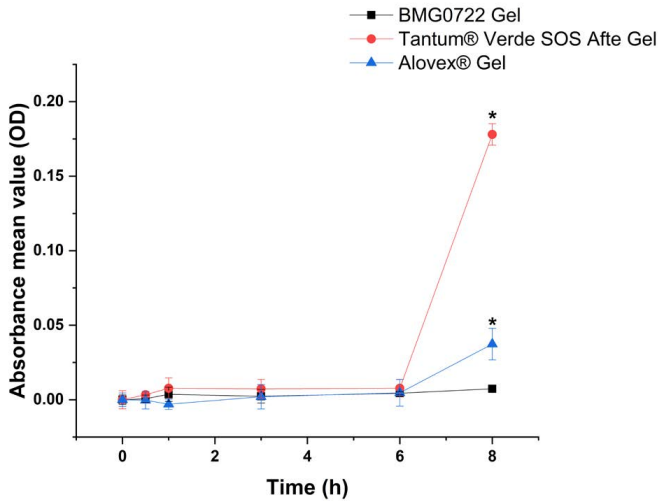

Figure 1A: Sodium hyaluronate-based gel formulation.

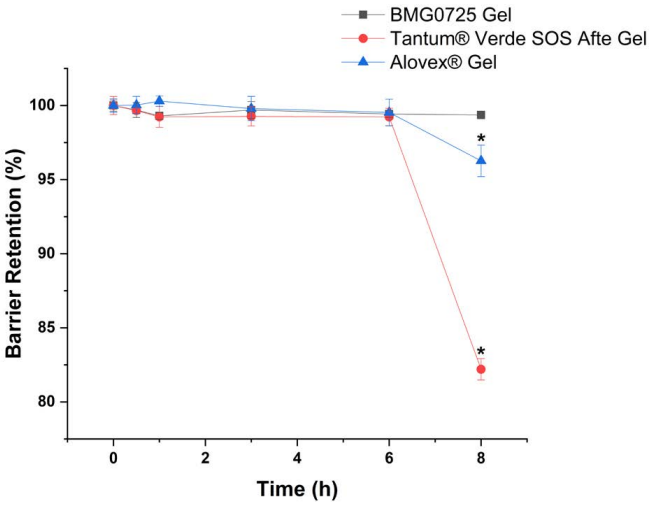

Figure 1B: Tested gel formulations are able to readily form an impermeable barrier.

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. BMG0722 GEL (Black Square and Line), Tantum® Verde SOS Afte Gel (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 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.

	Trypan Blue Absorbance (OD)		
Time (h)	BMG0722 Gel	Tantum® Verde SOS Afte Gel	Alovex® Gel
0	0.000 ± 0.003	0.000 ± 0.006	0.000 ± 0.005
0.5	0.001 ± 0.003	0.003 ± 0.002	0.000 ± 0.006
1	0.004 ± 0.005	0.008 ± 0.007	-0.003 ± 0.003
3	0.002 ± 0.005	0.007 ± 0.006	0.002 ± 0.008
6	0.004 ± 0.001	0.008 ± 0.006	0.005 ± 0.009
8	0.007 ± 0.002	0.178 ± 0.007	0.037 ± 0.011

Barrier effect of BMG mouth rinse (BMG0721) and spray (BMG0723) medical devices

Since they should be applied with the proper dispenser or, in the worst case, with a clean finger, filmogenic medical device in gel form

are usually preferred for easily accessible aphthae treatment. However, aphthae could be located in difficult-to-reach area. To improve the treatment of such aphthae, spray and mouth rinse formulations have been developed since they could easily access hidden region of the oral cavity. As for the gel formulations, filmogenic capability and barrier effect retention of a mouth rinse and a spray formulation of BMG products line were tested. Both the mouth rinse and spray formulation readily form a barrier (Figure 2 and Table 4) Interestingly, the mouth rinse (BMG0721 RINSE) shows a barrier effect retention compatible with gel formulations, with no marker permeation observed up to 8h **(Figure 1, Table 2,3, Figure 2 and Table 4).** Conversely, an increase in Trypan Blue absorption was observed starting from 3 h (Figure 2A) and **(Table 4)** for the spray formulation (BMG0723 SPRAY), indicating a shorter duration of its barrier effect retention (Figure 2B) and **(Table 4).**

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

	Barrier Retention (%)		
Time (h)	BMG0722 Gel	Tantum® Verde SOS Afte Gel	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

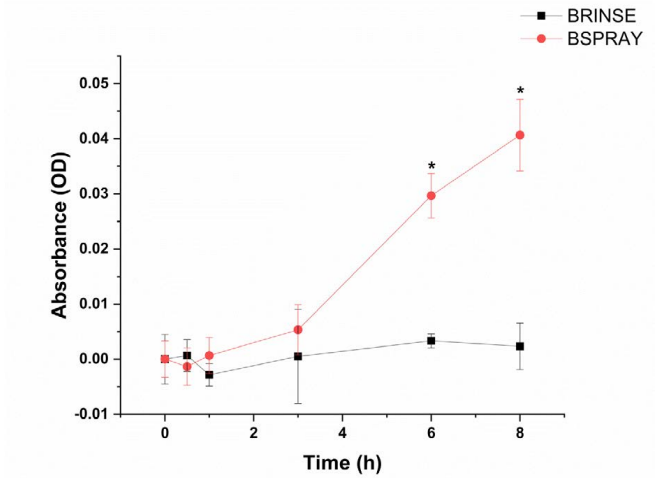

Figure 2A: Increase in Trypan Blue absorption.

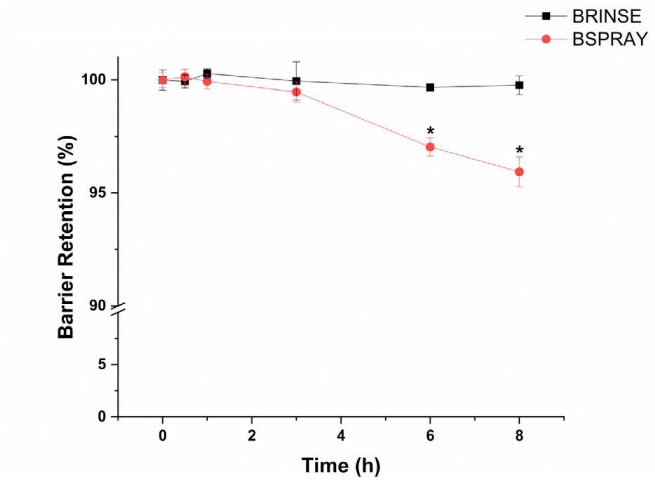

Figure 2B: Trypan Blue absorption indicating a shorter duration of its barrier effect retention.

Figure 2: Evaluation of the barrier effect of a mouth wash and a spray medical device. (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 spray and mouth rinse. BMG0721 RINSE (Black Square and line) and BMG0723 SPRAY (red circle and line). * P < 0.05.

Table 4: Absorbance values of 0.5% Trypan Blue solution permeated in the acceptor chamber and barrier retention. Spectrophotometric readings of acceptor chamber medium aliquots collected at selected time points (0, 0.5, 1, 3, 6 and 8 h) and barrier retention expressed as percentage (%). The results are reported as mean ± standard deviation.

	Trypan blue absorbance (OD)		Barrier retention (%)	
Time (h)	BMG0721 Rinse	BMG0723 Spray	BMG0721 Rinse	BMG0723 Spray
0	0.000 ± 0.003	0.000 ± 0.004	100.0 ± 0.5	100.0 ± 0.3
0.5	-0.002 ± 0.005	0.003 ± 0.005	99.9 ± 0.3	100.1 ± 0.3
1	0.006 ± 0.012	0.007 ± 0.002	100.3 ± 0.2	99.9 ± 0.3
3	0.005 ± 0.007	0.003 ± 0.006	100.0 ± 0.9	99.5 ± 0.5
6	0.005 ± 0.004	0.006 ± 0.002	99.7 ± 0.1	97.0 ± 0.4
8	0.005 ± 0.002	0.006 ± 0.003	99.8 ± 0.4	95.9 ± 0.7

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 micro biota. 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 sodium hyaluronate-based formulations produced by BMG PHARMA readily form a physical barrier on the application site effective up to 8 h for gel and mouth rinse formulations. 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 products line, especially if used in combination during the day, 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.

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