

MucoLox™

Assessment of the Mucoadhesive Properties of MucoLox Using a 3D Model of the Human Oral Mucosa

Abstract: The buccal mucosa is a common site for delivery of medication in the treatment of disease and conditions of the oral mucosa. However, low residence time at the site of action is a drawback for buccal delivery, increasing the need for mucoadhesive polymers. This study examines the mucoadhesive properties of MucoLox, a polymer gel, in comparison to a reference product, when applied on an EpiOral™ tissue model, a three-dimensional (3D) model of the human oral mucosa. Results show that sample retention for MucoLox was 24 times longer than for the reference product. The ability of MucoLox to prolong contact between the medication and the site of action has the potential to increase the efficacy of the compounded medication and to reduce the need for frequent dosing.

Introduction: Delivery of medication via the oral mucosa has been continuously evolving since the mid-1980s due to the development of novel delivery systems, allowing for increased efficacy upon delivery. Since then, the oral mucosa has been an ideal target for drug delivery due to the ability of the medication to bypass first-pass metabolism, avoid gastrointestinal degradation, and achieve more rapid onset of action [1]. Within the oral mucosa lies the buccal mucosa, which is composed of non-keratinized epithelial cells that line the inner cheeks. Buccal delivery is advantageous in that the buccal mucosa is highly vascularized, has low levels of enzymatic activity, and is fairly immobile, making it a suitable site for both local and systemic delivery of medication [2]. However, one of the greatest disadvantages of buccal delivery is the low residence time (time at site of action) of the medication. This can be due to various factors such as continuous secretion of saliva triggering involuntary swallowing, intake of food, and movement of the tongue. All these factors can influence the efficacy of the compounded medication [2, 3]. Recognition of the drawback has led to the development of mucoadhesive polymers, a delivery system that adheres to the mucosal lining of the cheeks and prolongs residence time [4]. The primary purpose of this study is to assess the mucoadhesive properties of MucoLox, a polymer gel, in comparison to a mucoadhesive commercial reference product, using the EpiOral model (MatTek Corporation), a highly differentiated three-dimensional (3D) model of the human oral mucosa [5]. MucoLox is a proprietary polymer gel designed to improve mucoadhesion and prolong retention of medications at application sites within the oral mucosa [6].

Methodology: The EpiOral (ORL-200) tissue model comprises of normal human-derived non-keratinized oral epithelial cells, cultured and differentiated to resemble the native buccal tissue of the human oral mucosa [5]. EpiOral tissues were first cultured within an air-liquid interface method and incubated at 37°C for 1 hr prior to sample application. The reference product and MucoLox were then labeled with appropriate quantities of sodium fluorescein using 1% NaFl stock solution and vortexed for 15 seconds within a tube that is protected from light. A 100 µL of each fluorescently labeled sample was applied to the apical surface of the EpiOral tissues (2 tissues for each sample) and incubated at intervals of 5, 10, 30, 40 min, 1, 2, and 5 hr. After each allotted incubation interval, tissue samples were removed and rinsed 3 times by immersing in 10 mL of DPBS (Dulbecco's Phosphate-Buffered Saline) and decanting within separate wells of a 6-well plate. In order to ensure that any loss of NaFl would be due to washing rather than leakage through the EpiOral tissues, culture supernatant was also collected and measured for NaFl content using a fluorescent plate reader. Two EpiOral tissues were left untreated to serve

as a negative control while another set of two unwashed EpiOral tissues exposed to the reference product and MucoLox samples for 10 min served as a positive control. For each incubation and washing cycle, images were acquired for each EpiOral tissue using an Olympus FV1000 confocal microscope. Through the images of the gel retention, mucoadhesive properties of the samples were then compared and analyzed.

Results and Discussion: For the EpiOral tissue treated with the reference product, the NaFl-labeled reference product was washed out after 5 min of incubation (Figure 1). This is evident by the absence of the fluorescein dye (green fluorescence) above the tissue area on the images captured following washing. For the tissue treated with NaFl-labeled MucoLox, the dye was well retained (remarkable green fluorescence) on the apical surface of the tissue for up to 40 min (Figure 2). There was limited sample retention (faint green fluorescence) noted at 1 and 2 hr following application. The absence of NaFl in the culture supernatant was also confirmed to show that there is no leakage of NaFl from tissues. Rather, the loss of fluorescent dye is purely a result of washing. Results show that MucoLox was superior to the commercial reference product in terms of mucoadhesive properties as the duration in which MucoLox was retained on the surface of the tissue was approximately 24 times longer than that of the reference product. As mentioned previously, one of the greatest barriers to buccal delivery of medication is the short residence time at the application site due to the surfaces of the cheeks being constantly washed with saliva, causing loss of medication [3]. Having longer mucosal retention potential, MucoLox offers an advantage over the reference product in allowing for prolonged contact between the tissue and the delivery system. This can help maintain the active ingredient at the site of action, potentially increasing efficacy of the compounded medication. Also, less frequent dosing will likely be required with MucoLox as a result of longer retention time [1].

Conclusions: Optimal mucoadhesive properties exhibited by MucoLox are ideal features sought after by many compounding pharmacists searching for bases to be used in the treatment of diseases and conditions of the oral mucosa. These conditions include, but are not limited to, mucositis (ulceration and inflammation of mucous membranes), candidiasis (fungal infection), recurrent ulcers (herpes virus), bacterial infections, and trauma of the oral mucosa. For instance, in the case of mucositis in cancer patients, the ulceration and inflammation of the mucous membranes as a result of radiation and chemotherapy can be very painful and uncomfortable for patients [7]. For this reason, pharmacists often want to compound medications that will not add additional burden to a patient's medication regimen. It is then beneficial to use a base with high mucoadhesive strength and long mucosal retention to prolong the contact between the medication and the site of action [4]. This reduces the need for frequent dosing as the effectiveness of each dose is optimized. The active ingredients are not washed away with the base by saliva and can remain at the affected site, facilitating the treatment process [1]. The concept of increased efficacy with less frequent dosing potentially achieved with MucoLox can be appealing to patients who are already in pain and discomfort from the underlying condition, overall, improving their compliance with the medication regimen.



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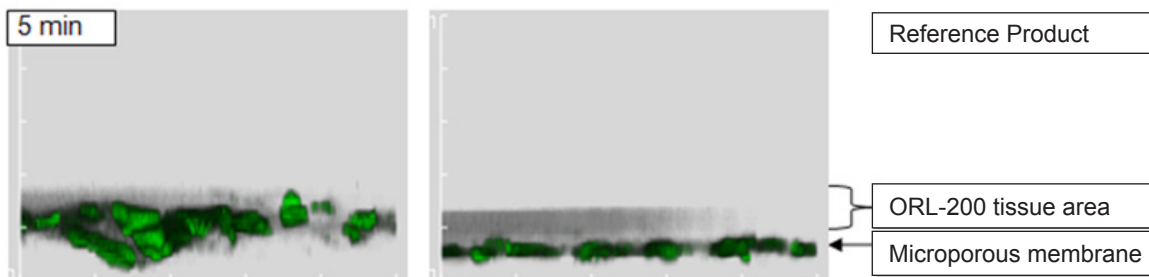


Figure 1. Showing disappearance of the reference product after 5 min of incubation and washing.

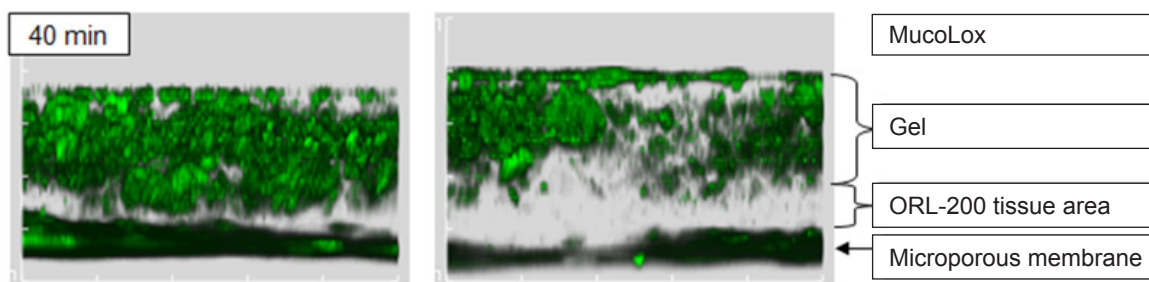


Figure 2. Showing gel retention following 40 min of incubation and washing.

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